Srinivasan, Venkatramanujam; Pandi-Perumal,Seithikurippu R.; Brown, Gregory M.; Cardinali, Daniel P.; Spence, D. Warren; Hardeland, Rüdiger

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Preprint del documento publicado en Progress in Neurobiology, 2011, 93, 350-384

Publicado en: Progress in Neurobiology 93, 350–384, 2011

Melatonin – a pleiotropic, orchestrating regulator molecule

Rüdiger Hardeland[a, CA], Daniel P. Cardinali[b], Venkatramanujam Srinivasan[c,d], D. Warren Spence[e], Gregory M. Brown[f] and Seithikurippu R. Pandi-Perumal[g]

[a] Johann Friedrich Blumenbach Institute of Zoology and Anthropology, University of Goettingen, Berliner Str. 28, D-37073 Goettingen, Germany

[b] Departamento de Docencia e Investigación, Facultad de Ciencias Médicas, Pontificia Universidad Católica Argentina, C1107AFD Buenos Aires, Argentina

[c] Sri Sathya Sai Medical, Educational and Research Foundation, Prashanthi Nilayam 40, Kovai Thirunagar Coimbatore – 641014, India

[d] Department of Physiology, Faculty of Medicine, Karpagam University, Eachanari, Coimbatore - 641021, India.

[e] 323 Brock Ave., Toronto, ON M6K 2M6, Canada

[f] Department of Psychiatry, Faculty of Medicine, University of Toronto, Centre for Addiction and Mental Health, 250 College St., Toronto, ON M5T 1R8, Canada

[g] Somnogen Inc., College Street, Toronto, ON M6H 1C5, Canada

[CA] Corresponding Author:

Rüdiger Hardeland

Tel.: +49-551-395414

Fax: +49-551-395438

E-mail: rhardel@gwdg.de

Abstract

Melatonin, the neurohormone of the pineal gland, is also produced by various other tissues and cells. It acts via G protein-coupled receptors expressed in various areas of the central nervous system and in peripheral tissues. Parallel signaling mechanisms lead to cell-specific control and recruitment of downstream factors, including various kinases, transcription factors and ion channels. Additional actions via nuclear receptors and other binding sites are likely. By virtue of high receptor density in the circadian pacemaker, melatonin is involved in the phasing of circadian rhythms and sleep promotion. Additionally, it exerts effects on peripheral oscillators, including phase coupling of parallel cellular clocks based on alternate use of core oscillator proteins. Direct central and peripheral actions concern the up- or downregulation of various proteins, among which inducible and neuronal NO synthases seem to be of particular importance for antagonizing inflammation and excitotoxicity. The methoxyindole is also synthesized in several peripheral tissues, so that the total content of tissue melatonin exceeds by far the amounts in the circulation. Emerging fields in melatonin research concern receptor polymorphism in relation to various diseases, the control of sleep, the metabolic syndrome, weight control, diabetes type 2 and insulin resistance, and mitochondrial effects. Control of electron flux, prevention of bottlenecks in the respiratory chain and electron leakage contribute to the avoidance of damage by free radicals and seem to be important in neuroprotection, inflammatory diseases and, presumably, aging. Newly discovered influences on sirtuins and downstream factors indicate that melatonin has a role in mitochondrial biogenesis.

Keywords: Aging; Circadian; Diabetes; Excitotoxicity; Melatonin; Mitochondria; Neuroprotection; Sleep

Abbreviations: 4P-PDOT, 4-phenyl-2-propionamidotetraline; AFMK, N^1-acetyl-N^2-formyl-5-methoxykynuramine; AMK, N^1-acetyl-5-methoxykynuramine; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; CCK, cholecystokinin; CNG, cyclic nucleotide-gated channel; CREB, cAMP response element binding protein; CRH, corticotrophin-releasing hormone; DSPS, delayed sleep phase syndrome; ETC, electron transport chain; GABA, γ-aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; GnRH, gonadotrophin releasing hormone; GPCR, G protein-

coupled receptor; GPx, glutathione peroxidase; GSK3β, glycogen synthase kinase 3β; hCG, human chorionic gonadotrophin; HDL, high density lipoprotein; HIF-1α, hypoxia-inducible factor 1α; HIOMT, hydroxyindole *O*-methyltransferase; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LH, luteinizing hormone; LPS, lipopolysaccharide (bacterial); M-CSF, macrophage-colony stimulating factor; $mGlu_3$, metabotropic glutamate receptor 3; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MT_1, melatonin receptor 1; MT_2, melatonin receptor 2; mtPTP, mitochondrial permeability transition pore; NF1, neurofibromatosis type 1; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; Nox, NAD(P)H oxidase; PACAP, pituitary adenylyl cyclase activating peptide; PARP, poly ADP ribose polymerase; PGC-1α, PPARγ coactivator-1α; PGE, prostaglandin E; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PK, protein kinase; PPARγ, peroxisome proliferator-activated receptor-γ; PT, pars tuberalis; QR2, quinone reductase 2; REM, rapid eye movements; RNS, reactive nitrogen species; ROR, retinoic acid receptor-related orphan receptor; ROS, reactive oxygen species; RZR, retinoid Z receptor; SCN, suprachiasmatic nucleus; SNP, single nucleotide polymorphism; SOD, superoxide dismutase; TGF, transforming growth factor; TNF, tumor necrosis factor; UCP, uncoupling protein; VNTR, variable-number tandem-repeat polymorphism.

Contents

1. Introduction

The methoxyindole melatonin (*N*-acetyl-5-methoxytryptamine) was first discovered in the nineteen-fifties as the hormone of the pineal gland (Lerner et al., 1958, 1959). Its name is indicative of melatonin´s first identified function, namely its skin-lightening properties in fish and amphibia. These properties, however, were only of interest to some specialists. Moreover, alteration in skin coloring was not applicable to mammals, whose melanocytes do not contain physiologically controlled, mobile melanosomes. The hormone received considerably more attention when melatonin was found to regulate and reset circadian rhythms (Redman et al., 1983; Armstrong et al., 1986) and, in species responding to photoperiodic changes, to be involved in the measurement of daylength, an environmental variable used for seasonal timing of reproduction, metabolism and behavior (Tamarkin et al., 1976, 1985; Arendt, 1986; Reiter, 1991, 1993b). The direct effects in regions containing high densities of melatonin receptors, such as the circadian pacemaker, the suprachiasmatic nucleus (SCN), or the pars tuberalis (PT), a site of particular relevance to photoperiodically controlled reproduction (Hastings et al., 1988; Lincoln and Maeda, 1992; Fraschini and Stankov, 1994; Gauer et al., 1994; Masson-Pévet et al., 2000; Pévet et al., 2002; Stehle et al., 2003) strongly supported the premier significance of this physiological role. In the perception by many investigators, the control of circadian and seasonal rhythmicities represents melatonin's main physiological function. Although this view is not generally disputed, the actions of the methoxyindole are by no means restricted to areas of high receptor density.

During more recent decades, melatonin has been shown to possess numerous additional functions and to act in tissues or cells that express melatonin receptors at much lower levels (Dubocovich and Markowska, 2005; Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2008; Hardeland, 2009b). The classic membrane-associated melatonin receptors, in mammals MT_1 and MT_2 (Reppert et al., 1994, 1995; Jin et al., 2003; Korf and von Gall, 2006; Dubocovich et al., 2010) transduce numerous chronobiological actions of the hormone and are, in particular, responsible for circadian phase shifting, the "chronobiotic" effects of melatonin (Dawson and Armstrong, 1996). Additionally, various other melatonin binding sites have been identified, but whose roles are either poorly understood or almost unknown (Hardeland, 2009b). The fact that the occurrence of melatonin is not restricted to vertebrates, but rather is almost ubiquitously present in numerous taxa including, e.g., bacteria, unicellular eukaryotes and plants (Hardeland and Fuhrberg, 1996; Hardeland and Poeggeler, 2003;

Hardeland et al., 2007b; Paredes et al., 2009) indicates that this molecule has gained many additional functions in the course of evolution (Hardeland et al., 1995; Tan et al., 2010a).

A further deviation from the classic view of melatonin's role results from the observation that it is, in mammals and other vertebrates, not only synthesized by the pineal gland or related structures, such as the retina, but also in quite a number of different organs or cells. These include the gastrointestinal tract, bone marrow, leukocytes, membranous cochlea, Harderian gland, and, perhaps, also skin and other brain areas (Raikhlin and Kvetnoi, 1974; Kvetnoi et al., 1995; Tan et al., 2003; Jimenez-Jorge et al., 2007; Hardeland and Poeggeler, 2007, 2008; Hardeland, 2009b). From these other sites of formation, melatonin is either poorly released or only in response to specific stimuli, e.g., as a post-prandial surge from the gastrointestinal tract (Huether et al., 1992; Huether, 1993, 1994; Bubenik, 2002). Relative to the amounts present in the pineal gland and the circulation, the quantities of melatonin in extrapineal tissues are by no means negligible, but, owing to the total size these organs, are orders of magnitude higher (Huether, 1993; Bubenik, 2002).

Melatonin displays an exceptional multiplicity of actions, as will be outlined in detail. These can only be understood on the basis of an integrative, orchestrating role by which melatonin is distinguished from many other important signal molecules. Deficiencies in melatonin production or melatonin receptor expression, and decreases in melatonin levels (such as those which occur during aging) are likely to cause numerous dysfunctions. In these cases, insufficient amounts of melatonin or poor melatonergic signaling can be associated with a multitude of pathophysiological changes, which, again, reflect the pleiotropy of this molecule.

2. Pleiotropy of melatonin

The pleiotropy of melatonin has to be analyzed at different levels, from the sites of synthesis and local dynamics, distribution of receptors and other binding sites in target organs, cell-specific differences in signaling as related to the presence of G protein variants, and intracellular effects – with a particular focus on mitochondrial actions – to numerous secondary changes induced by influencing other hormones, neurotransmitters, neurotrophins and further signal molecules. In functional terms, melatonin exerts a host of effects that can be under the control of the SCN and, in seasonal breeders, the premammillary hypothalamus and the PT, and may also have direct effects in numerous peripheral organs. In particular, melatonin is involved in sleep initiation, vasomotor control, adrenal function, antiexcitatory

actions, immunomodulation including antiinflammatory properties, antioxidant actions, and energy metabolism, influencing mitochondrial electron flux, the mitochondrial permeability transition pore (mtPTP), and mitochondrial biogenesis (reviewed in: Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2008; Hardeland and Coto-Montes, 2010).

2.1. Multiplicity of target organs

Melatonin receptors have been detected in numerous tissues. In preliminary investigations, this was revealed by [^{3}H]-melatonin (Cardinali et al., 1979; Niles et al., 1979) and subsequently, [^{125}I]-2-iodomelatonin binding (Vaněček et al., 1987). Later, after characterization of the membrane-bound receptors MT_1 and MT_2 (Reppert et al., 1994, 1995), corresponding data were obtained in expression studies at mRNA or protein levels. In many mammalian species, the membrane receptors have been identified in various sites of the central nervous system and in peripheral organs, such as gastrointestinal tract, liver, lung, skin, Harderian gland, adrenal gland, gonads and male accessory organs, mammary tissue, kidney, heart, blood vessels, adipose tissue, neutrophils, lymphocytes and lymphoid tissues (reviewed in: Dubocovich and Markowska, 2005; Sallinen et al., 2005; Pandi-Perumal et al., 2008b; Ishii et al., 2009). Because of considerable species differences in receptor distribution, the following section will mainly focus on human tissues, with reference to receptor subtype as far as this has been identified.

2.1.1. Receptors and other binding sites in peripheral organs

Among the peripheral organs, the membrane receptors were demonstrated in duodenal enterocytes (MT_2, Sjöblom et al., 2001, 2003; Flemström et al., 2003, 2010; Flemström and Sjöblom, 2005; Sjöblom, 2005), colon, caecum and appendix (subtype not identified, Poon et al., 1996, 1997), gallbladder epithelium (MT_1, Aust et al., 2004), parotid gland (MT_1, MT_2, Aras and Ekström, 2008), exocrine pancreas (MT_1, Aust et al., 2008), β cells of endocrine pancreas (MT_1, MT_2, Mühlbauer and Peschke, 2007; Ramracheya et al., 2008; Lyssenko et al., 2009; Mulder et al., 2009), skin (MT_1, MT_2, Slominski et al., 2002, 2003, 2004), breast epithelium (Dillon et al., 2002), myometrium (MT_1, MT_2, Schlabritz-Loutsevitch et al., 2003; Sharkey et al., 2010), placenta (MT_1, MT_2, Lanoix et al., 2006), granulosa and luteal cells (MT_1, MT_2, Yie et al., 1995; Niles et al., 1999; Woo et al., 2001; Tamura et al., 2009), fetal kidney (MT_1, Williams et al., 2001), cardiac ventricular wall (MT_1, MT_2, Ekmekcioglu et al.,

2001, 2003), aorta, coronary and cerebral arteries and other parts of peripheral vasculature (MT_1, MT_2, Savaskan et al., 2001; Ekmekcioglu et al., 2001, 2003; Ekmekcioglu, 2006; Cui et al., 2008), brown and white adipose tissues (MT_1, MT_2, Brydon et al., 2001; Ekmekcioglu, 2006), platelets (subtype not identified, Vacas et al., 1992), and various immune cells (MT_1, perhaps also MT_2, Konakchieva et al., 1995; García-Pergañeda et al., 1997; Pozo et al., 2004; Carrillo-Vico et al., 2003b; Lardone et al., 2009).

Additional information exists on the expression of MT_1 and MT_2 in various human cancer cell lines of different origin (Xi et al., 2000; Dillon et al., 2002; Ekmekcioglu, 2006; Lanoix et al., 2006; Aust et al., 2008; Nakamura et al., 2008; Carbajo-Pescador et al., 2009). Inasmuch as the expression has not yet been demonstrated in normal tissue, the presence or absence of melatonin receptors in tumor cells may have resulted from changes in differentiation state and thus do not allow conclusions regarding healthy organs. Moreover, the level of expression can be considerably altered in tumor cells. Strong negative correlations of MT_1 expression with tumor size and progression, along with antitumor properties of melatonin and growth inhibitions upon restoration of MT_1 expression, or MT_1 overexpression, have supported suggestions that this receptor subtype may represent a tumor suppressor (Yuan et al., 2002; Nakamura et al., 2008).

The membrane receptors do not represent the only binding sites of melatonin. A binding protein originally thought to represent a third membrane receptor ("MT_3"), turned out to be the primarily cytosolic enzyme quinone reductase 2 (= QR2 = NRH:quinone oxidoreductase 2 = NQO2; NRH = dihydronicotinamide riboside: Nosjean et al., 2000, 2001; Mailliet et al., 2005). Melatonin was shown to inhibit this enzyme, however, in the micromolar range (Delagrange and Boutin, 2006; Ferry et al., 2010). *N*-acetyl-5-hydroxytryptamine is a ligand of similar affinity (P. Paul et al., 1999) and resveratrol was shown to be more potent in this regard (Ferry et al., 2010). Despite the development of several QR2 ligands and the description of various effects, this binding site should no longer be considered as a receptor, or to be specific for melatonin. Its role should not be sought in the initiation of signaling pathways, but rather in the field of detoxification mechanisms of aromates. For instance, QR2 was shown to eliminate carcinogenic estrogen quinones (Gaikwad et al., 2009). The advantage of an inhibition remains, however, obscure. Nevertheless, this redox-sensitive enzyme seems to be of a certain importance. A gene polymorphism was associated with Parkinson's disease (Harada et al., 2001). Disruption of the gene led to myeloid hyperplasia in the bone marrow (Long et al., 2002). Tissue distribution has also been studied in mice,

hamsters, dogs and monkeys (*Macaca fascicularis*) (Nosjean et al., 2001). With some variation concerning relative expression levels, QR2 has been detected in liver, kidney, brain and heart, and, in lower quantities, in hamster brown adipose tissue and monkey kidney, liver and brain.

Melatonin also binds to transcription factors belonging to the retinoic acid receptor superfamily, in particular, splice variants of RORα (human gene ID: 6095), designated as RORα1 (= RORα isoform a), RORα2 (= RORα isoform b) and RORα isoform d (formerly called RZRα), and the product of another gene, RZRβ (= RORβ; human gene ID: 6096) (Carlberg and Wiesenberg, 1995; Wiesenberg et al., 1995; Mor et al., 1999; Carlberg, 2000; Carrillo-Vico et al., 2005a; Tomás-Zapico and Coto-Montes, 2005). A further splice variant, RORα3 (=RORα isoform c) has not been attributed to actions of melatonin. Although these nuclear binding proteins have for quite some time been a matter of debate and although their affinity to melatonin is lower, compared to MT_1, their classification as nuclear receptors now seems to be justified. A synthetic ligand, CGP 52608 (Wiesenberg et al., 1995) has been repeatedly used for identifying effects by these nuclear proteins.

At the level of these nuclear receptors, the pleiotropy of melatonin is even more obvious than in the cases of the membrane-bound receptors. RORα subforms are ubiquitously expressed in all mammalian tissues tested to date (Carlberg, 2000). Relatively high levels were detected especially in T- and B-lymphocytes, neutrophils and monocytes (García-Mauriño et al., 1997, 1998; Carlberg, 2000; Guerrero et al., 2000a; Guerrero and Reiter, 2002; Carrillo-Vico et al., 2005a, 2006). A particular functional relevance may also exist in bone (Schräder et al., 1996; Abdel-Wanis and Tsuchiya, 2002), skin, including hair follicles (Kobayashi et al., 2005; Fischer et al., 2008), and endothelial cells (Kim et al., 2008). RORα expression levels frequently depend on the differentiation state of cells or may vary within the cell cycle (Steinhilber et al., 1995; Carlberg, 2000; Kobayashi et al., 2005). Contrary to the ubiquitously present RORα, RZRβ is more or less specifically expressed in brain, pineal gland and retina, and is also found in spleen (Greiner et al., 1996; H.T. Park et al., 1996; Carlberg, 2000; Roy et al., 2001).

Melatonin binding sites have been also described for at least two other ubiquitously expressed proteins, which are of high relevance in calcium metabolism, calmodulin (CaM) (Benítez-King et al., 1993; Benítez-King and Antón-Tay, 1993) and calreticulin (Macías et al., 2003). Earlier studies on CaM indicated that its affinity to melatonin could suffice for binding at elevated physiological concentrations (Benítez-King et al., 1993; Benítez-King and Antón-

Tay, 1993), but more recent evidence suggests that it has a much lower affinity (Landau and Zisapel, 2007; Turjanski et al., 2007). Nevertheless, a physiological role cannot yet be ruled out, since the affinity determined for the CaM/CaM kinase II complex was considerably higher than that of CaM alone (Landau and Zisapel, 2007). It seems worth further efforts to measure melatonin binding to CaM complexes with other CaM-regulated proteins. The relevance of melatonin interactions with calreticulin is still uncertain, but, if found to be functionally important, would imply another host of pleiotropic actions. Two other, functionally not yet characterized nuclear proteins, one of them with a homology to calreticulin, were identified as further putative binding sites of melatonin (Macías et al., 2003). Again, the relevance of these proteins in melatonin signaling remains to be identified. The same holds true for direct melatonin binding to another ubiquitous protein, tubulin (Cardinali and Freire, 1975; Cardinali, 1980). However, there are numerous other effects of melatonin on cytoskeletal structure including tubulin rearrangements transmitted by other signaling pathways (Benítez-King, 2006).

The distribution of receptors and other binding sites indicates a remarkable pleiotropy of melatonin, which may potentially affect the majority of cells, in addition to other, receptor-independent chemical reactions such as free radical scavenging (Tan et al., 1993, 2007; Reiter, 1993a; Hardeland, 2005). Correspondingly, numerous effects in peripheral organs have been described. However, a clear-cut relationship to the respective receptors and signaling pathways is not always obvious. Therefore, we will preferably focus on effects which have been thoroughly or frequently studied and in which the underlying mechanisms are largely identified.

In the gastrointestinal tract, vagal and sympathetic stimulation causes enteroendocrine cells to mobilize melatonin, which stimulates, via MT_2 and elevation cytosolic Ca^{2+}, the secretion of bicarbonate by epithelial cells (Sjöblom et al., 2001, 2003; Flemström et al., 2003, 2010; Flemström and Sjöblom, 2005; Sjöblom, 2005). Moreover, the mucosal blood flow is increased by melatonin (Bubenik, 2008). In the colon, pharmacological doses lengthen transit time, effects that are associated with the regulation of fecal water content and reduction of motility (Bubenik, 2008; Lu et al., 2009). Decreases in motility have been frequently observed (Bubenik, 2002, 2008). The assumption that melatonin may also delay gastric emptying led to divergent results in different laboratories (Kasimay et al., 2005; Martín et al., 2005). This may, however, be a matter of experimental dosage, since, in another study, melatonin was shown to stimulate gastrointestinal motility at low concentrations, but was

inhibitory at higher, pharmacological levels (Thor et al., 2007). In the stomach, effects on motility may be indirectly regulated via secretion of enteral hormones. In fact, the methoxyindole elicited cholecystokinin (CCK) release and, thereby, induced pancreatic enzyme secretion (Leja-Szpak et al., 2004; Jaworek et al., 2007). In the rat parotid gland, melatonin stimulated protein and amylase secretion, an effect mainly mediated by MT_2 receptors and also observed in denervated glands (Aras and Ekström, 2008). More recently, melatonin has been shown to inhibit serotonin transporter activity in Caco-2 cells used as a model of intestinal epithelial cells (Matheus et al., 2010). However, these results, which did not seem to be mediated by MT_1 or MT_2, were obtained at pharmacological concentrations and may not reflect the physiological situation.

The situation in the gut is complicated by the fact that this organ is not only a source but also a sink of melatonin, which can be loaded from the circulation (Messner et al., 1998; Poeggeler et al., 2005). Moreover, the methoxyindole undergoes enterohepatic cycling and accumulates in the bile fluid (Tan et al., 1999). The gallbladder, apart from being influenced by melatonin-dependent CCK secretion, may directly respond via MT_1 stimulation (Aust et al., 2004), but the precise function has not been identified.

Melatonin also influences several other hormonal systems. Insulin secretion is inhibited by melatonin, by an MT_2-dependent mechanism. According to studies mainly based on INS1 insulinoma cells, the signaling pathway involves inhibition of cytosolic guanylate cyclase and cyclic nucleotide-gated (CNG) channels, in the absence of changes in NO levels (Peschke, 2008; Stumpf et al., 2008, 2009). In the presence of α-cells, an increase of insulin release from islets has been rather observed, an effect explained by the simultaneous stimulation of glucagon secretion, which overrides the melatonin-dependent inhibition (Ramracheya et al., 2008).

Melatonin has also been reported to modulate glucocorticoid secretion. Because of the inverse circadian phase relationship of glucocorticoids between nocturnal rodents and the diurnally active human, such comparisons would not be meaningful, since melatonin is secreted by the pineal gland in all vertebrates at night. In capuchin monkeys (*Cebus capucinus*), melatonin suppressed, via MT_1 receptors, ACTH-induced cortisol secretion and, in the fetal gland, production of 3β-hydroxysteroid dehydrogenase mRNA, indicating a downregulation of glucocorticoid synthesis (Torres-Farfan et al., 2003, 2004). These findings would be compatible with a corresponding circadian rhythm in MT_1 expression in the adrenal glands (Richter et al., 2008). However, the data do not seem to be applicable to humans which lack a

direct coupling between the two hormones (Hajak et al., 1997; Perras et al., 2005). Suppressive effects of melatonin on nocturnal cortisol secretion, as observed in blind individuals, seem to be indirectly mediated by sleep induction (Perras et al., 2005). In one study of human granulosa/luteal cells, melatonin was found to upregulate the LH receptor and to decrease GnRH and GnRH receptor mRNAs. It did not affect basal, but enhanced hCG-stimulated progesterone formation (Woo et al., 2001).

With the exception of the vascular and immune systems, much less is known about melatonin's physiological actions in other peripheral organs. In the human brown adipocyte line PAZ6, long-term exposure to melatonin decreased the expression of the glucose transporter Glut4 and glucose uptake via an MT_2-dependent decrease of cGMP (Brydon et al., 2001). Such findings have recently attracted considerable interest with regard to their potential for combating human obesity (Tan et al., 2010b).

In human myometrial smooth muscle cells, melatonin has been reported to act synergistically with oxytocin in stimulating contractility (Sharkey et al., 2009). Despite the presence of melatonin receptors in the cardiac ventricular wall, the precise function of the methoxyindole is poorly understood. Although effects via cAMP decreases and Ca^{2+} currents had been assumed (Ekmekcioglu, 2006), the direct evidence is largely missing. The relatively moderate expression of MT_2 in the rat AV node (Sallinen et al., 2005), which might indicate heart rate modulation, may not be found in the human. Other effects of melatonin on cardiac functions, including heart rate variability, are presumably related to the effects exerted on the circadian system and not caused by direct actions.

In the vascular system, the effects of melatonin strongly depend on the regional distribution of MT_1 and MT_2. MT_1 leads to a pertussis toxin-sensitive vasoconstriction via opening of BK_{Ca} channels, whereas MT_2 causes vasodilation (Mahle et al., 1997; Doolen et al., 1998; Régrigny et al., 1998; Dubocovich and Markowska, 2005; Hardeland and Poeggeler, 2007). In rats, constriction prevails in the cerebral vessels investigated so far. However, this effect is accompanied by a considerably enhanced dilatory response to hypercapnia (Régrigny et al., 1998). On this basis, melatonin has been shown to attenuate diurnal fluctuations in cerebral blood flow and to diminish the risk of hypoperfusion.

Other effects of melatonin concerning the immune system, growth control, antioxidant, antinitrosant and antinitrative actions, which are potentially relevant to all tissues, will be discussed below in separate sections.

2.1.2. Receptors and other binding sites in the central nervous system and associated tissues

Melatonin receptors in the CNS are accessible to their ligand via several routes. By virtue of its amphiphilicity, melatonin can easily cross the blood-brain barrier and it is especially taken up via the choroid plexus (Mess and Trentini, 1974; Smulders and Wright, 1980; Leston et al., 2010). To what extent physiological levels of the circulating hormone contribute to its brain concentrations is not fully understood, specially as the pineal itself can release the methoxyindole at much higher concentrations directly via the pineal recess to the third ventricle, findings that were mainly obtained in sheep (Tricoire et al., 2002, 2003a,b). Recently, melatonin has been demonstrated in the third ventricle of humans, but the amounts reported of about 8.75 pg/mL are relatively moderate (Leston et al., 2010) and even lower concentrations were found in the lateral ventricles. In a study comparing melatonin levels in mouse serum and cerebral cortex, the cortical concentrations amounted to only ≤ 1% of serum levels (Lahiri et al., 2004). However, concentrations may not appropriately reflect the quantities taken up, if the compound is rapidly metabolized (Hardeland, 2010b). In fact, cortical concentrations of the metabolite 6-sulfatoxymelatonin were reported to be about 3 orders of magnitude higher than those of melatonin (Lahiri et al., 2004). In addition to melatonin taken up from the circulation or via the pineal recess, the methoxyindole is synthesized or, in other areas, assumed to be synthesized in parts of the CNS (reviewed by: Hardeland and Poeggeler, 2007; Hardeland, 2010b). However, considerable uncertainty exists concerning the various (putative) sites of formation and the melatonin levels attained. The frequently demonstrated expression of arylalkylamine *N*-acetyltransferase cannot be taken as a criterion of local synthesis, since the product, *N*-acetylserotonin, is not always metabolized to melatonin and seems to possess actions of its own (Hardeland and Poeggeler, 2007; Hardeland, 2010b). Elevated levels of melatonin, as reported for, e.g., nucleus gracilis, pons, medulla oblongata and cerebellum may not necessarily reflect the site of synthesis. At least for the cerebellum, arylalkylamine *N*-acetyltransferase activity has been demonstrated. Melatonin formation in the brain is considerably supported by the finding that cultured cortical astrocytes from neonatal rats are capable of synthesizing melatonin at rates attaining about one third of those of pinealocytes under same conditions (Y.-J. Liu et al., 2007). Melatonin biosynthesis has been also demonstrated in the prenatal, developing brain,

including stages at which the pineal gland is not yet functional (Jimenez-Jorge et al., 2007), but these findings may not allow conclusions on the adult CNS.

Melatonin receptors are expressed in various parts of the CNS and associated tissues. MT_1 and MT_2 are not restricted to the sites of highest density, such as SCN or PT, but their presence has also been demonstrated in numerous other places. Restricting from consideration those structures specifically related to seasonality and breeding, the receptors have been found in prefrontal cortex, cerebellar cortex, hippocampus, basal ganglia, substantia nigra, ventral tegmental area, nucleus accumbens and, in the retina, horizontal, amacrine and ganglion cells (summarized by: Pandi-Perumal et al., 2008b), as well as in the choroid plexus (Cogé et al., 2009). In the human, MT_1 is found, besides the SCN, in various other parts of the hypothalamus and additional brain areas, such as paraventricular nucleus, periventricular nucleus, supraoptic nucleus, sexually dimorphic nucleus, the diagonal band of Broca, the nucleus basalis of Meynert, infundibular nucleus, ventromedial and dorsomedial nuclei, tuberomammillary nucleus, mammillary bodies and paraventricular thalamic nucleus (Wu et al., 2006b). Other detailed information on the expression of both MT_1 and MT_2 in the human brain are available for the cortex (Brunner et al., 2006), thalamus (Mazzucchelli et al., 1996; Ambriz-Tututi et al., 2009), cerebellar cortex, in which not only neurons, but especially Bergmann glia and other astrocytes express MT_2 (Al Ghoul et al., 1998), substantia nigra and amygdala (Adi et al., 2010) and hippocampus (Savaskan et al., 2002a, 2005). The presence of thalamic melatonin receptors in the human may be also deduced from the stimulation of spindle formation during sleep onset (Dijk et al., 1995; De Gennaro and Ferrara, 2003; Jan et al., 2009). In confirmation to early studies on pineal [^{3}H]-melatonin binding (Vacas and Cardinali, 1980), both MT_1 and MT_2 receptors were demonstrated in the human pineal gland (Brunner et al., 2006), a finding that is consistent with the frequently observed autocrine and paracrine actions melatonin exerts in addition to its role of a hormone (Tan et al., 2003). In the human retina, MT_1 is found in photoreceptor, amacrine and ganglion cells, in processes of the inner plexiform layer and central and some other retinal vessels (Meyer et al., 2002; Savaskan et al., 2002b; Scher et al., 2002, 2003), whereas MT_2 is expressed in ganglion and bipolar cells, the inner segments of photoreceptors and cell processes in the inner and outer plexiform layers (Savaskan et al., 2007). In many mammalian species, the presence of retinal melatonin receptors may, again, include the autocrine/paracrine aspect, since the methoxyindole is also synthesized in the eye (Cardinali and Rosner, 1971a,b; Rosenstein et al., 2010). In humans, the situation is less clear, since substantial rates of retinal melatonin

biosynthesis have been disputed. Despite nocturnal expression of arylalkylamine *N*-acetyltransferase, the enzyme catalyzing the subsequent step, hydroxyindole *O*-methyltransferase is poorly expressed (Bernard et al., 1995). However, recent data have shown HIOMT expression in a cultured human retinal pigment cell line, ARPE-19 cells (Zmijewski et al., 2009).

The presence of melatonin receptors in the hormone-secreting parts of the hypothalamus and in the pituitary are of particular interest. In most species investigated, this has only been studied in the context of seasonality and reproduction, but it may be applicable to disorders such as Seasonal Affective Disorders in the human (Brown et al., 2010). However, parvocellular neurons in the human paraventricular nucleus, which secrete corticotrophin-releasing hormone (CRH), were shown to express MT_1, and this subtype was highly abundant in the PT (Wu et al., 2006b). Although melatonin has also been effective in suppressing the human GnRH pulse generator (Silman, 1991) and although deviations in melatonin can be associated with reproductive disorders (Waldhauser et al., 1991; Walker et al., 1996; Luboshitzky et al., 2004), the presence of MT_1 in the human PT may not be related to the hypothalamic-pituitary-gonadal axis, but could be indicative of a control of other hypophyseal hormones. Melatonin receptors at CRH neurons may be suggestive of effects in the control of the adrenal cortex (cf. Wu et al., 2006b), but this is not supported by other data discussed above (Hajak et al., 1997; Perras et al., 2005).

With regard to the importance of the circadian pacemaker in influencing countless functions in the body, melatonin receptors in the SCN are of the foremost interest. This structure, in which the MT_1 receptor has been demonstrated in humans (Weaver and Reppert, 1996), has long been known as a site of the highest melatonin receptor density. However, the details of the internal receptor distribution in the human SCN have only recently been characterized. MT_1 is particularly expressed in vasopressin neurons (Wu et al., 2006b, 2007), a finding which is centrally relevant inasmuch as vasopressin release represents a major circadian output function of the SCN (Kalsbeek et al., 2006a, 2010; Wu and Swaab, 2007).

MT_2 was not detected in an earlier investigation of the human SCN (Weaver and Reppert, 1996). This receptor subtype is expressed in the SCN of numerous mammals and, where present, is particularly important for circadian phase shifting (C. Liu et al., 1997; von Gall et al., 2002; Dubocovich, 2007; Hardeland, 2009b). Certainty about the definite absence from the human SCN and exclusion of purely technical reasons of detecting the receptor at low levels of expression would be of utmost importance, particularly for reasons of therapy and

melatonergic drug design. If the human SCN lacks MT_2 receptors, phase shifts by melatonin, which have been demonstrated and which are documented in detail by a phase-response curve (Lewy et al., 1992; Burgess et al., 2008) would be induced via MT_1 signaling. Circadian phase shifting by melatonin is possible in other species in which MT_2 has been entirely lost in the course of evolution (Weaver et al., 1996).

The enzyme QR2, previously thought to represent another melatonin receptor, is also expressed in the mammalian brain (Jaiswal, 1994; Long and Jaiswal, 2000; Nosjean et al., 2001). However, in the absence of identified signaling pathways, if they exist at all, described changes can hardly be interpreted at a physiological level.

In addition to the RORα subforms, the nuclear melatonin receptor RZRβ is expressed in various regions of the mammalian CNS, such as SCN and other parts of the hypothalamus, thalamus, pineal gland, retina and spinal cord, and also in the PT (Becker-André et al., 1994; Baler et al., 1996; Greiner et al., 1996; H.T. Park et al., 1996, 1997; Schaeren-Wiemers et al., 1997; André et al., 1998b; Carlberg, 2000; Sumi et al., 2002). Interestingly, RZRβ is most strongly expressed in areas of highest MT_1 receptor density. This seems to indicate that some cooperation exists between the membrane and nuclear receptors, especially in structures involved in circadian rhythm control. In fact, RZRβ knockout mice showed changes in the circadian system, characterized by large advance parts of the phase response curve and extended periods required for complete resynchronization (André et al., 1998a; Masana et al., 2007).

Although membrane and nuclear receptors, as well as other, poorly investigated melatonin binding sites are widely distributed within the CNS, the functional significance of melatonergic signaling is only clear in a few aspects. The most frequently investigated action is that on the circadian system via the SCN. This role has been frequently reviewed (von Gall et al., 2002; Arendt and Skene, 2005; Dubocovich and Markowska, 2005; Challet, 2007; Pandi-Perumal et al., 2008b) and will not be discussed here in every detail. In mammals, phase shifting by melatonin reflects a feedback loop from the pineal gland to the circadian pacemaker, the SCN, i.e., a structure that controls the activity of the pineal via a well characterized neuronal pathway. Melatonin affects, under both *in vivo* and *in vitro* conditions, the phase as well as the amplitude of circadian oscillations. In animals expressing both melatonin receptor subtypes, phase shifting is preferentially exerted via MT_2, whereas neuronal firing is acutely suppressed through MT_1 (C. Liu et al., 1997; Hunt et al., 2001; Dubocovich et al., 2003). In species which do not or only poorly express MT_2, which may

include humans, phase shifting is exerted by MT_1, eventually in a concerted action with RZRβ.

Another specific effect of melatonin on the SCN is related to sleep. MT_1-mediated effects of melatonin in the SCN favor sleep initiation via the hypothalamic sleep switch, a structure characterized by typical on-off responses. This switch is thought to alternately activate either wake-related neuronal downstream pathways or promote the sleep-related ones (Saper et al., 2005; Fuller et al., 2006). Actions via the sleep switch do not seem to represent the exclusive route of melatonin-induced sleep onset. This is not surprising since sleep and also sleep initiation are complex phenomena, in which various brain areas are involved. The thalamus in particular contributes to the soporific effects of melatonin by promoting spindle formation, a characteristic feature of the transition from stage 2 sleep to deeper sleep stages (Dijk et al., 1995; De Gennaro and Ferrara, 2003; Jan et al., 2009). This requires an additional thalamocortical interplay known to occur under these conditions. Moreover, the thalamus and other brain areas feed back to SCN.

In addition to sleep promotion, melatonin exerts numerous other sedating and antiexcitatory effects that clearly go beyond sleep induction since they are also observed in nocturnally active animals (Hardeland and Poeggeler, 2008). This has been frequently studied in relation to anticonvulsant actions (Golombek et al., 1992a,b, 1996; Muñoz-Hoyos et al., 1998; Molina-Carballo et al., 2007; Solmaz et al., 2009), which have been linked to a facilitatory role of melatonin on γ-aminobutyric acid (GABA) transmission (Cardinali et al., 2008b).

The anticonvulsant activity of melatonin may be mediated by the membrane receptors, MT_1 and/or MT_2, since similar effects were observed with the synthetic, MT_1/MT_2-selective melatonergic agonist ramelteon (Fenoglio-Simeone et al., 2009). The antiexcitatory action of melatonin may represent an ancient property of the molecule, since reductions of locomotor activity were even observed in *Caenorhabditis elegans*, an organism devoid of a robust melatonin rhythm (Tanaka et al., 2007). In mammals, the antiexcitatory actions may be also related to additional anxiolytic, antihyperalgesic and antinociceptive effects (Golombek et al., 1991a,b, 1993; Pang et al., 2001; Papp et al., 2006; Ulugol et al., 2006; Hardeland and Poeggeler, 2008; Srinivasan et al., 2010b).

In the retina, melatonin appears to be negatively coupled with dopaminergic activity (Dubocovich, 1985) which is thought to be involved in light adaptation (Ekmekcioglu, 2006). Whether or not a mutual antagonism between melatonin and dopamine exists in man, as observed in non-human vertebrates (Zawilska and Nowak, 1997; Tosini et al., 2006), would

largely depend on the very levels of the methoxyindole in the human retina. An antagonism to the dopaminergic system may, however, exist in the central dopaminergic system (Zisapel and Laudon, 1982; Uz, et al., 2005; Willis, 2008).

2.2. Multiple levels of cellular actions

MT_1 and MT_2 are typical G protein-coupled receptors (GPCRs). The classical signal transduction of both receptors proceeds via pertussis toxin-sensitive G_i proteins, which cause a decrease in cAMP, followed by declines in PKA activity and CREB phosphorylation (Godson and Reppert, 1997; Dubocovich et al., 2003; Jin et al., 2003). In the context of SCN physiology, these G_i-mediated effects also antagonize the stimulation of adenylyl cyclase by PACAP (pituitary adenylyl cyclase activating peptide) and CREB phosphorylation (Jin et al., 2003; von Gall and Weaver, 2008). Interestingly, in one investigation melatonin failed to suppress the PACAP response of pCREB formation in aging mice (von Gall and Weaver, 2008).

The pleiotropy of melatonin at the signal transduction pathways is not sufficiently described by receptor distribution, but should be taken to include the relative abundance and availability of G proteins and other downstream factors (Hardeland, 2009b). The most frequently involved $G\alpha_i$ subforms are α_{i2} and α_{i3} (Brydon et al., 1999; von Gall et al., 2002; Pandi-Perumal et al., 2008b). Although α_i-mediated inhibition of adenylyl cyclase represents a prominent effect, signaling via MT_1 and MT_2 is, in fact, more complex (Godson and Reppert, 1997; Dubocovich et al., 2003; Hardeland, 2009b). This is not surprising, since downregulation of cAMP-dependent processes would hardly explain the numerous activating properties of melatonin, as observed in many tissues or cells.

Parallel or alternate signaling through different G protein subforms and also $\beta\gamma$ heterodimers has been repeatedly observed (summarized by: Hardeland, 2009b). However, signal transduction via different G protein subforms is strongly cell type-specific. It depends on the expression of the numerous variants of α subunits and on the availability of their downstream interaction partners. This leads to a fundamental problem for the interpretation of many cell biology data obtained in transfected, perhaps even multiply transfected cells. Such data can only identify a spectrum of possibilities, but do not identify the physiologically relevant route in a specific cell type *in vivo*. Moreover, overexpression of a receptor enhances the probability

of interactions with other partners including less abundant G proteins (cf. discussion in Hardeland, 2009b).

Parallel signaling via different G protein subunits has been demonstrated for both MT_1 and MT_2. In the mammalian SCN, multiple signaling has been reported for MT_2. Whether similar routes play a role in human SCN during phase shifting via MT_1 remains to be clarified. In the rat SCN, MT_2 activation has not only been shown to cause a decline in cAMP, but also to increase levels of PKC (protein kinase C), which were specifically blocked by the MT_2-selective antagonist 4-phenyl-2-propionamidotetraline (4P-PDOT) (McArthur et al., 1997; Hunt et al., 2001). This PKC activation was required for the phase shift of the circadian rhythm. MT_2-dependent PKC activation has been confirmed in immortalized SCN2.2 cells (Rivera-Bermúdez et al., 2004). PKC activation should be based on the involvement of other G protein subunits rather than decreases in cAMP. Multiple G protein-dependent activation mechanisms are also possible. Parallel signaling via both adenylyl cyclase inhibition and phosphatidylinositol 4,5-*bis*-phosphate cleavage has been demonstrated in transfected CHO cells (MacKenzie et al., 2002). Activation of the phospholipase C (PLC) isoforms PLCβ or PLCη can be conveyed either by α_i coupling to these enzymes, which would maintain the observed sensitivity to pertussis toxin, or alternately, by another α subform, such as α_q, or by βγ (Birnbaumer, 2007; Hardeland, 2009b).

PLC activation has been also demonstrated by increases in IP_3 (inositol-1,4,5-*tris*-phosphate), in insulinoma INS1 cells (Bach et al., 2005; Peschke et al., 2006a). Indirect effects via G protein-dependent opening of ion channels might also increase PKC activity at the membrane, but this possibility would require further substantiation. Coupling to α_q has, in fact, repeatedly been demonstrated (Brydon et al., 1999; Steffens et al., 2003; Bondi et al., 2008; Peschke, 2008). With regard to other α variants, such as α_z, α_o, α_{16}, and α_s subforms (Chan et al., 2002; Lai et al., 2002), which have only occasionally been investigated in transfected cells, the above-mentioned caution concerning transfection artifacts should be considered.

Downstream effects of melatonin-induced PLCβ activation can be highly tissue-specific. In rat uterine myocytes, this led to an opening of Ca^{2+}-activated K^+ channels (BK_{Ca}) (Steffens et al., 2003). Blockade of BK_{Ca} has been reported to inhibit the vasoconstrictor action of melatonin in cerebral and caudal arteries (Geary et al., 1997, 1998) and may reflect the same or a similar signaling mechanism, although this has not been completely confirmed (cf. Hardeland, 2009b). Antinociceptive effects of melatonin were also partially attributed to BK_{Ca} channels, with a contribution of K^+ channel activation by protein kinase G (Hernández-

Pacheco et al., 2008). In the rat hippocampus, melatonin stimulated BK_{Ca} channel opening under conditions of hypoxia (Tjong et al., 2008). In pancreatic β-cells, PLC activation has been shown to promote insulin release, although an α_i-dependent suppression of insulin secretion may prevail (Peschke, 2008). In retinal ganglion cells of the rat, MT_2 signaling stimulated, via the PKC/PLC pathway, glycine currents (Zhao et al., 2010). In the rat SCN, signaling via PLCβ was required for phase shifting the circadian rhythms (Hunt et al., 2001).

Inward rectifier K^+ channels (Kir channels) have been discussed as other downstream targets of melatonin. Activation of Kir3.1 and 3.2 via MT_1 has been shown in the *Xenopus* oocyte system (Nelson et al., 1996) and in transfected AtT20 cells (Nelson et al., 2001). In this case, activation was assumed to be mediated by βγ, since these heterodimers are known to directly couple to Kir channels. This is supported by site-directed mutagenesis in the *MT_1* gene, which allowed a dissection of cAMP downregulation and coupling to Kir3 channels (Nelson et al., 2001). High external K^+, in turn, opens voltage-dependent Ca^{2+} channels, an effect which is inhibited by melatonin in a time-dependent manner (Rosenstein et al., 1991). Modulation of Ca^{2+} channels by melatonin, as observed in the rat pituitary, may be likewise mediated by βγ (Nelson et al., 2001). These findings on MT_1 signaling towards Kir and calcium channels are of high potential importance because they can presumably explain the MT_1-mediated suppressive effects of melatonin on neuronal firing in the SCN, where these channels are expressed.

The pleiotropic effects of melatonin on ion channels are presumably even more complex. In cerebellar granule cells, melatonin stimulated, via MT_2 signaling, potassium currents of delayed outward rectifier K^+ channels (L.Y. Liu et al., 2007). Inhibition of these channels by melatonin, as described for hippocampal CA1 pyramidal neurons (Hou et al., 2004) may not be contradictory, but only represent a pharmacological effect at strongly elevated concentrations, and has not been attributed to MT_1 or MT_2. Divergent results have been obtained concerning the effects of melatonin signaling via cGMP, protein kinase G and the control of CNG channels (Hardeland, 2009b). The experimental analysis can be complicated insofar as melatonin downregulates the inducible and neuronal nitric oxide synthase subforms, iNOS and nNOS (summarized in: Hardeland and Coto-Montes, 2010), and significantly reduced the 24-h rhythmicity in their gene expression (Jiménez-Ortega et al., 2009). However, NO-independent mechanisms seem to exist, too. Inhibition of insulin secretion by melatonin in insulinoma INS1 cells and isolated islets have been shown to be mediated via decreases in cGMP and CNG (Peschke, 2008; Stumpf et al., 2008, 2009).

In the CNS, modulation of ion channels by melatonin is believed to contribute to the various antiexcitatory actions of the methoxyindole. Apart from the findings mentioned, various other mechanisms have been described, such as MT_2-dependent potentiation of light-evoked glycine receptor-mediated inhibitory post-synaptic currents in retinal ganglion cells (Zhang et al., 2007; Zhao et al., 2010), modulation of GABA and glutamate receptors (Rosenstein and Cardinali, 1990; Molina-Carballo et al., 2007), including secondary decreases in cytosolic Ca^{2+} via $GABA_c$ (Prada et al., 2005) or metabotropic glutamate $mGlu_3$ receptors (Prada and Udin, 2005). Finally, downregulation of nNOS (León et al., 2000; Acuña-Castroviejo et al., 2005; Entrena et al., 2005; Hardeland and Poeggeler, 2008; Jiménez-Ortega et al., 2009; Hardeland and Coto-Montes, 2010) as well as astrocytic and microglial iNOS (Jiménez-Ortega et al., 2009; Tapias et al., 2009; Hardeland and Coto-Montes, 2010) prevents or sets limits to neuronal overexcitation. The melatonin metabolite, N^1-acetyl-5-methoxykynuramine (AMK), which is a potent inhibitor of both nNOS (Entrena et al., 2005; León et al., 2006) and iNOS (Tapias et al., 2009), may contribute to these effects.

The numerous primary and secondary signaling mechanisms, including modulation of ion channels and cGMP, lead to a host of further effects, especially as far as Ca^{2+} levels are involved. Activations of PLC and PKC, and also βγ dimers released from G_i, stimulate factors of the MAP kinase pathway (MEK1/2, ERK1/2, c-Jun N-terminal kinase = JNK), phosphatidylinositol 3-kinase (PI3K) and its downstream elements, such as Akt (= PKB) and various transcription factors (summarized in: Hardeland, 2009b). The situation is even further complicated inasmuch as ERK can also be activated via β-arrestin 2 bound to the phosphorylated melatonin receptor (Chan et al., 2002; Bondi et al., 2008), as shown for many GPCRs (Maggio et al., 2005).

Recently it has been shown that GPCR including the MT_1 and MT_2 receptors exist in living cells as dimers. The relative propensity to form the MT_1 homodimer or the MT_1/MT_2 heterodimer formation is similar whereas that of the MT_2 homodimer is 3-4 fold lower (Ayoub et al., 2002; Daulat et al., 2007). A melatonin receptor ortholog, called GPR50, shares 45% of the amino acid sequence with MT_1 and MT_2 but does not bind melatonin (Reppert et al., 1996). It is unusual in that it lacks N-linked glycosylation sites and that it has a C-terminal that is over 300 amino acids long. It is of considerable interest that GPR50, though lacking the ability to bind melatonin, abolishes high affinity binding of the MT_1 receptor through heterodimerization (Levoye et al., 2006 a,b). Thus, GPR50 may have a role in melatonin function by altering binding to the MT_1 receptor (Jockers et al., 2008).

With regard to the possible and cell type-dependent complexity of these signaling pathways and their interconnections, more detailed information is required for relevant tissues *in vivo*, and generalizations should be avoided given the present state of knowledge.

Another potentially important downstream effect of MT_1 activation concerns the expression of RORα, as investigated in human peripheral blood mononuclear cells, in T-lymphocytes and in Jurkat cells. Decreases in MT_1 activity, by prostaglandin E_2, by luzindole or by *MT_1* antisense, have been shown to consistently promote downregulation of RORα expression (Lardone et al., 2009). The positive correlation between the membrane and the nuclear receptor may also indicate that signaling via MT_1 could, perhaps, upregulate RORα.

Should this be the case in other cells outside the immune system, too, many effects primarily initiated by MT_1 might be secondarily transmitted, or reinforced, by RORα subforms or, eventually, RZRβ. This would require sufficiently high melatonin levels, which should, however, be easily attained in melatonin-producing cells such as the lymphocytes. The spectrum of melatonin effects via RORα1, RORα2 and RZRβ has not yet been sufficiently explored. Several uncertainties exist on this point, although promoters of numerous genes contain putative response elements for these receptors. One problem with possible relevance to tissue specificity concerns heterodimerization with other members of the retinoid receptor family, a phenomenon not thoroughly studied with ROR/RZR receptors, but well established for the RXR/RAR subfamily (Schmuth et al., 2007; Lefebvre et al., 2010). Competition of RORs with other members of the superfamily, such as COUP-TF, RAR and Rev-ErbA has been described (Wiesenberg et al., 1998). One of the genes controlled by RORα is hypoxia-inducible factor 1α (HIF-1α), which was upregulated by melatonin and suppressed by RNAi against RORα (Kim et al., 2008). With regard to the ubiquity of RORα and wide distribution of HIF-1α, this may represent a generalized effect of melatonin. RORs have been shown to be required for the downregulation of the prooxidant enzyme 5-lipoxygenase, mainly in leukocytes (Carlberg and Wiesenberg, 1995; Steinhilber et al., 1995). Other possible effects in antioxidative protection may still be regarded as ideas to be experimentally supported in the future. Further actions of melatonin via RORs in leukocytes will be discussed in the immunological section.

3. Circadian regulation – an integrative role

The chronobiological role of melatonin as well as the involvement of its membrane receptors in the SCN are beyond doubt. The SCN controls, directly or indirectly, rhythms of countless functions in presumably all organs of the mammalian body (Kalsbeek et al., 2006b; Hastings et al., 2007; Dibner et al., 2010). In this context, melatonin fulfills a dual role, (i) as a potentially resetting feedback signal to the SCN and (ii) as an SCN-dependent output signal influencing cells in other areas of the CNS and in the periphery as well.

It seems important to be aware that the circadian system does not only consist of the pacemaker, SCN, but also comprises a complex rhythmic network within the CNS (Mendoza and Challet, 2009) and countless peripheral oscillators that rhythmically express clock genes (Stratmann and Schibler, 2006; Kornmann et al., 2007; Cuninkova and Brown, 2008; Vansteensel et al., 2008; Schibler, 2009). Circadian rhythms are primarily generated at the cellular level, but they may be coupled to more stably oscillating multicellular systems. Fundamental consequences arise from the existence of cellular oscillators. Their number in a body is enormous and many of them have to be influenced with regard to their circadian phase and amplitude individually, which is, in the periphery, most easily done on a humoral basis. Outside the SCN, melatonin has been shown to modulate, either positively or negatively, the expression of the following core oscillator genes, to mention only a few examples from mammalian systems: *Per2* and *Bmal1* (= *ARNTL*) in the heart of the rat (Zeman et al., 2009), *Per2*, *Clk* (=*Clock*), *Bmal1* and *Dbp* in a human prostate cancer cell line (Jung-Hynes et al., 2010a), *Cry1* in the ovine pars tuberalis (Johnston et al., 2006), and *Per1*, *Clk*, *Bmal1* and *NPAS2* in the mouse striatum (Imbesi et al., 2009). Other, similar results not discussed here in detail have been obtained in birds and fish. Effects on clock genes in the murine striatum were abolished in MT_1 knockouts (Imbesi et al., 2009). The importance of melatonin for oscillator gene expression in the periphery also became evident by comparisons between melatonin-deficient and -proficient mouse strains. In the adrenal cortex, PER1, CRY2 and BMAL1 protein levels oscillated with substantial amplitudes in melatonin-proficient mice, whereas the deficient animals did not exhibit robust rhythms in these core oscillator proteins (Torres-Farfan et al., 2006). Interestingly, corresponding rhythms were maintained in the adrenal medulla, indicating that the neuronal information was sufficient for keeping the oscillator working in the absence of melatonin. Although direct effects of melatonin on clock gene expression were usually reported to be relatively poor in the SCN, a potentially important finding has been obtained in the SCN of pinealectomized rats, which showed an abnormal phase relationship between the clock genes *Per1* and *Per2* of the two

parallel oscillators. Melatonin administration to the pinealectomized animals almost normalized the phase relationship (Agez et al., 2009).

Taken together, these results show that melatonin plays multiple roles in the complex circadian oscillator system, by influencing the phases of the pacemaker and of peripheral oscillators as well. Additionally, one should assume direct cellular control mechanisms for up- or downregulation of genes (e.g., Jiménez-Ortega et al., 2009), independently of and parallel to the oscillator function. This should reflect the time of maximal melatonin secretion in the night and, therefore, also transmit temporal information.

3.1. Circadian perturbations and their consequences

The circadian system reveals considerable interindividual differences. A frequently observed phenomenon concerns the length of the spontaneous circadian period, which leads to different phase positions relative to the external synchronizing cues, mainly the light/dark cycle and social zeitgebers. The observable morningness or eveningness of individuals usually remains in a normal physiological range but may, in the extreme cases, lead to disorders. This variability has been associated with polymorphisms in oscillator genes. Polymorphisms have been found in various human clock genes, in coding regions, in the promoters or other non-coding regions, and comprise single nucleotide (SNP) and variable-number tandem-repeat (VNTR) polymorphisms. They have been detected in the core oscillator genes *Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Clk*, *Bmal1*, *Bmal2*, *Tim* (timeless), *NPAS2*, casein kinase 1ε (*CNK1ε*) (Johansson et al., 2003; Mansour et al., 2006; Naguib et al., 2006; Ciarleglio et al., 2008; Hawkins et al., 2008; von Schantz, 2008; Zhu et al., 2009; Soria et al., 2010) and several other genes thought to be associated with rhythmic functions, such as those of the basic helix-loop-helix proteins BHLHB2 and BHLHB3 and of the nuclear receptors NR1D1 (= rev-erbA-α) and RORα (Soria et al., 2010). In several cases, alleles were detected that clearly affected the function of the circadian system, especially with regard to morningness/eveningness, which should either reflect changes in the length of the spontaneous period or differences in coupling of the oscillator to synchronizing time cues. Not surprisingly, this became obvious in sleep behavior, representing a parameter strongly influenced by the circadian system. A point mutation in the *Per2* gene caused a rare form of an advanced sleep phase syndrome (Hamet and Tremblay, 2006). Another point mutation, in *Per1*, has been shown to be responsible for extreme morningness (Carpen et al., 2006). A

long *Per3* allele with a VNTR containing 5 instead of 4 repeats has now been frequently studied. It is associated with extreme diurnal preference and occurrence of the delayed sleep phase syndrome (DSPS) (Ebisawa et al., 2001; Archer et al., 2003; Pereira et al., 2005; Groeger et al., 2008; Viola et al., 2008; Ellis et al., 2009; Dijk and Archer, 2010). Recently, two point mutations in the *Per3* promoter were also found to correlate with DSPS (Archer et al., 2010). Moreover, other pathological relationships were found, some of which may not be associated at first glance with circadian rhythmicity, but which obviously do have a physiological or cell biological connection to clock genes and, presumably, to rhythmicity, too.

Polymorphisms in the *Clk, Bmal1, Per3* and *Tim* genes indicated a higher susceptibility to mood disorders (Mendlewicz, 2009). Mutations in the *Cry1* and *NPAS2* genes were reported to correlate with major depressive disorder, whereas a *Clk* allele was associated with bipolar disorder (BP) (Soria et al., 2010). The long variant of the *Per3*-VNTR has been reported to favor an earlier onset of BP (Benedetti et al., 2008). It should be noted that the associations between clock gene polymorphisms and features of mood disorders are often described in rather small samples and replication in larger samples would be reassuring.

Finally, mutations in various oscillator genes were found to enhance the risk of prostate cancer (Chu et al., 2008; Zhu et al., 2009). These results may be regarded as a new facet of an emerging field, in which tumor suppressor functions of clock genes, in particular, *Per1* and *Per2*, are uncovered (Yang et al., 2009a,b) and in which circadian disruption, by mutation, inadequate signaling or frequently repeated phase shifts, reveals an increased cancer risk (Fu et al., 2002; Hardeland et al., 2003a; S. Lee et al., 2010). Meanwhile, numerous studies have shown that core oscillator proteins, such as PER1, PER2, PER3, CRY1, CRY2, CLK, BMAL1 and CNK1ε, are downregulated in various forms of cancer, e.g., by hypermethylation in their promoters, and are involved in chromatin remodeling, sensing of DNA damage, and/or actions as tumor suppressors (summarized in: Hardeland and Coto-Montes, 2010).

Circadian perturbations can have a variety of causes. These may be the result of gene polymorphisms, as in DSPS or familial advanced sleep phase syndrome, or due to poor synchronization because of blindness or other deficiencies in the light transmission pathways, or the result of external factors such as shift work or jetlag. In all of these cases, the chronobiotic and sleep-promoting properties of melatonin as well as synthetic melatonergic agonists, such as ramelteon, agomelatine or tasimelteon, can be helpful in treating these disorders (Cardinali et al., 2006; Arendt, 2006, 2010; Lockley et al., 2007; Skene and Arendt,

2007; Pandi-Perumal et al., 2007, 2008a; Srinivasan et al., 2008, 2010c; Brown et al., 2009; Hardeland, 2009d). The same should be assumed for all those mood disorders which are caused by circadian malfunction or poor synchronization with the environment.

A different situation exists in Smith-Magenis syndrome, a congenital disorder characterized, apart from developmental and neurobehavioral abnormalities, by an almost inverted melatonin rhythm and sleep difficulties (Potocki et al., 2000; De Leersnyder, 2006; De Leersnyder et al., 2006). Some success has been achieved by a combination of a β_1-adrenergic blocker in the morning, to suppress diurnal melatonin secretion, and melatonin in the evening (Carpizo et al., 2006; De Leersnyder, 2006; De Leersnyder et al., 2006).

3.2. Decreases in melatonin levels under physiological and pathophysiological conditions

It is now well established that nocturnal lighting acutely suppresses melatonin formation and secretion by the pineal gland, an effect that can be distinguished from the perturbation of the circadian system (Reiter and Richardson, 1992). This phenomenon has been studied in humans, with regard to light intensity and duration, as well as spectral sensitivity (Bojkowski et al., 1987; Strassman et al., 1987: McIntyre et al., 1989; Petterborg et al., 1991; M.A. Paul et al., 2009).

The particularly strong effect of blue light is now understood in terms of the spectral sensitivity of melanopsin-containing retinal ganglion cells, which transmit, in parallel with green-absorbing cones, the photic information to the SCN (Berson et al., 2002; Gooley et al., 2010; Lall et al., 2010) and from there to the pineal gland. The acute suppression of melatonin is especially relevant to shift-workers. In these individuals, the nocturnal light not only perturbs the circadian system, but additionally causes a transient melatonin deficiency, which is not compensated during later sleep phases for reasons of temporal position of the circadian clock. The lack of melatonin also implies gradual losses in antioxidant protection, immunological and antiinflammatory effects exerted by the hormone, which will be discussed in following sections.

Decreases in nocturnal melatonin are regularly observed during aging, although considerable interindividual differences exist in this regard (Brown et al., 1979; Reiter and Richardson, 1992; Kunz et al., 1999; Karasek and Reiter, 2002; Srinivasan et al., 2005). Two causes can contribute to this phenomenon: These are either due to normal age-dependent deterioration of the circadian pacemaker or neuronal transmission to the pineal, similar to that observed in

neurodegenerative disorders (Skene and Swaab, 2003; Srinivasan et al., 2005; Wu et al., 2006a; Wu and Swaab, 2007) or they are due to pineal calcification (Kunz et al., 1999).

Decreased levels of melatonin have been repeatedly described in neurodegenerative disorders, which can exceed that which is associated with normal aging (Skene et al., 1990; Uchida et al., 1996; R.Y. Liu et al., 1999; Mishima et al., 1999; Ohashi et al., 1999; Ferrari et al., 2000). In many affected individuals, nocturnal melatonin secretion is strongly suppressed and the melatonin rhythm practically abolished.

Dysfunction of the SCN can be assumed in cases involving hypothalamic hamartoma and, in fact, decreased melatonin secretion and, in juvenile subjects, precocious puberty have been observed (Commentz and Helmke, 1995). Reduced melatonin levels associated with rhythm abnormalities and sleep disturbances have been observed in craniopharyngioma patients (Müller et al., 2002, 2006), which persist in survivors (Lipton et al., 2009), a phenomenon which may be similarly attributed to damage to the SCN.

While the hypothesis that melatonin deficiency is due to neurodegeneration or tissue destruction appears to have some plausibility, decreases in melatonin have also been observed under various other, less severe conditions as well. This has been found in a number of schizophrenics, though not consistently in all individuals (Monteleone et al., 1992; Viganò et al., 2001), in multiple sclerosis patients with major depression (Akpinar et al., 2008) [whereas major depression alone has been frequently associated with phase shifts rather than declines in total melatonin (Crasson et al., 2004; Pandi-Perumal et al., 2009; Monteleone et al., 2010)], in primary obsessive-compulsive disorder (Catapano et al., 1992) and also in Menière's disease (Aoki et al., 2006). The changes in this last disease were also discussed in relation to stress evoked by tinnitus and vertigo in those patients. It seems that stressful conditions generally have the potential for depressing melatonin. Low levels of melatonin were also observed in women with fibromyalgia (Rohr and Herold, 2002; Acuña-Castroviejo et al., 2006; Reiter et al., 2007) and pain has been reported to be reduced by replacement therapy (Citera et al., 2000; Reiter et al., 2007; Sánchez-Barceló et al., 2010). Decreased melatonin has also been reported in patients with migraine (Claustrat et al., 1989, 1997). Although additional causes may contribute, the very low melatonin levels in critically ill patients (Perras et al., 2006, 2007; Srinivasan et al., 2010a) may be in accordance with the assumption of a stress-related suppression. This may also be the case in patients with advanced cancer, as reported for non-small cell lung cancer (Hu et al., 2009), although cancer *per se* may affect

melatonin levels and secretion patterns, as in the case of endometrial cancer (Grin and Grünberger, 1998).

Severe decreases in melatonin levels can be also associated with metabolic diseases. This has been, e.g., observed in acute intermittent porphyria (Puy et al., 1993), especially when accompanied with seizures (Bylesjö et al., 2000). Corresponding results were obtained in an experimental model of acute porphyria in the rat (Puy et al., 1996). In this disease, an additional cause for the decline of melatonin may contribute or be even decisive. The toxic metabolite, 5-aminolevulinic acid, is a free radical-generating compound which leads to oxidative stress (Hardeland, 2005). It has been observed that high levels of oxidants can promote increases in the consumption of melatonin, even in organisms producing melatonin in concentrations by orders of magnitude higher than in vertebrates (Hardeland et al., 2003a), and thus it may indicate that melatonin can be destroyed by free radicals generated at high rates. In one study in nephrectomized rats, which were used as a model of chronic renal insufficiency, pineal and circulating melatonin levels were markedly reduced, an effect that was reversed by erythropoietin (Vaziri et al., 1996). Although substantial decreases unrelated to hemodialysis were also observed in patients with chronic renal insufficiency, the relevance to humans remains to be further clarified.

Another area of interest concerns the effects of diabetes on circulating melatonin levels, mostly studied in type 2 diabetes. Data consistently show reductions of circulating melatonin in diabetic patients (O'Brien et al., 1986; Peschke et al., 2007). Corresponding results were obtained in plasma or pineal melatonin of experimental animals, such as diabetic Goto Kakizaki rats (Peschke et al., 2006b; Frese et al., 2009) and induced obesity in rats (Cano et al., 2008) . These findings are highly important, not only with regard to prevention and treatment of diabetes 2, a frequent and economically important disease, but extend to other related problems in which melatonin seems to be helpful and in which dysfunctions of melatonin levels or signaling may contribute to the etiology. Among these are problems such as general resistance to insulin, metabolic syndromes, and obesity (Hardeland, 2010a; Ríos-Lugo et al., 2010). This topic has been addressed in relation to melatonin, melatonin receptor signaling, polymorphism and dysfunction (Staiger et al., 2008; Bouatia-Naji et al., 2009; Shieh et al., 2009; Sparsø et al., 2009; Contreras-Alcantara et al., 2010; C. Liu et al., 2010; Müssig et al., 2010) as well as to novel synthetic melatonergic agonists (She et al., 2009).

3.3. Impact of melatonin deficiency

With regard to the orchestrating role of the pineal hormone, a plethora of effects can be expected to result from melatonin deficiency. To a considerable extent, these should be mediated by the circadian oscillator system. The changes observed in core oscillator protein expression, phasing and rhythm amplitude, as outlined in the beginning of section 3, are in full agreement with this conclusion. A complication may arise from the uncoupling of the parallel oscillators using either PER1 or PER2, as demonstrated in the SCN of pinealectomized rats (Agez et al., 2009). The consequences are still unclear, although one might assume an impaired coordination of slave oscillators. The relevance of melatonin has also been shown in another autonomous circadian oscillator of the CNS, the murine retina. In a melatonin-deficient mouse strain (C57BL), no significant rhythmicity of PER1, CRY2 and pCREB was demonstrable, in contrast to the prominent oscillations seen in a melatonin-proficient strain (C3H) (Dinet et al., 2007; Dinet and Korf, 2007).

A direct consequence of impaired melatonin secretion has to be expected in the regulation of sleep. In fact, elderly insomniacs exhibited strongly decreased levels and rhythm amplitudes of the excretion product, 6-sulfatoxymelatonin, compared to individuals of same age without sleeping difficulties (Haimov et al., 1994). The association of sleep difficulties with low levels of melatonin, often in conjunction with abnormal phasing of the residual secretion pattern, has been repeatedly observed (Haimov and Lavie, 1995; Zisapel, 1999; Haimov, 2001; Rohr and Herold, 2002; Lipton et al., 2009) and is not restricted to elderly individuals. Almost complete suppression of melatonin secretion after surgery in pediatric survivors of craniopharyngioma caused inappropriate daytime sleep and nocturnal awakenings, although the circadian rhythm of sleep/wakefulness was clearly discernible in the actograms (Lipton et al., 2009). The occurrence of daytime somnolence demonstrates that a mere correlation of nocturnal melatonin concentration and duration of sleep would insufficiently describe the soporific actions of the methoxyindole. Sleep is controlled by many factors and the homeostatic drive to sleep may sometimes prevail over the circadian phase. Somnolence occurring because of melatonin deficiency after pinealectomy (Lehmann et al., 1996) may be interpreted in terms of an obviously disturbed circadian system, which was corrected by administration of the methoxyindole. However, a lengthening of nighttime total sleep duration has also been observed after pinealectomy in another case, mainly as a consequence of increased REM sleep duration (Kocher et al., 2006).

The chronobiological role of the pineal hormone was also evident in a study of a child with congenital melatonin deficiency, who exhibited a non-24 hour sleep-wake rhythm. These

disruptions were corrected by treatment with melatonin (Akaboshi et al., 2000). An entirely different case of melatonin deficiency was recently reported (Leu-Semenescu et al., 2010). Because of a primary defect in the sepiapterin reductase gene, serotonin synthesis was impaired in this patient, so that the lack of the precursor prevented the formation of substantial amounts of melatonin. Although serotonin has its own role in sleep regulation, the symptoms of hypersomnia, consisting of a ca. 12-hour sleep-wake rhythm and hyperphagia, were normalized by melatonin treatment and could, therefore, be attributed to the deficiency of the pineal hormone (Leu-Semenescu et al., 2010).

Countless publications have dealt with experimental melatonin deficiency by pinealectomy in animals. A complete consideration of all these results would exceed by far the scope of this review. Apart from the many data concerning reproduction and seasonal rhythms, which will not be discussed here, pinealectomy has been also carried out in experiments designed to address issues relevant to clinical medicine. In one study using aging pinealectomized rats, oxidative damage to membrane lipids, protein and DNA was enhanced in various organs, compared to controls of the same age (Reiter et al., 1999), data completely consistent with the amply documented antioxidant properties of melatonin. Another study reported an increase of homocysteine because of pinealectomy, which might indicate a higher risk of cardiovascular disease, results that were in line with the homocysteine-reducing action of melatonin (Baydas et al., 2002). In models of neurodegeneration, based on focal brain ischemia or glutamate toxicity, the damaged areas were larger in pinealectomized rats than in control animals (Manev et al., 1996).

The risk of developing certain types of cancer is another area in which melatonin deficiency has been discussed. This assumption may have to be distinguished from the oncostatic actions of melatonin observed in various models and concerning growth or apoptosis of malignant cells (cf. Blask et al., 2002a,b). It appears rather to represent a physiological chemopreventive action of the pineal hormone and may involve the tumor suppressor actions of some core oscillator genes, as discussed in a previous section. In various studies, melatonin deficiency has been attributed to a higher incidence of prostate (Rohr and Herold, 2002), endometrial (Chubb, 1999; Viswanathan et al., 2007) and breast (Rohr and Herold, 2002; Schernhammer et al., 2010) cancers. The precise mechanisms of cancer prevention remain to be elucidated (Stevens, 2009).

3.4. Effects of melatonin receptor deficiency or dysfunction

A failure of melatonin signaling may not only be caused by low or defective melatonin secretion, but can also result from dysfunctional or downregulated signaling mechanisms. Experimentally this can be investigated, e.g., by targeted deletion of receptor genes. This has not only been done in the initial studies on the discrimination of MT_1 and MT_2 (C. Liu et al., 1997; Jin et al., 2003). In the murine retina, knockouts of either *MT_1* or *MT_1* and *MT_2* have been shown to produce considerable phase shifts in the circadian rhythm of PER1, without abolition of the rhythm itself (Dinet and Korf, 2007). Although this finding somehow contrasts with the absence of robust PER1 rhythmicity in a melatonin-deficient mouse strain, it may be taken as further proof of the important role of melatonin signaling in the phase control of autonomous oscillators.

In cultures of murine striatal neurons, *MT_1* knockout abolished melatonin-induced changes in the expression of various core oscillator genes (Imbesi et al., 2009). In cultured mouse cerebellar granule cells treated with nanomolar concentrations of melatonin, the deletions of either *MT_1* or *MT_2* caused losses in the inhibition of forskolin-stimulated cAMP synthesis and cFos expression, in the inhibition of Akt (= PKB) activation, and were reported to turn the normally observed suppression of the MAP kinase ERK into an upregulation (Imbesi et al., 2008b). In the future, it will be necessary to explain why the knockout of a single receptor was sufficient for these effects, so that the receptors did not compensate for each other, as discussed in section 2.1.2. Moreover, a convincing explanation will be required for the change from ERK downregulation to upregulation. Further, the question may arise as to whether binding sites different from the membrane receptors might have been responsible for the melatonin-dependent stimulation.

In another study, *MT_2* knockout mice were reported to be impaired in hippocampal long-term potentiation (Larson et al., 2006), a finding not only of interest in terms of neuronal plasticity, but also for learning. *MT_1* knockout mice exhibited gradual sensorimotor deficits and increased times of immobility in forced swim tests (Weil et al., 2006). Whether the last finding has to be taken as an indication of depressed-like behavior might be debated.

Melatonin receptor deficiency or malfunction was related to various diseases. The human *MT_2* polymorphisms associated with increased risk for developing diabetes type 2 (Staiger et al., 2008; Bouatia-Naji et al., 2009; Lyssenko et al., 2009; Shieh et al., 2009; Sparsø et al., 2009; C. Liu et al., 2010) may be interpreted in this context. These data are in accordance with changes in insulin secretion observed in *MT_2* variants (Müssig et al., 2010) and melatonin effects on the PKCζ/Akt/GSK3β signaling pathway (Shieh et al., 2009). The finding that the

MT_1 knockout causes insulin resistance in mice (Contreras-Alcantara et al., 2010) seems to support the general idea of intact melatonin signaling required for avoiding diabetes type 2, but may be also indicative species differences between mice and humans.

Various older publications have dealt with the role of melatonin in adolescent idiopathic scoliosis. Although this was originally attributed to melatonin deficiency, which was not always demonstrable in the respective patients, this disease now seems rather to be caused by defective melatonin signal transduction in osteoblasts (Moreau et al., 2004; Azeddine et al., 2007). The induction of experimental scoliosis in melatonin-deficient mice (Machida et al., 2006) does not represent a contradiction, since absence of the methoxyindole and impairment of signaling can lead to the same consequences.

Melatonin deficiency had also been assumed to be a cause of neurofibromatosis type 1 (NF1 = von Recklinghausen disease) (Namazi, 2007), but, with regard to the rareness of melatonin deficiency in younger individuals and to the identified defect in the neurofibromin gene, the disease may possibly be attributable to impairments in melatonergic signaling. Neurofibromin deficiency is known for deregulation of the Ras/Raf/MAP kinase, the Ras/PI3K/Akt, and the cAMP pathways (Larizza et al., 2009). The cAMP route, which is impaired in NF1, should not be relevant with regard to melatonin, which typically decreases the second messenger via G_i, but other pathways are also influenced, in certain cell types, by melatonin (Hardeland, 2009b). The cancer predisposition in NF1 (Larizza et al., 2009) may represent an additional example of interference with melatonin activity.

More specific data are available on losses of melatonin receptors in neurodegenerative disorders. In patients with Parkinson's disease, the expression of MT_1 and MT_2 declines in the substantia nigra and amygdala (Adi et al., 2010). Especially in Alzheimer's disease, decreases in histological densities of both MT_1 and MT_2 were detected in the cortex and pineal gland (Brunner et al., 2006), of MT_2 in the hippocampus (Savaskan et al., 2005) and retina (Savaskan et al., 2007), of MT_1 in the cerebrovascular system (Savaskan et al., 2001) and, most importantly, in the SCN (Wu and Swaab, 2007; Wu et al., 2007). Although these changes are consequences of neurodegeneration and become more severe with disease progression, the impaired functioning of melatonergic signaling may be a cause of further central nervous deterioration, including declines in memory and a breakdown of the circadian oscillator system. With the ongoing loss of melatonergic receptors, the chances of alleviating symptoms such as sundowning and disturbed sleep by melatonin treatment, which is

moderately possible in earlier stages (Furio et al., 2007; Riemersma-van der Lek et al., 2008; Cardinali et al., 2010) seem to vanish in late Alzheimer patients.

4. Immune modulation

The role of melatonin in the immune systems has been reviewed several times (c.f. Guerrero and Reiter, 2002; Carrillo-Vico et al., 2005a; Markus et al., 2007; Szczepanik, 2007; Cardinali et al., 2008a). The intention of this section is not to summarize in detail all of the knowledge in this field, but rather to highlight several facts which are of importance from a systemic point of view and to focus on some aspects of relevance to the following sections on cell protection, mitochondrial function and aging.

Melatonin is formed by various leukocytes, including monocytes, eosinophils, mast cells, T-lymphocytes, NK cells, bone marrow cells and several leukocyte-derived cell lines (Conti et al., 2000; Guerrero and Reiter, 2002; Carrillo-Vico et al., 2004, 2005b; Lardone et al., 2006). Melatonin biosynthesis has been also described in thymocytes (Naranjo et al., 2007; Sanchez-Hidalgo et al., 2009) and epithelial cells (Jiménez-Jorge et al., 2005). The simultaneous biosynthesis of melatonin and expression of MT_1 receptors in many of these cells (Konakchieva et al., 1995; García-Pergañeda et al., 1997; Carrillo-Vico et al., 2003b; Pozo et al., 2004; Lardone et al., 2009; Maldonado et al., 2010) not only indicates that the methoxyindole has a role in communication within the immune system, but also possesses autocrine, paracrine and, perhaps, intracrine functions. This is generally not uncommon with hormones, but, in this case it demonstrates that melatonin's actions in the immune system do not solely depend on the pineal gland. With regard to the numerous other extrapineal sources of melatonin, this conclusion may also be valid for other organs and, thus, be of more general relevance (cf. Tan et al., 2003). The partial independence of melatonin produced in the immune system is underlined by a recent report showing that the methoxyindole is synthesized in immune cells of otherwise melatonin-deficient mouse strains (Gómez-Corvera et al., 2009). This may be also taken as an indication that leukocytic melatonin accounts for only a small amount of the circulating hormone and, thus, for a primarily local action.

The simultaneous expression of membrane receptors and, sometimes all three (Pozo et al., 2004) RORα subforms in various leukocytes (García-Mauriño et al., 1997, 1998; Carlberg, 2000; Guerrero et al., 2000b; Pozo et al., 2004) seems to be of particular relevance for local actions, which might include a focal or intracellular accumulation of melatonin. The reported

positive correlation between MT_1 signaling and RORα expression (Lardone et al., 2009) indicates a concerted action of these two types of receptors. One intriguing question in this regard relates to the extent to which other immunological effects ascribed to the nuclear receptors may indirectly depend on functional membrane receptors.

It has been concluded that RORα stimulates the secretion of IL-2, IL-6 and IFNγ by T-helper cells type 1 and by monocytes (García-Mauriño et al., 1997, 1998; Guerrero et al., 2000a,b). Moreover, the nuclear receptors were implicated in the downregulation of 5-lipoxygenase (Carlberg and Wiesenberg, 1995; Steinhilber et al., 1995), a finding usually cited in the context of melatonin's antioxidant actions. However, melatonin does not generally function as an antioxidant in the complex network of the immune system. It has also been shown to stimulate the formation of reactive oxygen species (ROS) by monocytes (Morrey et al., 1994) and in the promonocytic cell line U937 (Cristofanon et al., 2009; Radogna et al., 2009a). Moreover, 5-lipoxygenase was obviously not markedly downregulated in U937, but rather promoted ROS formation under the influence of melatonin (Radogna et al., 2009b).

Melatonin augments $CD4^+$ lymphocytes and decreases $CD8^+$ lymphocytes in lymph nodes (Castrillón et al., 2001). The functional spectrum of immunomodulation by melatonin is highly complex and involves various cytokines. The main findings on this point comprise stimulation of IL-2, Il-6 and IFNγ formation in T-helper cells and monocytes (García-Mauriño et al., 1997, 1998; Carrillo-Vico et al., 2005b; Lardone et al., 2006), counteraction of the inhibitory effect of prostaglandin E_2 (PGE_2) on IL-2 production (Carrillo-Vico et al., 2003a), secretion of IL-1, IL-12, TNFα and M-CSF (macrophage-colony stimulating factor) in monocytes and/or monocyte-derived cells (Barjavel et al., 1998; García-Mauriño et al., 1999). These effects are not only related to cytotoxicity, prooxidant and pro-inflammatory actions, but also to differentiation and interactions of T-lymphocytes with antigen-presenting cells (= AP cells). Melatonin promotes the expression of MHC class II molecules and TGFβ in AP cells and influences, via IL-12, T-cell differentiation and growth in favor of T_h1 (García-Mauriño et al., 1999). In addition to stimulation via T-cell receptor and CD28, melatonin is thought to represent a third signal for T-cell activation and expansion (Raghavendra et al., 2001b; Černyšiov et al., 2010). In addition to T_h1 activation, melatonin has also been reported to promote T_h2 responses (Shaji et al., 1998; Raghavendra et al., 2001a; Černyšiov et al., 2010), findings that may require further substantiation and mechanistic explanation, since, under other conditions, such as trypanosome infection, melatonin was found to decrease T_h2 responses (Santello et al., 2008). Splenocytes were

shown to respond to the methoxyindole by releasing IL-1β, M-CSF, TNFα, IFNγ and stem cell factor (F. Liu et al., 2001). In thymocytes, melatonin promotes the formation of thymosin-α_1 and thymulin, which corresponds to a nocturnal increase in prothymosin-α expression (Molinero et al., 2000).

The pro- and antiinflammatory actions of melatonin deserve particular attention. At first glance, these effects appear to be contradictory. However, these actions have to be interpreted in the context of different conditions. As far as it enhances the immune response via AP cells and T-lymphocytes, as well as the activation of monocytes and other ROS-generating cells by the methoxyindole alone, melatonin behaves in a prooxidant way (Morrey et al., 1994; Carrillo-Vico et al., 2005c; Cristofanon et al., 2009; Radogna et al., 2009a,b). In the context of autoimmune diseases, this property is highly undesirable (Calvo et al., 2002; Cutolo et al., 2005; Maestroni et al., 2005; Forrest et al., 2007). Under other conditions, however, melatonin can reduce oxidative damage, which has been repeatedly shown in numerous experiments using bacterial lipopolysaccharide (LPS) (e.g., Sewerynek et al., 1995a,b; Maestroni, 1996; Crespo et al., 1999; Baykal et al., 2000; Wu et al., 2001; Escames et al., 2003; Requintina and Oxenkrug, 2003; d'Emmanuele, et al., 2004; H. Wang et al., 2004; Yerer et al., 2004; Carrillo-Vico et al., 2005c; Xing et al., 2005; Y.H. Chen et al., 2006). In particular, the proinflammatory cytokine TNFα is downregulated in the endotoxemia model (Fjaerli et al., 1999; Baykal et al., 2000; Silva et al., 2004; H. Wang et al., 2004; Perianayagam et al., 2005; Shang et al., 2009). Moreover, melatonin inhibits the LPS-induced expression of various CC chemokines in peripheral blood mononuclear cells (H.J. Park et al., 2007). The presence of melatonin as well as MT_1 and MT_2 in a mast cell line was recently taken as evidence implicating the methoxyindole´s modulatory effects in these cells, too (Maldonado et al., 2010), which might consist in an antiinflammatory action via inhibition of TNFα release. Other antiinflammatory actions of melatonin, in addition to downregulation of 5-lipoxygenase (Steinhilber et al., 1995) concern the antagonism to PGE_2 (Carrillo-Vico et al., 2003a) and the inhibitory effects on PG synthesis (Cardinali et al., 1980; Cardinali and Ritta, 1983). Melatonin as well as its metabolites N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N^1-acetyl-5-methoxykynuramine (AMK) were shown to downregulate cyclooxygenase expression in macrophages (Mayo et al., 2005b; Deng et al., 2006). Unfortunately, these studies were only undertaken at highly elevated concentrations. AMK has also been reported to be a cyclooxygenase inhibitor much more potent than acetylsalicylic

acid (Kelly et al., 1984). Perhaps, these effects are only relevant under pharmacological conditions.

One of the strongest antiiflammatory effects of melatonin concerns the downregulation and inhibition of inducible and neuronal NO synthases (iNOS and nNOS), actions which will be discussed in detail in section 6.2. Here, only two important facts will be mentioned: (i) Melatonin does not substantially interfere with basal or moderately elevated NO levels (Hardeland et al., 2003a). (ii) Melatonin and also AMK are highly effective in protecting from NO-mediated mitochondrial blockades and cell damage under severe inflammatory conditions such as sepsis (Escames et al., 2006a,c; L.C. López et al., 2006b; Hardeland, 2009a; Srinivasan et al., 2010a).

5. Cell protection

Cytoprotective properties have become an important field of melatonin research. Relevant actions have been studied in various organs, which were compromised by treatments such as exposure to oxidotoxins, ischemia/reperfusion, trauma, ionizing radiation, proapoptotic and proinflammatory signals (Bubenik et al., 1998; Karbownik and Reiter, 2000; Reiter et al., 2002c; Hardeland et al., 2003a; Jaworek et al., 2005; Tengattini et al., 2008). An area of particular interest and relevance concerns the neuroprotective actions (Reiter, 1998; Reiter et al., 2001; Srinivasan et al., 2005; Kaur and Ling, 2008; Korkmaz et al., 2009; X. Wang, 2009), which exceed the experimental challenges mentioned and include counteractions against neurodegenerative disorders, processes of normal aging and interventions to promote mitochondrial biogenesis and, where possible, neurogenesis (Hardeland, 2009c; Hardeland et al., 2009a; Hardeland and Coto-Montes, 2010).

5.1. Antioxidative protection – more than radical scavenging

After the first indications for interactions of melatonin with free radicals, as observed in photocatalytic and other radical-generating systems (Hardeland et al., 1991, 1993a,b), it was especially the discovery that this methoxyindole is a remarkably potent scavenger of the particularly reactive, destructive, mutagenic and carcinogenic hydroxyl radical (Tan et al., 1993), which initiated numerous studies on protection against free radicals. Melatonin was shown to be much more specific than its structural analogs in undergoing reactions which lead to the termination of the radical reaction chain and in avoiding prooxidant, C- or O-centered

intermediates (Hardeland et al., 1993c; Tan et al., 1993; Poeggeler et al., 2002). Moreover, melatonin scavenged numerous different free radical species and other oxidants, among which the carbonate radical (Hardeland et al., 2003b) will be especially mentioned because of its presumed role in mitochondrial damage (Hardeland, 2009a; Hardeland et al., 2009a; Hardeland and Coto-Montes, 2010).

Although direct radical scavenging has been effective under numerous experimental conditions, at clearly supraphysiological concentrations, its relevance at physiological levels has been questioned already for reasons of stoichiometry. However, this reservation is not generally valid, especially not for organisms producing by orders of magnitude higher levels of melatonin than vertebrates, such as various plants and dinoflagellates (Antolín et al., 1997; Hardeland et al., 2007b). Even though a single melatonin molecule may generate products in a scavenger cascade which may collectively eliminate up to ten free radicals (Rosen et al., 2006), such findings from chemical systems may not be fully applicable to physiological conditions. From a stoichiometric point of view, it may only contribute to antioxidative protection in some melatonin-producing vertebrate organs, such as the rodent Harderian gland, but, in most mammalian organs, the levels do presumably not suffice for a substantial contribution to radical detoxification.

Despite this conclusion, melatonin was shown to protect from oxidotoxicity already at physiological concentrations (Tan et al., 1994). Thereafter, various studies demonstrated the upregulation of several antioxidant enzymes by melatonin, such as glutathione peroxidase, glutathione reductase, γ-glutamylcysteine synthase, glucose-6-phosphate dehydrogenase, hemoperoxidase/catalase, Cu,Zn- and Mn-superoxide dismutases (reviewed in: Reiter et al., 2003; Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2008). However, the relevance of these findings may be easily overestimated, perhaps, with the exception of glutathione peroxidase, which has repeatedly, and widely consistently, been shown to be increased by melatonin (cf. Hardeland, 2005) and which has gained new relevance in the context of mitochondrial function (Wakatsuki et al., 2001; Reiter et al., 2002b; Acuña-Castroviejo et al., 2007; Rodríguez et al., 2007a,c; Hardeland and Coto-Montes, 2010). Glutathione reductase may mainly respond to changes in the redox equilibrium. The other enzymes, especially catalase and the superoxide dismutases, exhibited highly variable responses depending on sources and conditions. Sometimes, the increases were only in the lower percent range, often only demonstrated at the mRNA level (Jiménez-Ortega et al., 2009), and, in several cases, no effects (Okatani et al., 2001; Wakatsuki et al., 2001; Dzięgiel et al., 2003; Balkan et al., 2004;

Ohta et al., 2004; Mauriz et al., 2007) or even decreases (Gürdöl et al., 2001) were observed. Even glutathione peroxidase, which was mostly upregulated, was not stimulated, e.g., at protein level in the liver of young – but in aged – rats (Mauriz et al., 2007) or, in the murine cerebral cortex, at the mRNA level (Olcese et al., 2009). Notably, protection by melatonin was achieved in all these studies in which antioxidant enzymes were not or poorly upregulated. Therefore, explanations different from radical scavenging and enzyme induction have to be sought for the protective potential of melatonin, especially at physiological or low pharmacological concentrations.

5.2. The concept of radical avoidance

An alternate concept intends to explain the protective effects at the level of radical generation rather than detoxification of radicals already formed (Hardeland et al., 2003a, 2009a; Hardeland, 2005, 2009c). If melatonin is capable of decreasing the processes leading to enhanced radical formation, this might be achieved by low concentrations of the methoxyindole. Therefore, the main sources of free radicals should be investigated with regard to their modulation by melatonin. Apart from oxidants released by leukocytes, the isoforms of NAD(P)H oxidases (Nox) and mitochondria should be mentioned as main sources. Moreover, reactive nitrogen species (RNS) can secondarily give rise to the formation of ROS, both in and outside mitochondria, so that levels of oxidants can be considerably decreased by limitation of NO formation. Nox isoenzymes contribute to superoxide formation in a quantitatively substantial manner (L. Park et al., 2007; Chéret et al., 2008; Collins-Underwood et al., 2008; McCann et al., 2008; H. Chen et al., 2009; Schiavone et al., 2009). These often membrane-bound enzymes respond to various signals, but their metabolic regulation is not fully understood. Inductions of Nox isoforms have been repeatedly observed in various situations of stress, including oxidative stress, and also during aging (Chéret et al., 2008; Collins-Underwood et al., 2008; McCann et al., 2008; H. Chen et al., 2009). Social stress was shown to enhance Nox2 expression (Schiavone et al., 2009). Upregulation of some Nox isoforms, such as Nox1, can stimulate microglial NO formation (Chéret et al., 2008) so that a cross-connection exists to another source of oxidants. Nox4 has been recently reported to be mitochondrially located as a subunit of complex IV (cytochrome oxidase) (Block et al., 2009), indicating a further nexus to a radical-generating source.

To date, the effects of melatonin on Nox activities have only been poorly studied. A recent study shows that the methoxyindole inhibits ROS formation in microglia exposed to amyloid-

β_{1-42} by preventing the phosphorylation of the p47 Nox subunit via the PI3K/Akt pathway (Zhou et al., 2008). Generally one might assume that melatonin, because of its antioxidant, iNOS-downregulating and anxiolytic/antiexcitatory actions, may prevent the stimulation of Nox subforms, as occurring during oxidative, nitrosative/nitrative and social stress. Much more is known about the attenuation of mitochondrial free radical formation by melatonin, which will be discussed in section 6.

Radical avoidance by melatonin should be recognized as a highly complex phenomenon, which comprises the integrative, orchestrating role of this molecule with its numerous actions at different levels. All antiinflammatory effects of melatonin (cf. section 4), whether based on interference with prostaglandin formation, TNFα and chemokine release or inhibition of NO synthesis, should attenuate radical generation, whereas its proinflammatory actions observed under different conditions would rather enhance oxidant formation. The multiple antiexcitatory effects mentioned in section 2.2 should contribute to reductions in radical formation, especially via decreases in cytosolic Ca^{2+} (Prada et al., 2005; Prada and Udin, 2005), downregulation of nNOS (Acuña-Castroviejo et al., 2005; León et al., 2000, 2006; Jiménez-Ortega et al., 2009) and iNOS (Jiménez-Ortega et al., 2009; Tapias et al., 2009). Even through its chronobiological role, melatonin may reduce radical formation (Hardeland et al., 2003a). This assumption is based on the observation that disturbances in the circadian oscillator system, e.g., in short-period mutants, leads to enhanced oxidative damage, as found in organisms as different as *Drosophila* (Coto-Montes and Hardeland, 1999) and Syrian hamsters (Coto-Montes et al., 2001). Melatonin is very effective in protecting from *N*-nitrosodiethylamine-induced perturbation of 24-h rhythms in lipid peroxidation and SOD activity in rats (Subramanian et al., 2008). These findings are in accordance with health problems and reduced life spans observed upon repeated phase shifts (Hardeland and Coto-Montes, 2010). As far as correct phasing within the multioscillator system of a body is supported by melatonin, this should also reduce radical formation.

5.3. Cellular dysfunction and apoptosis

Cellular dysfunction can be caused in multiple ways, by physiologically or pathophysiologically enhanced radical formation inside or outside the cell, by exposure to oxidotoxins, by calcium overload, excess of nitrosative/nitrative damage and by intra- or extracellular signals. An organelle of critical importance for the survival of the cell is the mitochondrion, for various reasons. The electron transport chain is particularly vulnerable to

blockade by NO and to radicals especially formed under the influence of enhanced NO levels, and resulting bottlenecks of electron flux lead to enhanced ROS generation (Hardeland, 2009a,c; Hardeland et al., 2009a; Hardeland and Coto-Montes, 2010). iNOS is mostly upregulated in microglia and astrocytes by immunological or stress-related signaling, whereas nNOS, especially in glutamatergic neurons, depends on excitation-dependent Ca^{2+} entrance. Cytosolic Ca^{2+} can become critical for mitochondria, as soon as these ions are loaded in excess to these organelles, causing oxidative stress (Peng and Jou, 2010) and affecting the mitochondrial membrane potential ($\Delta\Psi_m$). Breakdown of $\Delta\Psi_m$ can initiate apoptosis via the intrinsic death pathway. Opening of the mitochondrial permeability transition pore (mtPTP) has also been observed under the influence of enhanced radical formation (Daiber, 2010; Sedlic et al., 2010). However, mtPTP opening should no longer be exclusively seen in connection with a fatal breakdown of $\Delta\Psi_m$ and apoptosis, since it has also been observed in conjunction with electron flux dynamics and the occurrence of superoxide flashes (Sheu et al., 2008; W. Wang et al., 2008). Thus, transient mtPTP openings now appear to be a normal phenomenon, which does not lead to cell death as long as the depolarization is sufficiently short.

Nevertheless, the specific and central role of mitochondria in apoptosis has been of high interest in melatonin research, especially in attempts of rescuing compromised cells from death. However, it should be emphasized that inhibition of apoptosis cannot be a general value *per se*, since this process is a requirement for avoiding hyperplasias and for eliminating virus-infected and immunologically undesired cells. Nevertheless, antiapoptotic actions are of special interest in terms of neuroprotection, with regard to the low or almost missing replacement of neurons. Antiapoptotic effects of melatonin have been described in numerous publications and summarized in several reviews (Sainz et al., 2003; Pandi-Perumal et al., 2006; Acuña-Castroviejo et al., 2007; X. Wang, 2009). As far as melatonin did not interfere with signaling by other hormones, the inhibition of cell death was mostly investigated under the influence of oxido- or excitotoxins (Sainz et al., 2003). In the studies demonstrating antiapoptotic actions, typical findings were increases in antiapoptotic proteins such as Bcl-2 or Bcl-x_L, decreases in their proapoptotic counterparts such as Bad and Bax, or changes in the ratios between these factors, inhibition of Bad dephosphorylation and of poly ADP ribose polymerase (PARP) cleavage, prevention of cytochrome c release and caspase-3 activation. However, the upstream signaling mechanisms involved have been investigated rather rarely. For instance, protection from cerebral ischemic injury was attributed to the maintenance of

signaling via the MAP kinase pathway, known to be controlled by MT_1 and MT_2 signaling (Chan et al., 2002; Hardeland, 2009b) and leading, in this context, ultimately to the prevention Bad dephosphorylation (Koh, 2008a). Similar findings were obtained in other systems, too (Luchetti et al., 2009, 2010). Other investigations focused on the role of Akt, which is also controlled by melatonin, e.g., via βγ-mediated activation of PI3K or, alternately, by downstream factors of the MAP kinase pathway (Hardeland, 2009b). In ischemic brain injury, melatonin inhibited the dephosphorylation of several downstream elements of Akt, such as mTOR, p70S6 kinase (Koh, 2008c) and the forkhead transcription factor pAFX (Koh, 2008d). Moreover, Akt was reported to favor the association of a 14-3-3 protein with pBad (Koh, 2008b) or with the forkhead transcription factor pFKHR (Koh, 2008d), thereby preventing the proapoptotic actions of the dephosphorylated proteins. Antiapoptotic actions of melatonin concerning the extrinsic pathway have been rarely studied. Reduction of Fas ligand expression were reported, e.g., in models of colitis (Mazzon et al., 2006) and nephrosis (Pedreañez et al., 2004).

Melatonin has also been reported to directly inhibit mtPTP opening (Andrabi et al., 2004). This effect may be related to antiapoptotic actions, but, with regard to a K_i value of 0.8 µM, requires elevated concentrations. This possibility of higher local levels cannot be entirely ruled out, since mitochondrial accumulation of melatonin has been described (Messner et al., 1998; A. López et al., 2009). Melatonin was repeatedly shown to prevent, at pharmacological concentrations, a fatal decline in $\Delta\Psi_m$, in various cell types and with high efficacy against different noxes. In cardiomyocytes, astrocytes and striatal neurons, it prevented calcium overload (Andrabi et al., 2004; Jou et al., 2004), counteracted the collapse of the mitochondrial membrane potential induced by H_2O_2 (Jou et al., 2004, 2007), doxorubicin (Xu and Ashraf, 2002) or oxygen/glucose deprivation (Andrabi et al., 2004).

Contrary to these effects desired in, e.g., neuroprotection, protection from damage by severe inflammation, and reduction of immune cells losses during aging, proapoptotic actions of melatonin were also frequently described. Pertinent findings mainly concern cell death of various cancer cells (Sainz et al., 2003). In these cases, increases in Bax levels and caspase-3 and/or -9 activities were reported (Bejarano et al., 2009; Cucina et al., 2009; Fan et al., 2010; Leja-Szpak et al., 2010), as well as decreases in Bcl-2 (Eck et al., 1998; Cucina et al., 2009; Joo and Yoo, 2009; Fan et al., 2010; Martín et al., 2010). In the human leukemia cell line HL-60, a corresponding breakdown of $\Delta\Psi_m$ was described (Bejarano et al., 2009). In several of these studies, apoptosis was induced at pharmacological concentrations or in combination

with other agents. In some cancer cells, no proapoptotic effects were observed (Sainz et al., 2003). However, in the frequently studied breast cancer cell line MCF-7, proapototic effects were demonstrated at 1 nM (Cucina et al., 2009). This investigation also discriminated between two apoptotic phases, an early one associated with a increase in the p53/MDM2 (murine double minute-2) ratio and release of apoptotic inducing factor (AIF), which was independent of transforming growth factor-β1 (TGF-β1) and caspase activation, and a late, TGF-β1-dependent response characterized by a decrease in the Bcl-2/Bax ratio, PARP cleavage and activation of caspases 9 and 7 (Cucina et al., 2009).

The signaling mechanisms involved in proapoptotic actions of melatonin require further elucidation. Based on experiments in colon and breast cancer cell lines and using synthetic ligands of membrane and nuclear receptors, RORα was concluded to be involved (Winczyk et al., 2001, 2002a, 2006; Sainz et al., 2003). However, effects were also obtained via membrane receptors (Winczyk et al., 2002b), but neither MT_1- nor MT_2-selective antagonists were able to sufficiently suppress melatonin-induced apoptosis (Winczyk et al., 2009). In MCF-7 breast cancer cells, the MT_1/MT_2-specific ligand S23478-1 upregulated Bax and downregulated Bcl-2 expression (Mao et al., 2010). Whether or not these findings are really contradictory may depend on possible interactions between membrane and nuclear receptors. If these are positively coupled in the carcinoma cells, too, as observed in T-lymphocytes and Jurkat cells (Lardone et al., 2009), a stimulation of apoptosis may be possible via either type of receptor.

The reports on either antiapoptotic or proapoptotic actions of melatonin appear, at least at first glance, contradictory and would require mechanistic explanations based on thorough cell biological studies that have to go beyond the description of changes in Bcl-2/Bax ratios or later events in the apoptotic signaling cascades. However, it seems important to recognize that many of the antiapoptotic actions can be presumably explained by melatonin's interference with the primary causes of damage, which, from a certain level on, lead to cell death. This may be especially valid for counteractions of oxidotoxicity, inflammation, damage by ischemia/reperfusion, neurodegeneration and excitotoxicity, all of which are overlapping phenomena. Attenuation of damage from such insults can lead to prevention of apoptosis, without an absolute requirement for direct interference with apoptotic pathways.

6. Melatonin and mitochondria

The presence of mitochondria in almost every cell type plus the numerous reports of the mitochondrial effects of melatonin in various organs are indicative of another aspect of melatonin's pleiotropy. Moreover, mitochondria are potentially affected by noxes of different origin, e.g., in relation to metabolic disorders, inflammation, neuronal overexcitation and, not least, aging. As outlined before, melatonin modulates or attenuates several of the undesired processes associated with such disorders and the organismal decline. The pathophysiological role of mitochondria is increasingly recognized, and the awareness of numerous mitochondrial diseases has led ironically to the designation of the mitochondrion as a "powerhouse of disease" (Lane, 2006). The involvement of mitochondria in cellular and organ dysfunction exceeds by far their participation in apoptosis, although this type of cell death can be consequence. The impairment of mitochondrial activity frequently starts with partial blockades of electron flux through the electron transport chain (ETC), leads to electron leakage and, thus, to oxidant formation in a self-stimulatory feedback loop.

6.1. Modulation of electron flux, bottlenecks and sites of electron leakage

Melatonin has been repeatedly shown to reduce, under various conditions, the mitochondrial formation of ROS and RNS, to protect against oxidative, nitrosative or nitrative damage of ETC proteins as well as lipid peroxidation in the inner membrane and, thus, to favor electron flux and energy efficiency (Reiter et al., 2002b; Acuña-Castroviejo et al., 2003, 2007; L.C. López et al., 2006b; Escames et al., 2006c, 2007; Rodríguez et al., 2007a, 2008; Hardeland and Poeggeler, 2008; Hardeland et al., 2009a; A. López et al., 2009; Hardeland and Coto-Montes, 2010). The mechanistic understanding of these findings requires a look at the sites of mitochondrial radical generation and causes of dysfunction.

Mitochondria as a major source of free radicals are of particular interest with regard to increases in oxidant formation and the potential for radical avoidance as well. Previously, electron leakage from the ETC had been mainly related to changes between respiration states, such as state 3 or 4 respiration. Although this is not irrelevant, actual research focuses on electron overflow and its relation to bottlenecks in the ETC (Genova et al., 2004; Gong et al., 2005; Hardeland, 2009a,c; Hardeland et al., 2009a; Henderson et al., 2009; J. Chen et al., 2010; Durand et al., 2010). In these considerations, the surprising and unexpectedly intense dynamics of electron flux have to be taken into account. As demonstrated by the appearance

of superoxide flashes (Sheu et al., 2008; W. Wang et al., 2008), electron transport is not at all a steady, continual process which may be modulated only smoothly and gradually. It is somewhat reminiscent of a flow of traffic with frequent stop-and-go episodes, during which some overflow into the side alleys takes place. The burst-like leakage of mitochondrial electrons, which can be observed as superoxide flashes, convincingly demonstrates major discontinuities of electron transport, whereas variable and pulse-like changes in electron flow seem to occur additionally. Superoxide flashes are observed at elevated rates under conditions of pathophysiological relevance, such as anoxia/reoxygenation (Sheu et al., 2008), a situation known to cause oxidative stress.

Electrons can dissipate from different sites of the ETC. Leakage from complexes I and III has been most frequently and most thoroughly studied. In complex I, the iron sulfur-cluster N2 has been identified as the site of electron transfer to O_2, a reaction resulting in the formation of the superoxide anion, $O_2^{\bullet -}$ (Genova et al., 2001, 2004; Ohnishi et al., 2005; Lenaz et al., 2006). Contrary to earlier assumptions, this does not require an intermediate step of electron transfer by a ubisemiquinone (Genova et al., 2001; Lenaz et al., 2006). N2 is located at the so-called amphipathic ramp, which extrudes into the matrix. Therefore, this ramp is particularly vulnerable to ROS and RNS present in the matrix and, moreover, $O_2^{\bullet -}$ is preferentially released to this compartment, in which it is either transformed to H_2O_2 by Mn-superoxide dismutase or undergoes reactions with the nitric oxide radical, •NO (summarized in: Hardeland et al., 2009a). Electron leakage from complex III has been attributed to electron bifurcation from ubiquinol to the high and low potential pathways (Staniek et al., 2002). More recently, $O_2^{\bullet -}$ was shown to originate from the Qo site as a consequence of an interruption of the intramonomer electron transfer between the two b_L hemes (Gong et al., 2005). At complex III, $O_2^{\bullet -}$ is released to both sides of the inner mitochondrial membrane (Miwa and Brand, 2005). Superoxide formation from complex IV requires detailed studies, but the assumed identity of Nox4 with a subunit of this complex (Block et al., 2009) would imply a significant contribution of this respirasome to radical formation.

Bottlenecks in the ETC that lead to enhanced electron leakage can be caused by oxidative, nitrosative and nitrative processes or, presumably, also by reduced expression of ETC subunits, most of which are nuclear-encoded. The strongly elevated levels of •NO seem to be critical for gradual or even almost total blockades within the ETC. Because of their negative control by melatonin (cf. section 2.2), iNOS and nNOS are of particular interest in this context. iNOS is mostly upregulated in macrophages, microglia and astrocytes by

inflammatory or stress-related signaling, whereas nNOS, especially in glutamatergic neurons, depends on excitation-dependent calcium entrance. Although moderately elevated concentrations of •NO are usually considered to be favorable for mitochondrial function (summarized in: Hardeland, 2009c), high rates of •NO formation, as observed under conditions of excitotoxicity and of inflammation, lead to sometimes severe ETC dysfunction. These effects are partially caused by •NO itself, but even more by its non-enzymatically formed metabolites. •NO and its reactive metabolites are, in the extreme condition of severe inflammation, capable of totally blocking respiration (Dungel et al., 2008). In view of its property as an iron ligand, •NO can bind to various ETC irons present in iron-sulfur clusters or hemes. Moreover, it can nitrosate protein residues, mainly sulfhydryl groups, also indirectly via its redox congeners formed (Hardeland, 2009c; Hardeland et al., 2009a), e.g., by disproportionation of two •NO to NO^+ and NO^- (readily protonated to HNO), as catalyzed by the mitochondrial Mn-superoxide dismutase (Filipović et al., 2007). Nitrosation is also possible by combinations of electron-abstracting radicals with •NO, by the •NO/•NO_2 adduct N_2O_3, or via transnitrosation by *S*-nitrosothiols including *S*-nitrosoglutathione and *S*-nitrosocysteine (Hardeland, 2009c; Hardeland et al., 2009a). Transnitrosation of protein thiols has been demonstrated in ETC subunits, especially in complex I, which causes increases in electron leakage (Brown and Bal-Price, 2003; Dahm et al., 2006). Nitrosation of aromates has been also discussed for the nitrosodioxyl radical (ONOO•; the radical analog of peroxynitrite), which can be generated by electron abstraction abstracted from peroxynitrite, e.g., by •NO_2 (Blanchard et al., 2000), but this has not yet been demonstrated in ETC proteins.

Among the numerous RNS interconversion reactions, a chemically and pathophysiologically critical step is the combination of •NO with the superoxide anion (O_2•$^-$). Because of the approximately same affinity of O_2•$^-$ to •NO and to SODs, this reaction is practically unavoidable. The resulting adduct, peroxynitrite ($ONOO^-$), is a highly reactive compound. Various interactions with biomolecules have been ascribed to $ONOO^-$, although direct reactions of peroxynitrite with organic compounds, including melatonin, can hardly be distinguished from others caused by peroxynitrite-derived free radicals (Hardeland, 2009a). Peroxynitrite undergoes two adduct reactions of high pathophysiological relevance. One of them, protonation of the anion yields an unstable compound, peroxynitrous acid (ONOOH), which readily decomposes to a hydroxyl radical (•OH) and nitrogen dioxide (•NO_2). The other one leads to an adduct with CO_2, i.e., an abundantly available compound in mitochondria. The resulting molecule, $ONOOCO_2^-$, decomposes to a carbonate radical (CO_3•$^-$

) and •NO_2 (Squadrito and Pryor, 1998; Ducrocq et al., 1999; Guenther et al., 2005; Hardeland, 2009a; Hardeland et al., 2009a). The carbonate radical is less reactive than •OH, but is likewise capable of abstracting electrons or hydrogens (Squadrito and Pryor, 1998; Zhang et al., 2000; Kalyanaraman et al., 2001; Hardeland et al., 2003b; Guenther et al., 2005; Hardeland, 2005). The damaging potential of CO_3•$^-$ should not to be underrated, since it has, owing to a much longer lifespan, a considerably larger radius of action than •OH. The oxidizing peroxynitrite derivatives, •OH and CO_3•$^-$, can oxidatively modify ETC proteins and peroxidize membrane lipids, among which cardiolipin is of special relevance to mitochondrial function, since it is required in the lipid environment for structural integrity of complexes III and IV (Klingen et al., 2007; Lesnefsky et al., 2009; Wenz et al., 2009). Additional effects in complex I in preventing electron leakage have been ascribed to cardiolipin, too (Petrosillo et al., 2009). When interacting with cytochrome c, it gains a peroxidase activity that further promotes cardiolipin peroxidation and, ultimately, cytochrome c release (Basova et al., 2007; Bayir et al., 2007; Ott et al., 2007; Kagan et al., 2009). Especially the combination of CO_3•$^-$ and •NO_2 represents a physiological nitration mixture (Zhang et al., 2000; Kalyanaraman et al., 2001; Guenther et al., 2005; Hardeland, 2009a), although the classic nitration of aromates is of a non-radical nature. Preferred nitration targets are accessible tyrosyl residues. Tyrosine nitration has a particular impact in mitochondria. In one study, after ischemia/reperfusion, 23 cardiac proteins were found to be specifically tyrosine-nitrated, among which 10 were mitochondrially located (B. Liu et al., 2009). Under conditions of strongly enhanced •NO synthesis, several subunits of complexes I and III as well as the ATP synthase α subunit were affected (H.M. Lee et al., 2009; B. Liu et al., 2009). In other systems, the complex I subunit NDUFB8 (Davis et al., 2010), the Fp subunit of complex II (C.L. Chen et al., 2008; Davis et al., 2010), mitochondrial creatine kinase, dihydrolipoamide dehydrogenase, and the voltage-dependent anion channel VDAC1 (Davis et al., 2010) were reported to be tyrosine-nitrated.

Collectively, all these findings demonstrate that supranormal increases in •NO formation can severely damage mitochondria in multiple ways. Melatonin is not only a potent scavenger of hydroxyl radicals (Tan et al., 1993; Reiter, 1993a; Reiter et al., 2002a; Hardeland, 2005), but also of carbonate radicals (Hardeland et al., 2003b). When given in high pharmacological doses, these properties may contribute to combat the oxidative damage caused by the reactive products mainly formed via peroxynitrite. However, it may be more important and also possible at high physiological or low pharmacological doses to suppress excessive upregulations of iNOS and/or nNOS. This intervention is capable of breaking the vicious

cycle of high •NO, which causes ETC blockades in multiple ways, especially by combining with O_2•$^-$ to give highly reactive products that damage respirasomes, interrupt electron flux, cause electron backflow and leakage, so that the newly formed O_2•$^-$ radicals combine again with •NO.

6.2. Prevention of blockades by •NO and •NO-derived intermediates: reduction of superoxide formation

The efficacy of melatonin in antagonizing •NO-dependent damage to mitochondria has been demonstrated in several studies. This is most impressively evident in models of excitotoxicity and of sepsis. Indications of similar processes leading to mitochondrial dysfunctions during aging and counteractions by melatonin will be discussed in section 9.

Although the antiexcitatory effects of melatonin seem to comprise inhibition of nNOS and although this action should contribute to the maintenance of ETC function (León et al., 1998, 2000, 2006; Chandrasekaran et al., 2004; Escames et al., 2004), little information is available on the role of this isoform in the protection of mitochondria. Even in the context of excitotoxicity, most data are related to iNOS, including its mitochondrial subform targeted to this organelle by protein modification. In models of Parkinsonism using the excito- and mitochondrial toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (= MPTP), melatonin was not only protective in the nigrostriatum according to histological results (Ma et al., 2009), but also attenuated oxidative stress and prevented the inhibition of complex I (Khaldy et al., 2003; Tapias et al., 2009). These effects were associated with corresponding changes in the mitochondrial variant of iNOS (Tapias et al., 2009).

Much more work has been published on the downregulation of iNOS in models of inflammation and sepsis (Srinivasan et al., 2010a). In liver and lung of LPS-treated rats, melatonin antagonized iNOS as well as NO-dependent decreases in the activities of complexes I and IV (Escames et al., 2003). In a sepsis model of cecal ligation and puncture, melatonin counteracted increases in mitochondrial iNOS, lipid peroxidation, shifts in the glutathione redox state (GSH/GSSG), decreases in the activities of complexes I, II, III and IV, and favored energy efficiency and ATP production in mitochondria from heart, diaphragm and skeletal muscle (L.C. López et al., 2006a,b; Escames et al., 2006b, 2007). These studies consistently showed that the damage to mitochondria was low in homozygous iNOS

knockouts, so that the deleterious effects could be, in fact, attributed to supranormal upregulations of this isoform under conditions of severe inflammation.

6.3 Additional mechanisms supporting mitochondrial function

When challenged by severe oxidative and/or nitrosative/nitrative stress, mitochondria have to be protected by pharmacological doses of melatonin. At these concentrations, the direct scavenging of free radicals may contribute to the protective effects. Moreover, the availability of reduced glutathione as well as the activity of mitochondrial glutathione peroxidase (GPx) may represent other critical parameters. In fact, melatonin stimulated both glutathione peroxidase and glutathione reductase and favored the reduced state of this antioxidant, also under conditions of sepsis (Escames et al., 2006c; L.C. López et al., 2006b). Although these studies did not specifically refer to the mitochondrial isoform GPx4, this enzyme should have been involved. GPx4 is insofar of additional interest, as its overexpression in transgenic mice protects against oxidative damage of the ETC, in particular peroxidation of cardiolipin, and cytochrome c release (Liang et al., 2007, 2009). Collectively, melatonin, GSH and GPx4 should help avoiding protein oxidation and nitration and cardiolipin peroxidation, thereby avoiding bottlenecks in the ETC. These activities may be further supported by other antiinflammatory actions of melatonin discussed in section 4.

However, increases in the activities of complexes I and IV, sometimes also complex III, attenuation of electron leakage and enhanced ATP production have been also observed in mitochondria from unchallenged animals (Martín et al., 2002; Acuña-Castroviejo et al., 2003; León et al., 2005; A. López et al., 2009). These effects were also seen at low, physiologically possible levels of the methoxyindole. Since the upregulations of respirasomal activities were observed in submitochondrial particles, they should not mainly reflect protection from damage, but presumably rather changes in the expression of subunits of the ETC complexes. In fact, increased expression of three subunits of complex IV was demonstrated (Acuña-Castroviejo et al., 2003).

The effects of melatonin on electron flux may go beyond the findings described. A suggestion by B. Poeggeler (mentioned in: Hardeland et al., 2003a; Hardeland, 2005) concerning a direct electron exchange between quasi-catalytic quantities of the methoxyindole and the ETC still awaits experimental substantiation. Other data that have not yet been published in detail, because the main researchers of the study left the field, but which have been mentioned

elsewhere (Hardeland and Poeggeler, 2007; Hardeland, 2009a), indicate the existence of a mitochondrial high-affinity binding site (K_i = 150 pM) for melatonin in complex I of brain mitochondria, which is, according to site-specific ligand competition studies, located in the amphipathic ramp close to iron-sulfur cluster N2. If these findings are confirmed, a modulation of electron throughput at complex I would appear to be possible.

6.4. Contributions of melatonin metabolites?

When high pharmacological levels of melatonin are used to combat oxidotoxicity, and also under conditions of inflammation, the metabolic route of pyrrole-ring cleavage leads to methoxylated kynuramine metabolites AFMK and AMK (Hardeland et al., 2009b). The relevance of this pathway under basal conditions is, however, uncertain in vertebrates. The antiiflammatory properties of AFMK and AMK (Kelly et al., 1984; Mayo et al., 2005b), potent inhibition of nNOS (Entrena et al., 2005; León et al., 2006) and downregulation of iNOS expression by AMK (Tapias et al., 2009) indicate that these kynuramines contribute to mitochondrial protection, at least in pharmacological experiments. Additionally, AMK was shown to be a potent scavenger of all NO congeners (Guenther et al., 2005; Hardeland et al., 2007a), of $CO_3^{\bullet -}$ and •OH (Ressmeyer et al., 2003; Guenther et al., 2005). In contrast to melatonin, the cyclic AMK-NO adduct does not re-donate NO. In fact, AMK was shown to protect mitochondria and to enhance complex I activity (Acuña-Castroviejo et al., 2003; Tapias et al., 2009).

6.5. Effects on sirtuins and the merging pathways of mitochondrial biogenesis

Sirtuins have become known as NAD^+-dependent protein deacetylases and promoters of longevity in numerous organisms. Their actions extend to energy metabolism (Guarente, 2008), so that mitochondria should be influenced by these enzymes already from this point of view (Hardeland and Coto-Montes, 2010). In fact, the seven mammalian subforms, SIRT1 to SIRT7, are multiply involved in mitochondrial function. SIRT3, SIRT4 and SIRT5 are mitochondrially localized and, at least, SIRT3 prevents mitochondrial lysine hyperacetylation (Lombard et al., 2007). Like another aging suppressor, klotho, SIRT3 modulates the FoxO signaling pathway by interacting with the mitochondrial FoxO3a homolog, daf-16 (Jacobs et al., 2008). A functional relationship between melatonin and daf proteins has been assumed in the context of antioxidant defense, insulin resistance and diabetes (Das, 1999, 2005). In

fibroblasts, SIRT3 was shown to physically interact with a complex I subunit, the 39-kDa protein NDUFA9, to enhance complex I activity and ATP levels (Ahn et al., 2008), at least a parallelism to findings with melatonin. Sirtuins do not only act intra-mitochondrially, but exert additional regulatory effects and stimulate mitochondrial biogenesis (Guarente, 2008). SIRT1, which is not mitochondrially localized, also modulates NO synthesis, the insulin/IGF-1 pathway, activates FoxO subforms and promotes the expression of antioxidant enzymes (Dilova et al., 2007; Guarente, 2008; Hardeland and Coto-Montes, 2010). The connection to free radical metabolism is, again, a striking parallelism to melatonin. Since SIRT1 may be also stimulated via the MAP kinase pathway (McCarty et al., 2009), which is also controlled by melatonin by the βγ heterodimers of G-proteins (Hardeland, 2009b), another cross-connection seems to exist. The requirement of SIRT1 for mitochondrial activity becomes obvious by its dependence on the AMP level, an indicator of ATP deficiency. SIRT1 and AMPK (=AMP-activated protein kinase) simultaneously respond to elevated AMP and act correspondingly in situations of stress, starvation or calorie restriction (Fulco and Sartorelli, 2008). The metabolic sensor AMPK seems to be additionally stimulated by SIRT1 (Hardeland and Coto-Montes, 2010). SIRT1 modulates mitochondrial ETC capacity by influencing mitochondrial biogenesis and, thus, the total mitochondrial volume per cell (Dilova et al., 2007; Guarente, 2008). The stimulation of mitochondrial biogenesis is mediated by either AMPK or SIRT1, which upregulate PGC-1α (= PPARγ coactivator-1α), an activator of the transcription factor PPARγ (= peroxisome proliferator-activated receptor-γ) (Kiaei, 2008; López-Lluch et al., 2008; Hardeland and Coto-Montes, 2010). PPARγ also antagonizes neuroinflammation and has been discussed with regard to its suitability for treating Huntington's disease and amyotrophic lateral sclerosis (Kiaei, 2008). SIRT1 has also been shown to act in another area normally associated with melatonin, namely, circadian rhythmicity. It modulates chromatin remodeling via the oscillator protein CLK and, moreover, seems to directly influence at least peripheral oscillators by interacting with the CLK/BMAL1 complex (Nakahata et al., 2008, 2009; Grimaldi et al., 2009), actions that should have numerous secondary effects. If SIRT1 has really to be classified as a direct modulator of a core oscillator protein (Belden and Dunlap, 2008), an interplay with melatonin seems highly likely.

Meanwhile, several studies have reported upregulations of SIRT1 by melatonin, e.g., in the brain of senescence-accelerated SAMP8 mice (Gutierrez-Cuesta et al., 2008) and in neuronal primary cultures from neonatal rat cerebellum (Tajes et al., 2009), or the prevention of SIRT1

decreases in the hippocampus of sleep-deprived rats (Chang et al., 2009). In the neuronal cultures from cerebellum, melatonin also enhanced the deacetylation of various SIRT1 substrates, such as PGC-1α, FoxO1, NFκB, and p53, effects which were largely reversed by the SIRT1 inhibitor sirtinol (Tajes et al., 2009). The melatonin-induced deacetylation of PGC-1α indicates that mitochondrial biogenesis might be stimulated by the methoxyindole *in vivo*.

Although the experimental basis for a relationship between melatonin and SIRT1 is still rather small, such an association, if verified, would have the potential to become a field with numerous implications for circadian rhythmicity, aging, neuroprotection and cancer, and these possibilities have been recently discussed (Hill et al., 2009; Jung-Hynes and Ahmad, 2009; Jung-Hynes et al., 2010b).

7. Energy efficiency, energy expenditure and body mass regulation

Energy efficiency is also a matter of mitochondrial function. At the organelle level, increases in energy efficiency in terms of ETC substrates required per ATP, as outlined in section 6, have been mainly studied under pathological conditions or in toxicological models. Similar observations, however, have also been made in the mitochondria of aging rodents (Rodríguez et al., 2007c, 2008; Carretero et al., 2009).

Mitochondrial functioning has to be distinguished from food efficiency. The energy balance, which is affected by calorie intake and energy expenditure, progressively gains importance with regard to obesity and numerous health problems arising thereof. Although a considerable body of evidence exists for the role of melatonin in the control of visceral fat masses in non-human mammals, these findings are frequently related to seasonality, but may provide mechanistic insights for understanding obesity in humans (Tan et al., 2010b).

Beyond the seasonal changes, many details remain to be clarified. In various species, an increase of visceral adipose tissue is observed with age, a change correlated with the decline of melatonin (summarized in: Pandi-Perumal et al., 2006). A functional relationship may be indicated by the observation that daily melatonin reduces visceral fat masses in rats, i.e., in a non-seasonal breeder. This was found in animals fed a high-fat diet (Ríos-Lugo et al., 2010), whereas pinealectomy led to weight gain (Prunet-Marcassus et al., 2003). The age-related gain in adipose tissue of rats was suppressed by melatonin, and this was notably associated with normalizations of insulin and leptin levels (Rasmussen et al., 1999; Ríos-Lugo et al.,

2010), and corresponding data were also obtained in middle-aged rats (Wolden-Hanson et al., 2000; She et al., 2009). Melatonin also prevented the increase in body fat induced by ovariectomy (Ladizesky et al., 2003).

In human PAZ6 adipocytes, MT_2 expression has been demonstrated (Brydon et al., 2001). However, the role of melatonin in human fat metabolism is less clear. The changes in human melatonin levels during youth and adolescence do not correlate with the quantities of adipose tissue, and young obese individuals tended to secrete more melatonin. Higher melatonin levels in pubertal obese males have been discussed as a possible cause of delayed puberty (Fideleff et al., 2006). Long-term melatonin administration to obese women, 53 – 57 years old at time of evaluation, indicated a retardation of body weight gain (Nachtigal et al., 2005). These data, however, require clinical confirmation using objective measures.

After the recent discovery of substantial amounts of functional brown adipose tissue in adult humans (Virtanen et al., 2009), this thermogenic tissue has to be considered in energy balance and expenditure. Although the effects of melatonin in brown adipose tissue have been long known in hibernating mammals (summarized in: Tan et al., 2010b), the physiologic context is clearly different in humans. At first glance, a stimulation of energy consumption by thermogenesis by melatonin seems illogical, since this hormone is usually known as a hypothermic agent (e.g., Kräuchi et al., 1997; Lushington et al., 1997; Gilbert et al., 1999b; Holmes et al., 2002). This is, however, an inappropriate simplification, since the reduction in core body temperature of about 0.1 - 0.4 °C has to be seen in the balance with increases of 0.3 – 1.7 °C in the peripheral temperature (Cagnacci et al., 1997; Gilbert et al., 1999a; van den Heuvel et al., 1999). The increase cannot be directly attributed to brown adipose tissue, but vasomotor changes also need to be taken into consideration. The presence of MT_1 in thermoregulatory centers of the human hypothalamus (Wu et al., 2006b) is indicative of a role of melatonin in thermoregulation, but not necessarily for the control of brown adipose tissue.

Thermogenesis in brown adipose tissue depends on relatively high mitochondrial electron flux and the expression of the uncoupling protein UCP1. Too little is known to date about the effects of melatonin on expression of respirasomal subunits and UCP1. The observation that the methoxyindole reduced cytochrome b expression in Siberian hamsters (Prunet-Marcassus et al., 2001) is not indicative of a thermogenic effect of melatonin. With regard to relatively high energy expenditure of brown adipose tissue, the idea of a control by melatonin (Tan et al., 2010b) is, nevertheless, potentially important and should be followed up.

Obesity is, among other health problems, a risk factor for metabolic syndrome and diabetes type 2, in conjunction with the polymorphisms of MT_2 (Staiger et al., 2008; Bouatia-Naji et al., 2009; Sparsø et al., 2009; C. Liu et al., 2010), which may also have effects at the levels of energy balance. In animals fed a high-fat/high-sucrose diet, melatonin and the melatonergic agonist NEU-P11 not only inhibited abdominal fat accumulation, but also reduced blood glucose, triglycerides and total cholesterol, enhanced HDL-bound cholesterol, normalized the time profiles of circulating insulin after a glucose load, prevented diet-induced lipid peroxidation and decreases in GPx and SOD activities (She et al., 2009; Hardeland, 2010a). In high-fat fed rats, melatonin attenuated body weight increase, hyperglycemia and hyperinsulinemia, as well as the increase in mean plasma adiponectin, leptin, triglycerides and cholesterol levels. The high-fat diet disrupted normal 24 h patterns of circulating adiponectin, insulin and cholesterol, the effects on insulin and cholesterol being counteracted by melatonin (Ríos-Lugo et al., 2010). Melatonin and, even more efficiently, NEU-P11 stimulated the expression of insulin receptor substrate 1 (IRS-1), but reduced its Ser307 phosphorylation as well as protein kinase C-θ activity muscle, liver and adipose tissue (She et al., 2009). These findings are encouraging for future studies on the suitability of melatonin or melatonergic agonists as agents for combating insulin resistance. Moreover, this concept is strongly supported with the induction of insulin resistance by disrupting MT_1 in mice (Contreras-Alcantara et al., 2010).

8. Melatonin, melatonin receptor agonists and upregulation of neurotrophins

Post-developmental neurogenesis occurs at relatively low rates, but seems to be important in some areas, such as the hippocampus, where this may be required for maintaining the capability of efficient learning. Neurotrophins are not only involved in developmental and adult neurogenesis, but additionally in neuroplasticity. They display neuroprotective effects (Webster and Pirrung, 2008; Saragovi et al., 2009) and support restorative processes after brain injury (Kidd, 2009). Melatonin, which has been shown to be neuroprotective in numerous experimental systems, also influences the expression and release of neurotrophic factors.

From an experimental point of view, several approaches and conditions have to be distinguished. Studies in neural stem cells provide information other than that obtained from

tissue *in vivo*. Moreover, experiments based on toxicological lesions can lead to seemingly contrary results in different models and also in comparison with non- or less compromised tissues or cells. For instance, GDNF (= glial cell line-derived neurotrophic factor) increases in the rat striatum lesioned by 6-hydroxydopamine (Sharma et al., 2006), and BDNF (= brain-derived neurotrophic factor) is elevated in SHSY5Y neuroblastoma cells by Aβ (Olivieri et al., 2003), but, in both cases, melatonin decreases the expression of these neurotrophins. Such results have to be interpreted as a return to normality. Another study reported enhanced GDNF expression in the striatum in response to either MPTP insults and to melatonin (Tang et al., 1998).

However, upregulation of GDNF by melatonin was reported for primary astrocyte cultures (P.J. Kong et al., 2008) and rat C6 glioma cells (Armstrong and Niles, 2002). Melatonin also stimulated GDNF expression under conditions of neuroprotection against oxidative stress in the locus coeruleus of rats (K.B. Chen et al., 2003) and against kainic acid in the murine hippocampus (S.H. Lee et al., 2006). These effects had previously been observed in the cultures at nanomolar levels or lower and are, according to inhibitor studies, presumably mediated by the membrane receptors. In the astrocytes, the upregulation of GDNF was transduced via the PI3K/Akt pathway (P.J. Kong et al., 2008), which has repeatedly been shown to be activated by melatonin. Akt has also been assumed to be upregulated in hippocampal neurons (S.H. Lee et al., 2006).

Divergent effects were obtained concerning the role of melatonin in the regulation of BDNF (= brain-derived neurotrophic factor). Stimulation or support of BDNF expression by the melatonergic agonist agomelatine was repeatedly reported (Soumier et al., 2009; Molteni et al., 2010; Païzanis et al., 2010). However, these effects were mostly not obtained with melatonin (Imbesi et al., 2008b; Soumier et al., 2009; Molteni et al., 2010), or only and surprisingly in MT_2 knockouts, as reported for cerebellar granule cells (Imbesi et al., 2008b). This might be explained by agomelatine's additional property as a 5-HT_{2C} receptor antagonist. This interpretation is supported by a corresponding stimulation of hippocampal cell growth by other 5-HT_{2C} antagonists, SB243,213 and S32006 (Soumier et al., 2009). However, another study conducted in the prefrontal cortex did not find a direct effect on BDNF by S32006, as observed with agomelatine (Molteni et al., 2010). The issue does not appear to be definitely settled, since another melatonergic agonist, ramelteon, which is devoid of this serotonergic inhibition, was reported to upregulate BDNF in cerebellar granule cells of wild-type, MT_1 or MT_2 knockout mice (Imbesi et al., 2008a), whereas this was seen with

melatonin only in the *MT_2* knockouts (Imbesi et al., 2008b). Another hint for an eventual relationship between melatonin and BDNF may be deduced from studies on the effects of valproic acid in C6 glioma cells, in which the drug stimulated concomitantly the expression of *MT_1*, *BDNF* and *GDNF* mRNAs (Castro et al., 2005), but it will be necessary to ascertain that the glioma cells respond in the same way as non-transformed cells.

Much less is known of the effects of melatonin on NGF (= nerve growth factor). NGF was reported to be upregulated by melatonin in murine submandibular glands (Pongsa-Asawapaiboon et al., 1998). The only indication for a relevance in the CNS comes from a study in SHSY5Y neuroblastoma cells, in which decreases in NGF secretion, induced by Aβ or H_2O_2, were reversed by melatonin (Olivieri et al., 2002), but this may only reflect protection against oxidative damage.

An entirely different situation may be uncovered in direct studies using neural stem cells. A few promising results have been obtained in this emerging field. In neural stems cells from rat midbrain, both BDNF and GDNF were increased by melatonin (X. Kong et al., 2008). Similarly, C17.2 stem cells, which express MT_1 receptors, responded to melatonin by substantial increases of GDNF (Niles et al., 2004). In the same cells, nanomolar concentrations of melatonin induced neurite outgrow, expression of nestin mRNA, and several histone H3 acetylases (Sharma et al., 2008).

9. Aging

An age-associated decline in the secretion of a pleiotropically acting hormone such as melatonin (cf. 3.2), which orchestrates numerous functions at different levels, has to have profound consequences for the functioning of the organism. It may not always be easy to distinguish between a primary dysfunction of the SCN, or its input and output pathways, and damage to the pineal gland. This distinction is not unimportant, since a replacement therapy will be of limited success in cases in which the SCN is damaged because of neurodegeneration, so that functions depending on the primary circadian pacemaker would not be easily readjusted. However, effects on melatonin on peripheral oscillators, on mitochondria and various cellular parameters may still be possible.

9.1. Melatonin and normal aging

Continuous administration of melatonin, e.g., via drinking water, as it is possible in nocturnally active rodents, has generally not been found to extend the lifespan (Poeggeler, 2005), although some reports have indicated this to be the case. In this context, factors such as a contribution of body weight and causes of death have to be considered. In several mouse strains, especially those which are melatonin-deficient, animals die from cancer, and melatonin administration may result in a kind of chemoprevention. Instead of prolongation of the lifespan, melatonin-treated rodents frequently show the so-called “Methuselah syndrome“ (Poeggeler, 2005), i.e., they remain in apparently healthy condition concerning mobility, glossy fur, absence of skin inflammations and low osteoporosis. Usually these animals die without a prolonged phase of poor health state. These observations may be taken as a perspective for healthy aging.

Melatonin may contribute in many fold ways to healthy aging, by various actions discussed in the preceding sections. This should include phasing of the circadian system, having important consequences for sleep, support of the immune system, antioxidant and antiinflammatory actions, perhaps oncostatic effects, prevention of neuronal overexcitation and, not least, safeguarding of mitochondrial electron flux and minimizing electron leakage.

In relation to aging, the beneficial effects of melatonin at the mitochondrial level have been repeatedly described. In old animals of a normally aging mouse strain (SAMR1), melatonin caused increases in hepatic complex I activity (Okatani et al., 2003b). In SAMR1, melatonin given from 7 months on, 1-year old animals exhibited significant increases in respiratory control index, state 3 respiration, dinitrophenol-uncoupled respiration (roughly an indicator of respiratory capacity), and complex I and IV activities (Okatani et al., 2002b). Melatonin-induced increases in complex I activity were also observed in brain mitochondria of aging rats, effects that were accompanied by a reduction of cardiolipin peroxidation (Petrosillo et al., 2008; Paradies et al., 2010). Increased cardiolipin peroxidation has also been assumed to be the cause of a higher susceptibility of cardiac mitochondria to Ca^{2+} overload leading to mtPTP opening and cytochrome c release, as observed in 2-year old rats, changes which were, again, antagonized by melatonin (Petrosillo et al., 2010). Changes in Ca^{2+}-dependent secretion and mitochondrial membrane potential ($\Delta\Psi_m$) as well as counteractions by melatonin were also reported for pancreatic acinar cells from aged mice (Camello-Almaraz et al., 2008).

Especially with regard to the long-lived cells in brain and heart, age-associated mitochondrial changes concerning intracellular distribution merit a special consideration. In aging cardiomyocytes, a profound difference exists between subsarcolemmal and interfibrillary

mitochondria. While the subsarcolemmal subpopulation does not show signs of dysfunction, interfibrillary mitochondria exhibit decreases in complex III and IV activities and increased electron leakage, especially because of a defect at the Qo site of complex III, which may involve alterations of cardiolipin (Lesnefsky et al., 2001; Hoppel et al., 2002; Lesnefsky and Hoppel, 2008). In the aging brain, changes in mitochondrial length and distribution have been mainly studied in neurodegenerative disorders (Hardeland, 2009c), but similar changes seem to exist in the normally aging brain, though to a much smaller extent. Main findings will be discussed in section 10.

9.2. Lessons from senescence-accelerated mice

What is already seen in normally aging animals becomes ever more obvious in the senescence-accelerated mouse strain SAMP8. Additional aspects of melatonin's actions have been addressed, too, such as suppression of age-related inflammatory processes (Rodríguez et al., 2007c), maintenance of pyramidal cell number and peripheral localization of mitochondria in the hippocampal C1 layer (Cheng et al., 2008), prevention of decreases in SIRT1 expression, stimulation of p53 phosphorylation, reductions in Aβ aggregates, decreases in Bid and increases in Bcl-x_L (Gutierrez-Cuesta et al., 2008) and also improvements of neurological parameters, such as reduction of p35 cleavage to Cdk5 hyperactivator p25, in line with decreases in Cdk5 expression, and inhibition of Tau hyperphosphorylation by the Tau kinase GSK3β (Gutierrez-Cuesta et al., 2007). Reductions in oxidative damage of lipids, proteins (Okatani et al., 2002c; Caballero et al., 2008) and DNA in the brain (Morioka et al., 1999) may indicate antioxidant actions, but, with some likelihood, also attenuations of mitochondrial radical formation. Moderate elevations of GPx were also observed (Okatani et al., 2002c), but may have been too small for profound antioxidant actions. Age-related decreases in GPx activity were, however, more clearly prevented by melatonin in the liver of SAMP8 (Okatani et al., 2002a; Rodríguez et al., 2007c, 2008).

Improvements of mitochondrial function by melatonin have been identified in various organs of SAMP8 mice. In the liver, melatonin increased complex I and complex IV activities, the respiratory control index, state 3 and dinitrophenol-uncoupled respirations (Okatani et al., 2002a, 2003a). In the heart, increases in complex I and III activities were observed and, to a smaller extent, in that of complex IV (Rodríguez et al., 2007b). In the diaphragm, increases in

ATP were achieved and, in addition, in mitochondrial GSH content, GPx and glutathione reductase activities (Rodríguez et al., 2007b, 2008). Brain mitochondria responded by elevations of complex I activity and ATP, whereas changes in complex III and IV activities remained negligible (Carretero et al., 2009). One of these studies (Rodríguez et al., 2008) also reported a life extension by melatonin in SAMP8 mice, with increases in mean lifespan from about 18 to 23 months and in maximal lifespan from about 24 to 27 months. The corresponding data for the normal aging SAMR1 mice showed considerably smaller effects.

Collectively, the data from SAMP8 mice indicate an important, perhaps decisive role of mitochondria in the aging processes as well as the suitability of melatonin in counteracting the undesired changes. Final judgments on these, doubtlessly promising, findings largely depend on the causes of accelerated aging in SAMP8 in relation to the effects of melatonin on redox balance and mitochondrial function. The main question is that of whether the accelerated aging properly reflects the normal aging process. An acceleration *per se* does not warrant this, as readily becomes obvious by a look at progerias. As discussed elsewhere (Hardeland and Coto-Montes, 2010), a laminopathic progeria would not mislead one to conclude that instabilities of the nuclear lamina are the main cause of normal aging. In relation to melatonin, the reasons for a higher vulnerability to oxidative stress (Zhang et al., 2009) and for progressing mitochondrial impairments have to be convincingly identified, i.e., the upstream processes leading to losses in complex I activity, respiratory efficiency, ATP production etc.

Interestingly, a chronobiological difference between SAMP8 and SAMR1 mice exists, too, although a relationship to aging is not yet obvious. SAMP8 mice were shown to oscillate with a somewhat longer spontaneous circadian period than their normally aging counterparts (Asai et al., 2000). Both strains exhibited age-dependent elongations of the free-running period. Another described difference in phase-shifting was based on only a single 8-hour phase advance, compared in melatonin-treated and untreated animals, but this should better be decided on the basis of phase-response curves, which may differ in these strains.

10. Consequences for neuroprotection

At the level of animal and *in vitro* models, the neuroprotective potential of melatonin is amply documented (Reiter et al., 1998, 2001; Pappolla et al., 2000; Matsubara et al., 2003; Beni et al., 2004; Kilic et al., 2005; Mayo et al., 2005a; Vega-Naredo et al., 2005; Srinivasan et al.,

2005, 2006; Furio et al., 2008; Das et al., 2010). A full review of these findings would exceed the scope of this article. In studies of acute stress models in living animals, such as ischemia/reperfusion, brain trauma, injections of neurotoxins or oxidotoxins, high pharmacological doses were mostly applied, which may not be suitable for treating humans. This is even more valid for studies in tissue and cell cultures, in which sometimes concentrations of up to 1 mM were used. The route of administration via drinking water, as used in nocturnal rodents, is not applicable to humans because of the circadian phase. In animals, the procedure has the advantage of permitting repeated drug intake throughout the night. It remains to be demonstrated

whether extended release pills taken at bedtime would make melatonin sufficiently available over the sleeping phase to suffice for neuroprotection. Another limit of particular importance in neurodegenerative disorders concerns the onset of treatment. An initiation of melatonin administration during the early weeks of life proved to be beneficial in retarding symptoms in a transgenic mouse model of Alzheimer's disease (Matsubara et al., 2003) but was inefficient at a later onset of treatment (Quinn et al., 2005). A clinical correlation exists since administration of melatonin to humans with mild cognitive impairment is considerably more effective to control cognitive, sleep and mood decay than in fully expressed Alzheimer´s disease (Cardinali et al., 2010).

In neurodegenerative diseases in humans, an onset of treatment before the appearance of symptoms may be done in the future in cases of genetic predispositions. Moreover, surveillance of nocturnal plasma melatonin levels could be useful after reaching an age of 50 years or older, or when patients complain about sleep difficulties.

On the other hand, a continuous treatment with melatonin or melatonergic drugs may be problematic in individual cases, if the concerns about the progression of Parkinson's disease and irritable bowel syndrome type II (Willis, 2008) turn out to be justified. Apart from these and a few other reservations, melatonin is usually remarkably well tolerated (Korkmaz and Reiter, 2008; Sánchez-Barceló et al., 2010). In the extreme, 300 mg melatonin/day were given enterally for up to 2 years to amyotrophic lateral sclerosis patients and found to be safe (Weishaupt et al., 2006).

Evidence is increasing that a well functioning circadian system is important for healthy aging. Correctly timed melatonin may contribute to the proper functioning of the circadian system, including the maintenance of internal phase relationships of parallel oscillators. This may be supported by photic time cues, e.g., bright light in the morning. It may not be necessary to

give melatonin or melatonergic drugs every day over extended periods. The possibility should explored whether melatonin or a melatonergic agonist administered for a few consecutive days may suffice for normalizing circadian amplitudes and phase relationships, a treatment that may be repeated from time to time.

The key role of mitochondria in neurodegenerative diseases indicates that supporting the integrity and functioning of these organelles should be given a high priority, thereby reducing electron leakage and radical formation. To what extent this will be possible with melatonin, perhaps, in conjunction with photic stimulation of the circadian oscillators and/or calorie restriction, remains to be thoroughly studied. In various neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis, mitochondrial changes are not only observed at the level of ETC dysfunction, electron leakage and oxidative, nitrosative or nitrative damage, but also in a disturbed balance between mitochondrial fusion and fission, with consequences for intracellular distribution of these organelles (X. Wang et al., 2008, 2009; Su et al., 2010). In the course of disease progression, mitochondria are becoming shorter and mitochondrial density decreases preferentially in the cell periphery of neurons. In Alzheimer's disease, fusion-promoting proteins, such as DLP1 (= Drp1), OPA1, Mfn1 and Mfn2, become downregulated, along with increases of the fission-promoting Fis1, changes which can be induced by APP (= amyloid precursor protein) overexpression. The peripheral mitochondrial depletion is associated with reduced $\Delta\Psi_m$ and ATP production, increases in radical formation and losses of spines at neurites (X. Wang et al., 2008, 2009). Although mitochondrial fission has been also regarded as a firewall allowing the separation of damaged organelle sections from intact parts (Jou, 2008), the steady continuation of this process leads to mitophagy, decreases in mitochondrial capacity and, ultimately, losses of neuronal connectivity. Apart from strategies of radical avoidance (Hardeland, 2005, 2009c), the stimulation of mitochondrial biogenesis seems to be major goal of antagonizing disease progression. The melatonin-induced effects via SIRT1, PGC-1α and PPARγ may indicate a chance for using melatonin in maintaining mitochondrial capacity. The accessibility of the CLK/BMAL1 complex in the circadian core oscillator by SIRT1 (Grimaldi et al., 2009; Nakahata et al., 2009) may provide another possibility of influencing the system by melatonin, in addition to the primary MT_1/MT_2-mediated effects. With regard to the lingering, atypical inflammatory processes observed in neurodegenerative diseases (Hardeland and Coto-Montes, 2010), melatonin may be also beneficial because of its

antiiflammatory properties, including the suppression of neuroinflammation by PPARγ (cf. Kiaei, 2008).

Neuroprotection after acute insults such as trauma or stroke may be another area of application of melatonin. In these cases, the concerns related to long-term treatment are not applicable. The numerous reports about reduction of infarct size in animal models (e.g., Joo et al., 1998; Sinha et al., 2001; Pei et al., 2003; Kilic et al., 2005; E.J. Lee et al., 2005; Zou et al., 2006; Koh, 2008b,c,d), also stated when melatonin was given after ischemia, should encourage to test the suitability of melatonin clinically. Compared to the dramatic consequences of stroke or brain trauma, a risk possibly resulting from a high dose of melatonin appears negligible. Moreover, melatonin may, in fact, be needed under ischemic or reperfusion conditions, if, as has been shown in studies involving pinealectomy in animals, the lack of the hormone leads to more severe neurodegeneration after experimental stroke (Manev et al., 1996; Joo et al., 1998). With regard to the age-dependent decline in melatonin secretion, this might be of particular importance in elderly stroke patients.

11. Conclusion

Melatonin's remarkable multiplicity of actions is often not sufficiently recognized by researchers, although this theme has been addressed in the past (Pandi-Perumal et al., 2006; Hardeland and Poeggeler, 2008). Its membrane receptors are found in various organs and cell types. The almost ubiquitous expression of nuclear receptors of the ROR family and other binding sites indicates a corresponding potential for additional systemic actions, which is, however, poorly understood to date. Concerning the membrane receptors, parallel signaling has now become current knowledge. However, it seems important to not reduce these actions to the alternative of G_i or G_q, but to also see the numerous downstream effects that may be cell-specifically coupled to the respective pathways (Hardeland, 2009b).

With good reason, melatonin is regarded as a chronobiotic and, also, as a chronobiological regulator molecule in the periphery. In fact, its influence on the circadian pacemaker is of utmost importance, and this causes a host of secondary effects via the circadian system. Because of the existence of parallel oscillators in both the CNS and the peripheral organs, including a variable, alternate use of core oscillator proteins, the observed effects of melatonin on phase coupling of the parallel oscillators (cf. section 3) may be of particular

significance for optimal phase coordination and functioning of organs. This line of research should be continued and may become an emerging field.

However, melatonin is not exclusively a pineal hormone. In quantitative terms, by orders of magnitude, more melatonin is found in peripheral organs than in the pineal gland and in the circulation (Huether, 1993; Bubenik, 2002). In some peripheral organs, such as the gastrointestinal tract or in the rodent Harderian gland, the amplitudes of circadian melatonin rhythms can be considerably smaller than in pineal or circulation or even be virtually absent (Hardeland et al., 2003a; Hardeland, 2005; Poeggeler et al., 2005), so that the dynamics of melatonin fluctuations as known from the circulating hormone cannot simply applied to these tissues. Although this is not an exclusive property of melatonin, its additional actions as a paracrine, autocrine and, perhaps, even intracrine regulator molecule have to be considered, too (Tan et al., 2003).

With regard to the multiplicity of functions and the diversity of physiological adaptations of organisms, one cannot expect that melatonin functions in precisely the same way in every species, not even within mammals. Already the distribution of receptors and receptor subtypes varies between organisms. Therefore, findings from laboratory animals cannot be always applied to humans. Some major differences concern seasonality, differences in reproductive physiology and circadian rhythms, and may be also found in the functionally divergent digestive tracts. Actions related to seasonality and reproductive physiology in other mammals must not be assumed to be similarly present in the human, especially with regard to the control of respective hormonal axes. Another important difference exists with regard to nocturnally and diurnally active animals, in which high circulating melatonin is either associated with neuronal and locomotor activity or inactivity. Although this distinction seems to be basic , it is, in practice, frequently disregarded. Using melatonin or melatonergic agonists for sleep promotion in nocturnally active animals is highly questionable, and observations of sedation may not be related to normal sleep (Hardeland, 2010a).

Another emerging field of potential significance concerns melatonin’s mitochondrial actions. The attenuation of electron leakage and protection against mitochondrial dysfunction has been convincingly demonstrated especially in models of sepsis and some investigations using neurotoxins such as MPTP (cf. sections 6.2 and 6.3). These results were obtained under pharmacological conditions, but appear to be of high practical value. To what extent the same or similar actions are of importance for healthy aging and neuroprotection in slowly developing neurodegenerative disorders remains to be demonstrated, although some

promising results have already been obtained. These findings also extend to mitochondrial biogenesis and signaling pathways of aging suppressor genes. A further promising area seems to emerge in the field of diabetes research, insulin resistance and metabolic syndrome, in which evidence is coming from various lines of investigation, such as receptor polymorphism (cf. section 3.4), decreases of melatonin in diabetic patients, pharmacological effects on insulin secretion and identification of signaling pathways.

The numerous findings of melatonin's beneficial effects in various models of diseases have sometimes provoked the ironic comment that "melatonin helps against everything". To be sure, this is not and cannot be the case. However, the exceptional pleiotropy of this orchestrating hormone simply implies that the administration of melatonin can readjust numerous physiological functions, in cases of deficiency, circadian dysphasing or disease. What else should one expect from a neurohormone and tissue factor with such a role?

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