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The role of serotonergic system at the interface of aggression and suicide

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Abstract

Alterations in serotonin (5-HT) neurochemistry have been implicated in the aetiology of all major neuropsychiatric disorders, ranging from schizophrenia to mood and anxiety-spectrum disorders. This review will focus on the multifaceted implications of 5-HT-ergic dysfunctions in the pathophysiology of aggressive and suicidal behaviours. After a brief overview of the anatomical distribution of the 5-HT-ergic system in the key brain areas that govern aggression and suicidal behaviours, the implication of 5-HT markers (5-HT receptors, transporter as well as synthetic and metabolic enzymes) in these conditions is discussed. In this regard, particular emphasis is placed on the integration of pharmacological and genetic evidence from animal studies with the findings of human experimental and genetic association studies.

Traditional views postulated an inverse relationship between 5-HT and aggression and suicidal behaviours; however, ample evidence has shown that this perspective may be overly simplistic, and that such pathological manifestations may reflect alterations in 5-HT homeostasis due to the interaction of genetic, environmental and gender-related factors, particularly during early critical developmental stages. The development of animal models that may capture the complexity of such interactions promises to afford a powerful tool to elucidate the pathophysiology of impulsive aggression and suicidability, and find new effective therapies for these conditions.

Keywords

Impulsive-aggressive behaviours; Suicide; 5-HT; 5-HT receptors; Tryptophan hydroxylase; 5-HT transporter; Monoamine oxidase A

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1. INTRODUCTION: CHALLENGING THE 5-HT DEFICIENCY HYPOTHESIS IN SUICIDAL BEHAVIOUR

The definition of suicidal behaviours encompasses a broad constellation of heterogeneous entities, ranging from suicidal thoughts and death wishes to attempted and completed suicide. The great diversity of suicidal behaviours reflect their comorbidity with different psychiatric disorders, including affective disorders, psychoses, alcohol abuse and/or dependence, etc. In particular, numerous studies have been shown a very robust association between multiple aspects of suicidal conducts and aggression. In keeping with this idea, multiple studies have pointed to pathological aggression and antisocial personality as major risk factors for suicide (Conner et al., 2001; Gureje et al., 2011).

The bulk of evidence points to the existence of at least two major subtypes of aggression, characterized by distinct behavioural profiles and neural underpinnings: *proactive aggression*, typically calculated and instrumental to gaining rewards; and *reactive aggression*, which is generally enacted impulsively as a stress-coping response to potentially threatening contingencies (Poulin and Boivin, 2000). Research has shown that both subtypes of aggression may influence suicidal conduct. Indeed, reactive aggression and impulsive personality characteristics have been recently highlighted as major risk factors for suicidal ideation and behaviour (Pfeffer et al, 2000; Conner et al, 2003; Dougherty et al, 2004; Hull-Blanks et al, 2004; Smith et al, 2008). Nevertheless, impulsive actions have been shown to often result in higher likelihood of self-inflicted painful and provocative experiences, but are a relatively rare cause of attempted and completed suicide, which typically requires prior planning (Baca-Garcia et al, 2005; Wyder and De Leo, 2007; Smith et al, 2008; Witte et al, 2008). Conversely, while proactive aggression has been often considered as unrelated to suicide, recent studies have shown that, in men but not women, this subtype is actually associated to suicide attempt (Connor et al, 2009), further underscoring the complex, multifaceted relationship existing between aggressive manifestations and suicidal behaviours.

The neurobiological link between aggression and suicide appears to be contributed by dysregulations in serotonin (5-hydroxytryptamine; 5-HT) neurotransmission. Findings from preclinical and clinical studies have indicated that dysregulations of 5-HT release, signaling and/or turnover may be robust correlates of violent reactivity, suicide (Higley and Linnoila, 1997; Mann et al., 2001; Stanley et al., 2000; Virkkunen et al., 1995) and impulsive-aggressive behaviours (IABs), which have been recently highlighted as critical intermediate phenotypes for suicidal conduct (Mann et al., 2009; Turecki, 2005; Zouk et al., 2007). Notably, both reactive aggression and suicide are affected by multiple biological variables that influence the regulation of 5-HTergic neurotransmission, including psychosocial stress, traumatic experiences, pathological personality traits, mental disorders, alcohol abuse and nicotine addiction (Gibb et al., 2006; Mann et al., 2009; Nock et al., 2008; Pivac et al., 2010; Turecki, 2001). For several decades the link between 5-HT and aggression was explained by a “5-HT deficiency hypothesis”, which posited a direct association of reduced CSF concentrations of 5-HT and/or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and suicidal/aggressive behaviour. Accumulating evidence, however, shows that this theory is inadequate to account for the pleiomorphic role of 5-HT in the modulation of pathological aggression and suicidal behaviours; thus, current views postulate that IABs may be the final outcome of different homeostatic imbalances of the 5-HT system.

In the following section, we will briefly describe the 5-HT innervations of the forebrain regions involved in impulsive-aggressive behaviours and suicidal behaviours, such as the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), amygdala and nucleus accumbens (Davidson et al., 2000) (Fig. 1). In addition, we will overview the preclinical and

clinical evidence on the best-characterized 5-HT-ergic targets implicated in violent and suicidal behaviours, including its receptors, its key biosynthetic enzyme tryptophan hydroxylase (TPH), its transporter (5-HTT) and the main catabolic enzyme, monoamine oxidase (MAO) A (Fig. 2).

2. THE SEROTONERGIC SYSTEM IN AGGRESSION AND SUICIDE

One of the oldest biologically active compounds, 5-HT is found across all eukaryote kingdoms, including protists, plants, fungi and animals. Given its ubiquitous presence in the body, it is not surprising that 5-HT is involved in a plethora of physiological and pathophysiological processes (Jacobs and Azmitia, 1992). Based on the distribution of 5-HT in the organism, its system can be divided into a central and a peripheral subsystem (Murphy et al., 2008a); the latter, which includes the gastrointestinal (GI) tract, lung, heart, pancreatic tissue, blood vessels and platelets (Cirillo et al., 2011; Thompson, 1971), contains the greatest concentration (90%) of 5-HT (up to 10 mg in humans). Conversely, only a relatively small amount of 5-HT is found in the central nervous system (CNS). The central 5-HT subsystem is one of the diffusively organized projection systems of the mammalian brain and it is topographically organized with respect to anatomic and functional properties (Abrams et al., 2004). The majority of the cell bodies of the 5-HT-ergic neurons are located in the raphe nuclei, within the reticular formation of the brainstem. Although the 5-HT-ergic neurons are multipolar, their size and orientation vary considerably across distinct locations; in fact, their complex axonal systems innervate virtually all CNS regions, although their distribution is particularly dense in the cerebral cortex, limbic structures, basal ganglia, many regions of the brainstem and the gray matter of the spinal cord.

Dahlstrom and Fuxe (Dahlstrom and Fuxe, 1964) clustered the 5-HT neurons in the rat brainstem into nine nuclei, termed B1 to B9 (B1 being the most caudal one) (Fig. 1). In addition, these midline clusters can be further categorized into two major groups:

- the caudal or inferior group, localized in the medulla, which contains three nuclei projecting essentially to the grey matter of the spinal cord: the nucleus raphe magnus (NRM, cell group B5), nucleus raphe obscurus (NRO, cell groups B1-B2-B3), and nucleus raphe pallidus (NRP, cell group B4);
- the rostral or superior group, situated in the pons and midbrain, which contains the dorsal raphe nucleus (DRN, cell groups B6 and B7, estimated to contain 235,000 neurons in the human brain (Baker et al., 1990) and the median raphe nucleus (MRN, cell group B8) (Fig. 1). The main target regions of these 5-HT-ergic projections are located in the forebrain and spinal cord.

2.1. Serotonergic innervation and 5-HT receptors distribution in prefrontal cortex (PFC), amygdala and nucleus accumbens

The ascending projections of 5-HT neurons are very extensive, and their collateral branches innervate numerous regions of the cerebral cortex, basal ganglia, limbic system and diencephalon. Although all the axons travel within the medial forebrain bundle in their initial tracts, many of them extend from this structure, following other fiber pathways up to their target areas.

2.1.1 The 5-HT-ergic system in the PFC—The 5-HT innervation of the cerebral cortex originates from the midbrain DRN and MRN, and spreads to every allo- and iso-cortical area, with variable fiber density across the different layers. In primates, the 5-HT-ergic innervation of the cortex is particularly dense in the granular cell layers (layer IV) (Hillegaart, 1991; Van Bockstaele et al., 1993). The rich 5-HT-ergic innervations of the

mPFC (as well as most of the frontal cortex) originates almost exclusively in the DRN (Van Bockstaele et al., 1993). The OFC is also primarily innervated by the DRN (Murphy et al.), and contains an extremely dense plexus of fine axons featuring minute varicosities. Axonal tracing studies show that DRN neurons project to the frontal cortex following well-characterized rostro-caudal and dorso-ventral topographic patterns (Waterhouse et al., 1986). The MRN innervation consists of few thick, beaded serotonergic axons with large spherical varicosities (Wilson and Molliver, 1991). The distribution of the 5-HT-ergic innervation varies according to the types of cortex and the cytoarchitectonic regions; thus, 5-HTT density in agranular/dysgranular (caudal) OFC is higher than that in granular (rostral) OFC, and there is a medial-to-lateral decreasing gradient within the agranular/dysgranular regions (Way et al., 2007). The OFC and mPFC send direct projections down to the raphe nuclei, providing a substrate for top-down control over the 5-HT-ergic forebrain pathways.

The PFC features an abundant expression of several 5-HT receptor families. In particular, members of the 5-HT₁ receptor family such as 5-HT_{1A} and 5-HT_{1B}, are localized both presynaptically (autoreceptors) on the dendrites of 5-HT fibres and postsynaptically (heteroreceptors) on pyramidal cells and different types of interneurons (Azmitia et al., 1996; Santana et al., 2004). Activation of postsynaptic 5-HT_{1A} and 5-HT_{1B} receptors in the pyramidal cells of cortex produces hyperpolarizing responses, while presynaptic 5-HT₁ receptors, reduces the amplitude of electrically evoked excitatory postsynaptic potentials (EPSPs), including both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors (Tanaka and North, 1993). Conversely, *in vivo* treatment with a low dose of 5-HT_{1A} receptor agonist 8-OH-DPAT activates these receptors on Y-amino-butyric-acid (GABA)-ergic interneurons, leading to an indirect increase of the discharge rate of pyramidal neurons in mPFC (Llado-Pelfort et al., 2012). 5-HT_{2A/2C} receptors are also densely distributed in the PFC; 5-HT_{2A} are co-expressed with 5-HT_{1A} in pyramidal cells and parvalbumin (PV)- and calbindin (Mann et al.)-containing GABA-ergic interneurons (Santana et al., 2004). 5-HT_{2A} receptors activation induces depolarization of both cell types (Aghajanian and Sanders-Bush, 2002). Electrophysiologically, in layer V pyramidal cells, synaptic events induced by 5-HT_{2A} consist largely of excitatory postsynaptic potentials (EPSPs) although inhibitory postsynaptic potentials (IPSPs) can be recorded due to GABA-ergic interneurons activation (Aghajanian and Sanders-Bush, 2002). The 5-HT_{2C} receptor is primarily expressed in the deep layers of the rat mPFC by calcium-binding proteins-positive GABAergic interneurons in rat pyramidal cells (Liu et al., 2007), while its mRNA is absent in pyramidal-shaped cells in both human and monkey PFC (Pasqualetti et al., 1999). Activation of 5-HT_{2C} receptors induces neuronal depolarization (Di Giovanni et al., 2008b; 2011). Thus, the pyramidal cell inhibition seen by stimulation of the 5-HT_{2C} receptor is likely due to excitation of PV-positive interneurons in the mPFC (Di Giovanni et al., 2011). The expression of 5-HT_{2C} receptors in the deep layers of the rat mPFC (layers V–VI), suggests that the action of 5-HT_{2C} receptor may modulate the neuronal output in these layers (Liu et al., 2007).

Several lines of evidence indicate that the other 5-HT receptors are also expressed in the neocortex. In particular, 5-HT₃ receptors are mainly localized in the superficial layers of the cortex and particularly abundant in GABAergic interneurons (Miquel et al., 2002; Morales and Bloom, 1997; Puig et al., 2004; Tecott et al., 1993). With respect to the distribution of other 5-HT receptors in the PFC, 5-HT₄ are particularly expressed in superficial layers (Varnäs et al., 2003) and mostly in pyramidal neurons (Lambe et al., 2011); conversely, 5-HT₆ are relatively sparse (Marazziti et al., 2012) and mostly localized in the interneurons (Lambe et al., 2011). Finally, 5-HT₇ receptors have also been documented in the frontal pole of the neocortex of rodents and humans (Gustafson et al., 1996; To et al., 1995). The function of these receptors in the cortex is still poorly understood.

2.1.2. The 5-HT-ergic system in the amygdala—In all species studied to date, the amygdala features an exceptionally rich 5-HT-ergic innervation, arising mainly from the DRN (Smith and Porrino, 2008); virtually all neuropeptide Y (NPY)-immunoreactive (ir) neurons receive peri-somatic serotonergic innervations (Bonn et al., 2012). 5-HT_{1A}, 5-HT_{2A} expression has been found in both pyramidal cells and inhibitory interneurons (Aznar et al., 2003; McDonald and Mascagni, 2007). 5-HT_{1B} receptors are also expressed in different amygdaloid nuclei and their expression increases in rats exposed to aggression only in the basolateral amygdala (Suzuki et al., 2010). The cellular expression of 5-HT_{2C} receptors in pyramidal neurons of the amygdala has not been studied yet, but recent evidence shows that NPY mRNA-producing interneurons co-express both 5-HT_{1A} and 5-HT_{2C} mRNAs (Bonn et al., 2012). Although these anatomical findings are difficult to reconcile with the anxiogenic activity of 5-HT_{2C} and the anxiolytic or mixed effects of 5-HT_{2A} and 5-HT_{1A} receptor activation, it is likely that these divergent roles reflect the high complexity of the circuits for emotional regulation, as well as the different patterns of 5-HT receptor neuronal distribution (Holmes, 2008). Of the other 5-HT receptors, 5-HT₃, 5-HT₄ and 5-HT₇ have been shown to be fairly abundant in amygdala (Gustafson et al., 1996; Miquel et al., 2002; Reynolds et al., 1995; Varnäs et al., 2004; Waeber et al., 1994), but their role in behavioral regulation awaits further examination.

2.1.3. The 5-HTergic system in the NAc—The NAc receives an extensive, dense innervation by 5-HT-ir axons, which are tortuous and of consistent morphology (Van Bockstaele and Pickel, 1993). Both the NAc core and shell are densely innervated by 5-HT-ergic projections from the cell bodies in the dorsal raphe; these projections differ in regional distribution, morphology, and 5-HTT expression, and can be divided into two distinct types of 5-HT axons (Brown and Molliver, 2000). Furthermore, within the NAc, the shell contains a higher density of 5-HT axons than the core (Brown and Molliver, 2000). The NAc contains several types of 5-HT receptors. 5-HT_{1A} receptors are expressed in very low levels (Aznar et al., 2003), while 5-HT_{1B} receptors are expressed on the soma of GABAergic neurons, as well as on the terminals of the axons that project to the ventral tegmental area (VTA) (Morikawa et al., 2000). Moreover, 5-HT_{1B} heteroreceptors are also distributed in presynaptic glutamate elements (Muramatsu et al., 1998). Both 5-HT_{2A} and 5-HT_{2C} receptors are expressed in moderate-to-high abundance within both the cell body and terminal regions of the NAc (Di Giovanni et al., 2011; Di Matteo et al., 2008). Investigations on the role of 5-HT_{2A/2C} receptors in the NAc have revealed a complex scenario, with opposing effects for 5-HT_{2A} and 5-HT_{2C} receptors (Robinson et al., 2008). In addition, 5-HT₄ and 5-HT₆ receptors have been shown to be highly abundant in the NAc (Bonaventure et al., 2000; Compan et al., 1996; Gerard et al., 1997; Hamon et al., 1999; Marazziti et al., 2012; Varnäs et al., 2003), although their functional roles in this area remain largely elusive.

2.2. The role of 5-HT₁ receptors in aggression and suicide

The 5-HT₁ receptor class is comprised of five receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}), which, in humans, share 40–63% overall sequence identity, and couple preferentially, although not exclusively, to Gi/o proteins to inhibit cAMP formation. While no physiological role has been found for the 5-HT_{1E} and 5-HT_{1F} receptors, the function of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors has been demonstrated in many tissues across various species (Di Giovanni et al., 2008a). Although all 5-HT receptor subtypes are localized postsynaptically on 5-HT target cells (including all key regions involved in hostile and suicidal behaviours), the 5-HT_{1A} and 5-HT_{1B} subtypes are also present in the presynaptic elements of 5-HT neurons. In the raphe nuclei, 5-HT_{1A} autoreceptors are localized on 5-HT cell bodies and dendrites; conversely, 5-HT_{1B} receptors are expressed presynaptically on 5-

HT nerve terminals, where they subserve the regulation of 5-HT release (Di Giovanni et al., 2008a).

2.2.1. 5-HT_{1A} receptors—The implication of 5-HT_{1A} receptors in aggression and suicide is supported by numerous lines of evidence. In particular, several studies have documented that 5-HT_{1A} receptor agonists attenuate offensive-aggressive (but not defensive) responses in animal models, even at doses that do not appear to cause motor impairments (Bell and Hobson, 1994; Lopez-Mendoza et al., 1998; Muehlenkamp et al., 1995; Olivier et al., 1989; Sanchez et al., 1993; White et al., 1991; Yoshimura and Ogawa, 1991). The effects of 5-HT_{1A} agonists on the modulation of aggressive responses have been shown to depend on the activation of multiple populations of 5-HT_{1A} receptors, located across several brain regions, including periaqueductal gray (Beckett et al., 1992; De Almeida and Lucion, 1997; Mann et al., 2009), raphé nuclei (da Veiga et al.,; Mos et al., 1993), medial septal area (De Almeida and Lucion, 1997) and ventral OFC (Centenaro et al., 2008). While the administration of 5-HT_{1A} receptor antagonists blocks the antiaggressive effects of 5-HT_{1A} receptor agonists (Sanchez and Hyttel, 1994) [but see also (Pruus et al., 2000) for contrasting results], these compounds elicit no significant effects on offensive, defensive and social behaviours (Bell et al., 1999; Lopez-Mendoza et al., 1998).

In general, the antiaggressive effects of systemic 5-HT_{1A} receptor agonists are likely to mostly reflect the anxiolytic effects of autoreceptor activation, in consideration of the predominance of this subpopulation of 5-HT_{1A} receptors, as well as the well-known role of anxiety and fear as primary triggers for aggressive responses. In this perspective, it is possible that the selective activation of post-synaptic 5-HT_{1A} receptors in specific forebrain areas may lead to different modulatory effects on hostile behaviours. Accordingly, rodents genetically selected for high levels of aggressive behaviour exhibit distinct alterations of expression and sensitivity of 5-HT_{1A} receptor across cortical and subcortical regions (Caramaschi et al., 2007; Korte et al., 1996; Popova et al., 2007; Popova et al., 2005).

Most studies have indicated that aggressive animals and individuals exhibit blunted behavioural and neuroendocrine responses to 5-HT_{1A} receptor agonists (Cleare and Bond, 2000; Coccaro et al., 1990; Popova et al., 2005); in addition, the levels of lifetime aggression were negatively correlated with overall levels 5-HT_{1A} receptor binding (Parsey et al., 2002). However, it should be noted that aggressive subjects were also reported to exhibit higher 5-HT_{1A} receptor binding levels in the prefrontal and anterior cingulate cortex (Witte et al., 2009), probably in view of the differential role of auto- and heteroreceptors in the regulation of aggression.

The potential involvement of 5-HT_{1A} receptors in suicidal behaviours has been studied through post-mortem brain assessments of the kinetic characteristics of these receptors in suicide victims. The results of these studies, however, are often affected by a number of experimental confounds, such as the lack of adequate controls or the comorbidity of suicide with other anxiety and mood disorders, whose pathophysiology may reflect different (and sometimes opposite) patterns of 5-HTergic alterations than those typically associated with aggression. For example, 5-HT_{1A} binding was found to be *increased* in the dorsal and ventral DRN (Stockmeier et al., 1998) and cortex (Arango et al., 1995) of suicidal subjects with major depression; conversely, another study found no alterations in binding to 5-HT_{1A} receptors in 5-HTergic terminal areas, such as frontal and occipital cortices, hippocampus and amygdala in depressed suicide victims (Lowther et al., 1997). In addition to the methodological caveats listed above, these discrepancies may also reflect different influences of gender-related factors (Anisman et al., 2008).

The potential implication of 5-HT_{1A} receptors in suicide has also been analyzed with genetic approaches. 5-HT_{1A} receptor is coded by *HTR1A*, an intronless 2.1 kb gene located at position 5q11.2-q13, whose expression is likely regulated by two transcription factors: Nuclear deformed epidermal auto regulatory factor-1 (NUDR/Deaf-1) and Hes5 (Czesak et al., 2006; Lemonde et al., 2003; Szewczyk et al., 2009) (Table 1). NUDR/Deaf-1 is a repressor at somatodendritic 5-HT_{1A} receptors (Lemonde et al., 2003), but serves as a transcription enhancer in non-5-HT-ergic neurons that express postsynaptic 5-HT_{1A} receptors. Although several single nucleotide polymorphisms (SNPs) have been found in *HTR1A* (Drago et al., 2008), the best-characterized one is C-1019G (rs6295), a functional polymorphism in the promoter region that regulates gene expression (Lemonde et al., 2003). In particular, it has been suggested that the G-1019 may modulate negatively the function NUDR/Deaf-1 on *HTR1A* (Lemonde et al., 2003), possibly leading to compensatory increases in expression of presynaptic 5-HT_{1A} but decreases in expression of the postsynaptic 5-HT_{1A} receptors in G-1019 allele carriers (Albert and Francois, 2010). Nevertheless, it should be noted that no significant association was found between C-1019G genotype and regional binding potential of two selective 5-HT_{1A} antagonists ¹¹C-WAY100635 (David et al., 2005) or ¹⁸F-MPPF (Lothe et al., 2010) using positron emission tomography (PET) in healthy subjects.

Among the many studies conducted on potential associations between *HTR1A* variants and suicide in Caucasian (Lemonde et al., 2003; Serretti et al., 2009; Serretti et al., 2007; Videtic et al., 2006; Wasserman et al., 2006) and Japanese (Nishiguchi et al., 2002; Ohtani et al., 2004) populations, only one (Lemonde et al., 2003) has documented a significant association between higher frequency of G-1019 allele and GG genotype in patients with depression and suicide victims than in non-suicidal healthy controls. The authors have posited that this association may be explained by a reduction of 5-HT-ergic activity in G carriers due to the inhibitory actions of this variant on NUDR/Deaf-1-mediated repression of 5-HT_{1A} autoreceptors (Lemonde et al., 2003). Notably, recent evidence has documented an association between homozygosity for the G variant and impulsiveness (Benko et al., 2010), a trait typically linked to reduced 5-HTergic activity.

In summary, the available evidence on the implication of 5-HT_{1A} receptors appears to converge on the idea that IABs may be associated with a reduced activity and/or expression of the autoreceptors. The functional evidence from evidence supports the possibility that, while these receptors may not play a primary causal role in impulsivity and aggression, their key involvement in anxiety regulation and in the adaptive responses to abnormalities of 5-HTergic homeostasis may highlight them as attractive therapeutic targets to reduce the impact of the conditions that trigger explosive and violent behaviours. Nevertheless, further studies will be needed to elucidate the nature of the multiple discrepancies emerging from the preclinical and clinical literature, as well as the putative roles of pre- and post-synaptic 5-HT_{1A} receptors in the regulation of violent and suicidal behaviours, also with respect to multiple comorbid entities.

2.2.2. 5-HT_{1B} receptors—In rodents, activation of 5-HT_{1B} receptors induces a marked reduction of escalated aggression in a highly specific fashion, which appears to be dissociated from alterations of exploration, locomotion and anxiety-related behaviours (Bell et al., 1995; de Almeida et al., 2001; Fish et al., 1999; Miczek et al., 1989; Mos et al., 1992; Muehlenkamp and Gutierrez, 2004; Sijbesma et al., 1990). The systemic effects of 5-HT_{1B} receptor agonists are reproduced by microinjections of these compounds in the ventral OFC and raphe nuclei, but not infralimbic prefrontal cortex (Bannai et al., 2007; Centenaro et al., 2008; De Almeida et al., 2006). The mechanism underpinning the role of 5-HT_{1B} in the modulation of reactive aggression may reflect its role on both post-synaptic heteroreceptors (Mos et al., 1992; Olivier, 2004) as well as 5-HT_{1B} autoreceptors (Clark and Neumaier,

2001; de Boer and Koolhaas, 2005), probably in relation to different facets of aggressive conduct. This pharmacological evidence is complemented by the finding of overt impulsive and antagonistic behaviours, behavioural disinhibition and increased alcohol intake (Bouwknicht et al., 2001; Crabbe et al., 1996; Risinger et al., 1999; Saudou et al., 1994) in 5-HT_{1B} knockout (KO) mice. Collectively, these preclinical results support a highly more specific and direct role of these receptors in the pathophysiology of reactive aggression, suicidal behaviour and alcoholism (Cao et al., 2011; Soyka et al., 2004).

The human 5-HT_{1B} receptor is a 390 amino acid-long peptide, encoded by *HTR1B*, an intronless gene (1.1 kb long) located on chromosome 6 (6q14.1) (Sanders et al., 2001) (Table 1). Seventy-two polymorphisms have been discovered in the coding sequence and surrounding 5' and 3' untranslated regions. Using denaturing gradient gel electrophoresis (DGGE), Sanders and colleagues (Sanders et al., 2001) characterized 12 SNPs and two insertion/deletion (INS/DEL) polymorphisms within *HTR1B* gene. The INS/DEL polymorphisms are -179INS/DEL-178 and -182INS/DEL-181. Among SNPs, G-511T and T-216G are detected in the 5' (Nothen et al., 1994; Sanders et al., 2001, 2001) and A-161T in 3' noncoding regions (Sanders et al., 2001). Four SNP are synonymous or silent mutations: C129T (Ser43Ser), G276A (Ala92Ala), C705T (Ala235Ala) and G861C (Val287Val) (Cargill et al., 1999; Lappalainen et al., 1995; Ohara et al., 1996; Sanders et al., 2001). The latter genotype is in almost complete linkage disequilibrium with C129T (Huang et al., 1999) and T317G (Sanders et al., 2001), and may be linked to functional differences. In fact, C allele carriers have been shown to display lower binding of ³H-5-HT to 5-HT_{1B} receptors (Huang et al., 1999). Other non-synonymous polymorphisms have been found to change the amino acids in second (T371G; Phe124CysT), fifth (T655C; Phe219Leu) and seventh (A1099G; Ile367Val9) transmembrane and intracellular C terminal (G1120A, Glu374Lys), His452Tyr regions of 5-HT_{1B} receptors (Sanders et al., 2001).

The association studies that investigated allelic variability at the *HTR1B* in suicide attempters and suicide completers have led to inconsistent results. No association was found between genotype or allele frequency of G861C or A-161T polymorphisms and suicide or suicide history in Caucasians of German (Rujescu et al., 2003; Stefulj et al., 2004), Croatian (Stefulj et al., 2004), Slovenian (Videtic et al., 2006) and French Canadian (Turecki et al., 2003) origin, as well as in African American (Huang et al., 1999; Huang et al., 2003), Japanese (Nishiguchi et al., 2001), or Han Chinese (Hong et al., 2004; Tsai et al., 2004) subjects. In contrast, New et al (New et al., 2001) found that Caucasian patients with personality disorder and a history of suicide attempts had higher frequency of G allele of G861C polymorphism than patients without suicide history. Another study reported an association between the T allele in the A-161 T polymorphism and suicide or impulsive-aggressive behaviour. However, no association was found with other four SNPs (T261G, C129T; G861C; A1180G) (Zouk et al., 2007). Other variants associated with microRNA-directed silencing of 5-HT_{1B} transcription were recently correlated with higher risk for conduct disorder and greater anger and hostility in young men (Conner et al., 2010; Jensen et al., 2009).

Taken together, preclinical and clinical evidence appears to concur in assigning a putative causal role for hypofunctional 5-HT_{1B} receptors in IABs. Despite these promising research leads, further studies on the selective role of pre- and post-synaptic receptors and clinical studies with larger number of subjects are needed to clarify the association between 5-HT_{1B} receptors and aggressive-impulsive endophenotypes, as well as their involvement in suicidal behaviours.

2.3. The role of 5-HT₂ receptors in aggression and suicide

5-HT₂ receptors form a closely related subgroup of G-protein-coupled receptors, functionally linked to the phosphatidylinositol hydrolysis pathway and currently classified as 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} subtypes, based on their close structural homology and pharmacology (Di Giovanni et al., 2008a). Initial studies on 5-HT₂ receptor signalling showed that these receptors activate the heterotrimeric G proteins that contain the α_q subunit, thereby stimulating phospholipase C β and leading to phosphatidyl inositol hydrolysis (Di Giovanni et al., 2011). These receptors also stimulate phospholipase A2 and the NO/cyclic GMP (cGMP) pathway. However, some differences in the signal transduction characteristics of these receptors have been reported (Di Giovanni et al., 2011; Imbrici et al., 2000). Studies focusing on the regulation of the 5-HT₂ receptor family have also indicated that 5-HT₂ receptors are non-classically regulated and show constitutive activity (Di Giovanni et al., 2008a; 2011).

2.3.1. 5-HT_{2A} receptors—Although both agonists and antagonists of 5-HT_{2A} receptors have been shown to reduce hostile behaviours (Olivier et al., 1995; Sakaue et al., 2002; White et al., 1991) [for contrasting results, see (Skrebuhhova-Malmros et al., 2000)], the interpretation of these findings is often complicated by the side effects of these compounds, such as the cognitive deficits induced by 5-HT_{2A} agonists and the sedative and hypolocomotive effects of their blockers (de Almeida et al., 2005). Little is currently known about the roles of different regions in the role of 5-HT_{2A} receptors in aggression; however, local infusion of 5-HT₂ agonists into the PAG was found to attenuate maternal aggression in rats (de Almeida et al., 2005).

In contrast with evidence on rodents, converging lines of evidence have pointed to the implication of 5-HT_{2A} receptors in aggression. For example, 5-HT_{2A} receptor expression in platelets has been correlated to the severity of hostile traits (Coccaro et al., 1997); however, this index has been shown to be unreliable as a suicidality marker (Lauterbach et al., 2006). Other studies have identified inverse correlations between 5-HT_{2A} expression and activity in the PFC and OFC with aggression. For example, low levels of 5-HT_{2A} binding potential have been found in the PFC of violent aggressive individuals (Meyer et al., 2008). In males, a negative correlation was found between 5-HT_{2A} binding in left orbital and medial frontal cortex and aggression severity (Soloff et al., 2010). In contrast with these data, prefrontal 5-HT₂ binding (as tested by ³H ketanserin) has been found to be directly correlated with lifetime aggression scores in suicidal subjects (but not in their controls) (Oquendo et al., 2006); furthermore, 5-HT_{2A} receptor availability in the OFC has been recently correlated with a state measure of impulsive aggression (Rosell et al., 2010).

Another important line of research to assess the implication of 5-HT_{2A} receptors in the pathophysiology of aggression comes from genetic association studies. The 64 kb gene coding the 5-HT_{2A} receptor (*HTR2A*) is located on the long arm of chromosome 13 at position 13q14-q21 (Sparkes et al., 1991), and is comprised of three exons and two introns, with translation length of 471 residues (NCBI Gene 2012) (Table 1). A silencer element found downstream of the second promoter element suggests that *HTR2A* contains two alternative promoters (Myers et al., 2007; Serretti et al., 2007). Although almost 300 different SNPs within *HTR2A* have been listed (Fanous et al., 2009; Serretti et al., 2007) (Table 2), only a few are well-documented (Serretti et al., 2007):

- two silent mutations in the coding region, T102C and C516T (Spurlock et al., 1998);
- nine polymorphisms are located in the promoter region (Myers et al., 2007), the best-characterized of which is the A-1438G;

- five non-synonymous polymorphisms in the extracellular N terminal (polymorphism Thr25Asn), fourth transmembrane (Ile197Val) and intracellular C terminal (Ser421Phe, Ala447Val, His452Tyr) regions (Davies et al., 2006).

The synonymous mutation T102C (rs6313) is located in the first exon of the *HTR2A*. The substitution of base thymine (T) with cytosine (C) encodes in both cases for the amino acid serine in codon 34 of the *HTR2A* and do not change the amino-acid sequence of the protein. Although T102C represents a silent polymorphism, it is positioned close to the promoter region and could be involved in gene regulation (Serretti et al., 2007) by changing the secondary structure of transcript or by prevention of gene expression by methylation of cytosine in position 102 (Vaquero-Lorenzo et al., 2008).

The G to A base change at position -1438 (rs6311) is in total linkage disequilibrium with T to C base change at silent polymorphism T102C (Kouzmenko et al., 1999; Ono et al., 2001; Spurlock et al., 1998) implying these two polymorphisms could be considered together. The functional role of SNP T102C or A-1438G is not clear. In healthy individuals, TT carriers were shown to exhibit a higher number of 5-HT_{2A}R binding sites (B_{max}) in blood platelets (Khait et al., 2005) and brain (Turecki et al., 1999), as compared with TC and CC genotype carriers. Post-mortem brain analyses have shown higher expression of *HTR2A* mRNA in temporal cortex of healthy subjects with TT genotype in some (Poleskaya and Sokolov, 2002) but not all (Bray et al., 2004) studies. In contrast, the A-1438G genotype was found to have no association with the 5-HT_{2A}R density in post-mortem samples of the lateral frontal cortex of schizophrenia patients and healthy probands (Kouzmenko et al., 1999).

The 5-HT_{2A} His452Tyr (1354 C/T; rs6314) polymorphism is positioned in exon 3 of the *HTR2A* gene. This missense mutation consists of a C-T base substitution, resulting in the change of the amino acid histidine (His) into tyrosine (Tyr) at position 452 in the C-terminal region of the 5-HT_{2A}R receptor. The most common variant is C allele (His452His), while the frequency of T allele is approximately 9% in Caucasians (Filippini et al., 2006). The His452Tyr is a functional polymorphism that regulates the 5-HT_{2A}R activity throughout the regulation of Ca²⁺ fluctuation in cells (Ozaki et al., 1997) and activation of phospholipases C and D (Hazelwood and Sanders-Bush, 2004) with 452Tyr being the less active variant.

Several studies have documented significant associations between the severity or the incidence of aggression and anger traits with specific polymorphic functional variants of the gene encoding for this receptors, including the SNPs T102C (Assal et al., 2004) and the A1438G genotypes (Berggard et al., 2003). Interesting, the latter polymorphism has been shown to influence the risk of impulsive behaviour (Nomura and Nomura, 2006) and suicidality (Giegling et al., 2006). Finally, the SNP His452Tyr has been associated with rule-breaking components of antisocial behaviour in adolescence, but not physical aggression (Burt and Mikolajewski, 2008). It should be mentioned, however, that other studies have failed to identify associations between genetic variants of 5-HT_{2A}R and aggression in suicide victims (Videtic et al., 2006) and alcoholic patients (Preuss et al., 2000). Furthermore, most of the studies failed to find a significant association between T102C or His452Tyr and suicidal ideation (Bondy et al., 2000; Fanous et al., 2009; Preuss et al., 2000) suicide attempts (Arias et al., 2001; Correa et al., 2007; Etain et al., 2004; Giegling et al., 2006; Khait et al., 2005; Oswald et al., 2003; Preuss et al., 2000; Saiz et al., 2008; Tan et al., 2002; Zalsman et al., 2005; Zhang et al., 2008), severity of suicidal behaviour (De Luca et al., 2008a), suicide (Bondy et al., 2000; Crawford et al., 2000; Faludi et al., 2000; Ono et al., 2001), suicidal behaviour (Ertugrul et al., 2004; Murphy et al., 2011) or completed suicide (Turecki et al., 1999). Few studies found significant association between T102C CC genotype and suicide in suicide attempters compared to healthy control but not psychiatric controls (Vaquero-Lorenzo et al., 2009), or in depressed patients with

suicide ideation (Du et al., 2000). In addition, C allele of the T102C was found to represent a risk factor for depressed patients to attempt suicide (Arias et al., 2001).

In summary, the involvement of 5-HT_{2A} receptor in the enactment of aggressive and impulsive responses remains poorly understood, in view of experimental limitations (such as the lack of highly selective 5-HT_{2A} receptor agonists for experimental studies) and differential roles played by these post-synaptic targets across different brain regions. It is likely that regional subpopulations of 5-HT_{2A} receptors (such as those in the PFC and OFC) may participate in the emotional and cognitive appraisal of environmental triggers for aggressive and suicidal responses, and thus help convey some of the neurochemical signals related to the ideation, planning, initiation, execution and extinction of IABs. The diverse contributions of these regional subgroups of 5-HT_{2A} receptors may explain the associations between HTR2A variants and different aspects of aggression and suicidal behaviours. However, further studies on the functional significance of the different clusters of 5-HT_{2A} receptors are needed to define the specific relevance of these targets in IABs and suicide-related traits, as well as the comorbid emotional disturbances associated with aggression.

2.3.2 5-HT_{2C} receptors—In contrast with the other major 5-HT receptors, the role of 5-HT_{2C} receptors in aggression has long remained elusive, and has been investigated only recently, thanks to the development of novel selective ligands. The few data currently available indicate that stimulation of these targets reduces aggressive responses and enhances the display of submissive behaviour (Dekeyne et al., 2012; Harvey et al., 2012; Rosenzweig-Lipson et al., 2007). These effects, however, may result from a general enhancement in social anxiety (Kantor et al., 2000). The possible implication of 5-HT_{2C} receptor in suicidal behaviours has been studied in genetic association analyses. The gene that codes this receptor (*HTR2C*) is located at position Xq24 (Milatovich et al., 1992) and consists of six exons and five introns (Xie et al., 1996) (Table 1). According to NCBI SNP Database, there are several thousand SNP within *HTR2C*. Among them, the best-characterized one is the polymorphism Cys23Ser (rs6318), consisting of two variants, C and G and resulting in the change of the amino acid Cysteine into Serine in the N-terminal region of the protein. Of note, 5-HT_{2C} is altered post-transcriptionally, and differences in pre-mRNA editing of 5-HT_{2C} receptors were found between control subjects and suicidal victims (Dracheva et al., 2008; Gurevich et al., 2002). In contrast, most studies failed to identify significant associations among polymorphisms of this receptor and suicidal attempts (Arias et al., 2001; Serretti et al., 2009; Serretti et al., 2007; Turecki et al., 2003; Zhang et al., 2008), completed suicide (Stefulj et al., 2004), the severity of suicidal behaviours (De Luca et al., 2008b; Di Giovanni et al., 2011) or suicide risk and deliberate self-harm (Pooley et al., 2003). To the best of our knowledge, only one study detected a significant association between completed suicide and the variants of the SNP rs6318, with the excess of GG genotype and allele G in suicide victims (Videtic et al., 2009).

2.4. The role of other 5-HT receptors in aggression and suicide

2.4.1. 5-HT₃ receptors—In contrast with the other 5-HT receptors, 5-HT₃ is a pentameric, ion-gated channel that mediates fast synaptic transmission. In the CNS these receptors are located in many areas relevant to emotional regulation, including the neocortex, amygdala, hippocampus, nucleus accumbens and brainstem. Of the five subunits identified to date, termed 5-HT_{3A} to 5-HT_{3E}, only the first two (A and B) have been sufficiently characterized. Several preclinical experiments have shown that 5-HT₃ receptors exert a complex influence on aggressive responses in rodents. For example, pharmacological tests suggests that these receptors participate in alcohol- and cocaine-induced aggression (Ricci et al., 2004; McKenzie-Quirk et al., 2005). In general, several 5-HT₃ antagonists have been shown to reduce aggression in a fashion dependent on the genetic background and the

baseline proclivity to engage in fighting behaviour (McKenzie-Quirk et al, 2005; Cervantes et al, 2010). Conversely, other lines of evidence indicate that these compounds are often inefficacious in affecting isolation-induced aggression (White et al, 1991; Sanchez et al, 1993). Notably, 5-HT₃ agonists have also been shown to exert anti-aggressive properties in some (Poncelet et al, 1995; Rudissaar et al, 1999), but not all studies (Ricci et al, 2005).

In contrast with the rich associations between 5-HT₃ receptors and aggression, their possible involvement in suicidal behaviour has been challenged by genetic association studies (Souza et al, 2011) and post-mortem assessments of their binding in the cortex of suicide victims (Mann et al, 1996).

2.4.2 5-HT₄, 5-HT₆ and 5-HT₇ receptors—Our current knowledge on the 5-HT receptors coupled to Gs proteins (5-HT₄, 5-HT₆ and 5-HT₇) with respect to the modulation of aggression and suicide is still rudimentary. Initial studies appear to implicate a significant up-regulation of 5-HT₄ receptors in the frontal cortex and caudate nucleus of depressed suicide victims (Rosel et al, 2004). Studies on the C267T polymorphism of the human 5-HT₆ gene have shown a possible implication of this SNP in suicide of male patients (Azenha et al, 2009; but see Okamura et al, 2005 for contrasting findings). The same SNP was not found in association with aggressive behaviour in schizophrenia patients (Tsai et al, 1999). Although the role of 5-HT₇ in aggression and suicidal behaviour remains elusive, preliminary pharmacological studies appear to temper the possibility of a direct implication of this target in the modulation of aggression (Navarro et al, 2004).

2.5. The role of TPH in aggression and suicide

The synthesis of 5-HT depends on the specific action and rate-limiting step of the enzyme l-tryptophan-5-monooxygenase (EC 1.14.16.4), commonly termed tryptophan hydroxylase (TPH). A member of the aromatic amino acid hydroxylases (AAAH) family, TPH converts tryptophan to 5-hydroxytryptophan (5-HTP) using molecular oxygen, ascorbic acid, and biopterin. The two TPH isoenzymes known to date, TPH₁ and TPH₂ (Walther et al., 2003), are respectively encoded by genes located on chromosome 11 and 12 in humans. Although the two enzymes share considerable sequence identity, their regulatory domains differ substantially (Murphy et al., 2008b). As far as their anatomical distribution is concerned, TPH₁ is expressed mostly in peripheral tissues (with the exception of the pineal gland) while TPH₂ is predominant in the CNS, and typically expressed in the raphe nuclei as well as the brain areas targeted by 5-HTergic projections (Carkaci-Salli et al., 2011) (Table 3). The Km of partially purified TPH for tryptophan is approximately 30–60 μM. Considering the brain concentrations of tryptophan, TPH is not expected to be saturated with substrate, and the formation of 5-HT in brain is predicted to rise as the brain concentration of tryptophan increases (Leathwood and Fernstrom, 1990). Unfortunately, tryptophan-rich diets produce a simultaneous increase of peripheral 5-HT, with important side effects. On the contrary, selective targeting of TPH₂ can selectively boost the synthesis of 5-HT in the brain, increasing the stored amount and evoked release of the neurotransmitter; this pharmacological strategy may be highly promising for the development of novel antidepressants (Torrente et al., 2012). The product of TPH-mediated reaction, 5-HTP, is decarboxylated into 5-HT by L-aromatic amino acid decarboxylase (AADC) (EC 4.1.1.28). Interestingly, AADC catalyzes the decarboxylation of both 5-HTP and 3,4-dihydroxyphenylalanine (DOPA) in catecholaminergic neurons. The gene encoding the enzyme is referred to as *dopa decarboxylase (DDC)*, and located on chromosome 7 in humans (Scherer et al., 1992). Almost 30 genetic mutations of *DDC* have been characterized in patients with AADC deficiency (Haavik et al., 2008).

Both clinical and preclinical evidence indicate that Impulsive-aggressive behaviours and other aggressive phenotypes are modulated by both TPH isoenzymes. In laboratory animals, acute pharmacological inhibition of TPH typically enhances inter-male aggression by reducing 5-HT levels (Vergnes et al., 1986). Because of its role as the rate-limiting enzyme of 5-HT biosynthesis, TPH expression and activity are normally affected by chronic exposure to environmental conditions that facilitate or reduce aggression, such as repeated victory or defeat (Amstislavskaya and Kudryavtseva, 1997), or by genetic selection for aggressiveness or docility (Popova et al., 1991). In line with the general variability observed across most 5-HT targets, the heterogeneity of these variations documented by different studies is likely to signify that changes in TPH may reflect compensatory adaptive mechanisms probably aimed at restoring 5-HT homeostasis. Notably, mice hypomorphic or deficient in TPH2 were recently reported to exhibit high aggression, as well as other emotional alterations (Beaulieu et al., 2008; Mosienko et al., 2012). In contrast, the G allele of the murine C1473G polymorphism was found to be associated to lower TPH2 activity in the midbrain (Kulikov et al., 2005), as well as lower aggression and reduced depression-like behaviour in the forced swim test (Kulikov et al., 2005; Osipova et al., 2009).

Most clinical studies have been focused on genetic associations between SNP variants of the *TPH1* gene and several indices of aggressive personality or prevalence of suicidal behaviour. For example, the L allele of the A218C polymorphism located in intron 7 of *TPH1* was associated with higher Buss-Durkee Hostility Inventory (BDHI) scores (New et al., 1998), and occurred with higher frequency in violent males (Nolan et al., 2000). Subsequent analyses, however, found that carriers of the U allele had a greater tendency to express their anger outwardly, and experience unprovoked anger (Manuck et al., 1999). The same genotype was found to be associated with impulsive behavioural tendencies (IBTs) (Staner et al., 2002) and anger-related traits (Rujescu et al., 2002).

The A779C polymorphism was found to be significantly related to aggressive hostility, with the highest aggression levels for the genotype AA and the lowest aggression levels for the genotype CC in volunteers (Hennig et al., 2005). Conversely, another study on Korean individuals found that CC homozygotes in the major depression disorder group scored significantly higher in terms of verbal aggression and total aggression than A carrier genotypes, regardless of sex and age (Koh et al., 2012).

Several post-mortem studies have found an increased expression of TPH2 mRNA (Bach-Mizrachi et al., 2008; Bach-Mizrachi et al., 2006; Perroud et al., 2010) and higher levels of the TPH2 protein (Boldrini et al., 2005; Bonkale et al., 2006; Underwood et al., 1999) in the brain of depressed suicide victims. Bach-Mizrachi et al. (Bach-Mizrachi et al., 2008) proposed that a higher TPH2 expression could be a response to deficient 5-HT levels in the brains of depressed suicides.

The human *TPH2* gene covers about 93.5 kb, consists of 11 exons, and exhibits hundreds of SNPs and multiple post-translational modifications (Zhang et al., 2006). Most of the detected sequence variants in *TPH2* gene are SNPs, mainly located in noncoding regions of the gene. In the association and linkage disequilibrium study on suicide victims, evaluating 10 SNPs in the *TPH2*, a significant association between SNP rs1386494 in intron 5 and suicide was found (Zill et al., 2004). A haplotype analysis showed a significant association with suicide for three haplotypes (Zill et al., 2004). This result could not be replicated by Lopez de Lara et al. (Lopez de Lara et al., 2007). These last authors (Lopez de Lara et al., 2007) investigated 14 SNPs (9 intronic, 2 exonic and 3 SNPs in the 5' upstream region of the gene). They found a significant overrepresentation of alleles T, G, G and C of the SNPs rs4448731 (*TPH2* upstream region), rs6582071 (*TPH2* upstream region), rs4641527 (intron 1), and rs1386497 (intron 8), respectively, in depressed suicide completers. No association

was found regarding functional SNP G1463A (rs120074175) in exon 11 (Lopez de Lara et al., 2007), similarly to the findings of other studies (Delorme et al., 2006; Garriock et al., 2005). Results obtained for rs6582071 were not confirmed by other studies (Mouri et al., 2009; Must et al., 2009). Most of the studies that have focused on the SNPs placed in the *TPH2* upstream region, that has an impact on protein expression, relate to rs4570625 (located in the promoter region of the gene). Yoon et al. (Yoon and Kim, 2009) showed a positive association of rs4570625 with suicide attempt and concluded that the observed increased frequency of G allele may be associated with elevated suicidal behaviour. Several other studies, however, did not confirm this association (Mouri et al., 2009; Stefulj et al., 2011; Zhou et al., 2005; Zill et al., 2007). The human *TPH2* promoter polymorphism rs11178997 is another SNP in the promoter region that has an impact on *TPH2* expression (Chen et al., 2008), but according to results obtained by several different groups (De Luca et al., 2005b; Lopez et al., 2007; Must et al., 2009; Zhou et al., 2005), it has no impact on suicide attempt and completion. SNP rs7305115, which is located at approximately 1077 bp from the 7 exon, could be involved in the control of *TPH2* mRNA expression (Lim et al., 2007) and it could also influence suicidal behaviour (Ke et al., 2006; Zhang et al., 2010). Grohmann et al. (Grohmann et al., 2010) reported a higher frequency of rs4290270 AA genotype in suicide completers and found evidence that rs4290270 affects *TPH2* alternative splicing and editing. *TPH2* SNP variants have also been recently associated with the association of affective lability, aggression and suicidal behaviour (Perez-Rodriguez et al., 2010).

Taken together, emerging evidence suggests that *TPH2* may have a direct implication on the pathophysiology of IABs and other aspects of aggression and suicidality. However, evidence in this respect is still preliminary and awaits more thorough characterization by means of selective inhibitors and brain-regional infusion studies in animal models, as well as studies on potential associations between its as-yet poorly examined SNPs, and specific endophenotypes of aggression (also in association to environmental triggers and gender-specific factors).

2.6. The role of 5-HTT in aggression and suicide

The extracellular levels of 5-HT are regulated by 5-HTT, both in central and peripheral 5-HT-ergic subsystems (Lesch et al., 1993b). The human gene for 5-HTT, termed *SLC6A4*, is located in the chromosome 17, and codes a protein comprised of 630 amino acids with 12 transmembrane domains (Lesch et al., 1993a; Mayser et al., 1991). 5-HTT is localized on the terminals of 5-HT neurons, where it ensures the recapture of 5-HT. It is the pharmacological target of selective reuptake inhibitors (SSRIs) mainly used as antidepressants (Geddes et al., 2000).

The implication of 5-HTT in the regulation of aggressive behaviour is cogently indicated by the well-documented anti-aggressive effects of SSRIs, both in psychiatric patients and healthy volunteers (Barkan et al., 2006; Blader, 2006; Bond, 2005; Carrillo et al., 2009; Coccaro et al., 1997; Reist et al., 2003; Walsh and Dinan, 2001). Similarly to the time-frame of the antidepressant effects of these agents, their antiaggressive potential is generally observed only following prolonged treatment (2–3 weeks), likely as a result of neuroplastic adaptive mechanisms resulting in receptor desensitization or synaptic remodelling. Chronic SSRI administration has been shown to restore the metabolic activity of the PFC (New et al., 2004), suggesting that the reduction in aggression induced by these compounds may depend on the integrity of prefrontal function, which is essential for impulse control as well as emotional appraisal of social contexts. In support of this possibility, Troisi and colleagues (Troisi et al., 1995) documented that, in a subset of patients affected by mental retardation and epilepsy, chronic treatment with fluoxetine led to *enhanced*, rather than reduced aggressiveness.

The evidence on the effects of SSRIs on aggression is generally paralleled by findings in rodents (Carrillo et al., 2009; Delville et al., 1996; Olivier et al., 1989; Pinna et al., 2003). However, a critical difference between the effects of SSRIs in humans and most rodent models of aggression is that, in the latter, the ameliorative effects of these compounds is already significant after acute administration, and sometimes even reversed after chronic treatment (Mitchell, 2005; Mitchell et al., 1991; Mitchell and Redfern, 1992). While the neurochemical underpinnings of these phenomena remain poorly understood, these divergent findings may reflect the intrinsic limitations of the experimental manipulations used to elicit aggressive reactions in rodents, such as social isolation (which may lead to enhanced territorial behaviour and instrumental aggression).

Notably, genetic deficiency of 5-HTT in mice results in lower levels of aggression in the resident-intruder paradigm, with longer latency to the first attack and fewer fighting encounters, but no changes in social investigations (Holmes et al., 2002). 5-HTT KO mice display lower 5-HT reuptake and higher 5-HT forebrain concentrations compared to wild-type (WT) conspecifics (Mathews et al., 2004). In addition, these mutants exhibit improved inhibitory control (Homberg et al., 2007) and are less likely to obtain a dominant status in comparison with WT mice. In this respect, it is worth noting that the levels of aggression shown by 5-HTT KO mice are greatly influenced by the opponent's behaviour, as well as the venue of the aggressive encounter (Jansen et al., 2011).

While few authors have investigated platelet 5-HTT binding as a potential biomarker of aggression with variable results (Barkan et al., 2006; Coccaro et al., 2010), recent studies have shown higher 5-HTT binding in the brainstem in impulsive and aggressive humans (Rylands et al., 2012) and rats (Kerman et al., 2011), suggesting that this index may be a valuable cross-species parameter for translational studies.

The role of 5-HTT in the modulation of aggression is also strongly supported by several genetic studies on *SLC6A4* polymorphic variants. *SLC6A4* is among the most frequently studied candidate genes for psychiatric disorders and suicidal behaviour (Lesch and Gutknecht, 2005). The best-characterized polymorphism of 5-HTT is 5-HTTLPR (5-HTT-linked promoter region), a 43-bp insertion/deletion variation within the promoter region, which is thought to regulate variations in transcriptional activity: the long variant (L allele, with 16 repeats) has higher basal activity and expression than the short variant (S allele, with 14 repeats) (Heils et al., 1996; Lesch et al., 1996). Another recently detected SNP (rs25531) consisting in an A → G substitution in the 6th motif upstream the 5-HTTLPR locus, has been shown to influence the binding for Activator Protein-2 (AP2), a transcriptional suppressor of the *5-HTT* (Kraft et al., 2005). The G allele of the rs25531 is associated with low level of 5-HTT mRNA expression, which makes it similar to allele S of the 5-HTTLPR, while the A allele is associated with high level of mRNA expression (Hu et al., 2006), which is similar to allele L of the 5-HTTLPR. Therefore, more recent studies analyze 5-HTTLPR and rs25531 as a triallelic system (Bozina et al., 2012; De Luca et al., 2008a), in which L_A allele (allele L with rs25531 A variant) is associated with high 5-HTT functionality, while the S and L_G (L allele with rs25531 G variant) alleles are linked to lower 5-HTT expression (Bozina et al., 2012; Hu et al., 2006; Zalsman et al., 2006).

Most genetic studies have pointed to an association between the S haplotype of 5-HTTLPR and the prevalence or severity of several emotional disturbances, encompassing anxiety, depression, impulsivity, hostility, anger, novelty-seeking behaviour and worse therapeutic responsiveness to SSRIs (Courtet et al., 2001; Evans et al., 1997; Gerra et al., 2005; Hallikainen et al., 1999; Lesch and Merschedorf, 2000; Silva et al., 2010). The same variant has been linked to aggressive reactivity in children and conduct disorder in adolescents (Beitchman et al., 2006; Haberstick et al., 2006; Sakai et al., 2006). In addition, the presence

of one or two S alleles of 5-HTTLPR has been associated with most suicidal behaviours, including violent suicide (Bellivier et al., 2000; Bondy et al., 2006; Campi-Azevedo et al., 2003; Li and He, 2007), violent or impulsive suicide attempts (Baca-Garcia et al., 2005; Neves et al., 2010; Neves et al., 2008) re-attempted suicidal attempts (Courtet et al., 2004), suicide attempts in abused children (Gibb et al., 2006), suicide attempts with high medical damage (Wasserman et al., 2007), and a life-time risk of suicide attempts in male subjects (Limosin et al., 2005).

Nevertheless, other studies found no significant association between 5-HTTLPR and suicidal attempts (Akar et al., 2010; Bah et al., 2008; Chen et al., 2007; De Luca et al., 2008a; De Luca et al., 2006; De Luca et al., 2005b; Gerra et al., 2004; Roy et al., 2007; Shen et al., 2004; Zalsman et al., 2006), suicide history (Malloy-Diniz et al., 2011; Yen et al., 2003), family history of suicidal behaviour (Correa et al., 2004), severity of suicidal attempt (De Luca et al., 2005b) or completed suicide in suicidal victims (Mann et al., 2000; Pungercic et al., 2006). The lack of significant association between suicide attempt or ideation and 5-HTTLPR was confirmed in the large European multicenter case-control (Mendlewicz et al., 2004), or twin sample (Coventry et al., 2010), evaluating both biallelic (5-HTTLPR) and triallelic (5-HTTLPR + rs25531) classification (Coventry et al., 2010; De Luca et al., 2006).

These discrepancies might be partially explained by the numerous methodological issues such as lack of statistical power, differences in the diagnostic criteria and inclusion of patients with different psychiatric diagnoses and healthy control subjects and different severity of suicidal behaviour (ranging from suicidal ideation to completed suicide). In addition, studies evaluating biallelic 5-HTTLPR classifications may yield different results from those using triallelic models (Bozina et al., 2012).

An alternative explanation for the numerous discrepancies in association studies may lie in the possibility that multiple biological and environmental factors may moderate the relation between 5-HTTLPR and suicide or aggression. For example, Cadoret and co-workers (Cadoret et al., 2003) have suggested that, in contrast with males, female carriers of short variants display lower levels of conduct disorder and aggressiveness. On the other hand, the LL genotype was also significantly associated with suicide attempts in women, but not in men (Gaysina et al., 2006).

Ethnic (Noskova et al., 2008) and/or socio-cultural components may also differentially influence the association of 5-HTTLPR polymorphic variations and aggression; for example, no significant correlation was identified in groups of African-Americans (Patkar et al., 2002) or Spanish suicide attempters (Baca-Garcia et al., 2004), and only a marginal association between the s variant and aggressiveness was found in Korean schizophrenia patients (Kim et al., 2009).

Additional lines of research suggest that the relevance of 5-HTTLPR with respect to aggression may be related to specific gene \times environment interactions; for example, carriers of the short-allele variant were found to exhibit greater proclivity to aggression and suicidal ideation in response to stressful events (Caspi et al., 2003; Conway et al., 2012; Verona et al., 2006). These data may suggest that 5-HTT genotype may exert a direct influence on cognitive and emotional modalities of stress-coping, which may result in increased aggression, poor impulse control and suicidal tendencies in the presence of unfavourable psychosocial contingencies. Thus, the association between the S variant and aggression may depend on the function of the prefrontal cortex, in a fashion similar to what could be postulated for the therapeutic effects of SSRIs. Accordingly, several studies have shown that, in Alzheimer's disease patients or individuals with intellectual disabilities, aggression

is associated with the long allelic variant, rather than the short one (May et al., 2010; Sukonick et al., 2001; Sweet et al., 2001).

A VNTR polymorphism has been found in intron 2 of the 5-HTT, containing 9, 10 or 12 copies of a 17-bp repeat element. It is assumed that the transcriptional regulatory activity depends on the number of repeat copies; thus, the 12-repeat allele has higher activity than the 10- and the 9-alleles (Fischerstrand et al., 1999; MacKenzie and Quinn, 1999). The association between 5-HTT VNTR intron 2 and suicide has been investigated (Bah et al., 2008; Bellivier et al., 2000; De Luca et al., 2007; De Luca et al., 2006; De Luca et al., 2005a; Gaysina et al., 2006; Ho et al., 2001; Hranilovic et al., 2003; Jernej et al., 2004; Lopez de Lara et al., 2007; Pungercic et al., 2006; Shen et al., 2004; Yen et al., 2003), yielding mixed results. Whereas one study found a protective effect of the 10-repeat allele against suicidal behaviour and an association of this variant with lower suicidal scores in schizophrenic patients (De Luca et al., 2006), another report documented that the same allele was more common among depressed suicide attempters (Lopez de Lara et al., 2007).

2.7. The role of MAO A in aggression and suicide

Monoamine oxidases (MAOs; E.C. 1.4.3.4) are flavin-adenosine-dinucleotide (FAD)-containing enzymes that catalyze the degradation of biogenic amines. The two MAO isoforms, termed MAO-A and MAO-B, differ in molecular weight (527 and 520 amino acid, respectively), inhibitor sensitivities and substrate affinities: while MAO-A prefers 5-HT, norepinephrine and epinephrine, MAO-B has a high affinity for β -phenylethylamine. In most vertebrate species, dopamine metabolism is served by both forms. Both MAOs are coded by genes located in the X chromosome, but are transferred to the outer mitochondrial membrane. The distribution patterns of MAOs in the organism are also strikingly divergent. Within the central nervous system, MAO-B is expressed at highest levels in the cell bodies of 5-HT-ergic neurons, histaminergic neurons and glial cells, while MAO-A is primarily expressed in catecholaminergic neurons (Jahng et al., 1997; Luque et al., 1995; Saura et al., 1994; Westlund et al., 1988). In the peripheral tissues, MAO-A is particularly abundant in the placenta (Egashira and Yamanaka, 1981), liver, and gastro-intestinal tract, while MAO-B is the only isoform expressed in platelets and lymphocytes (Bond and Cundall, 1977). Human MAO-A and MAO-B show 70% homology in amino acid sequence (Chen and Shih, 1998).

Multiple lines of evidence have indicated that MAO-A deficiency leads to impulsive aggression in animals and humans. The nonsense mutation of *MAOA* gene results in Brunner syndrome, a X-linked condition characterized by marked proclivity to engage in violent and antisocial behaviours (including attempted rape, murder and arson) in response to relatively minor stressors, as well as borderline mental retardation, stereotyped hand movements and sleep disturbances. These behavioural abnormalities are accompanied by high 5-HT and low urinary 5-HIAA concentrations (Brunner et al., 1993a; Brunner et al., 1993b). The symptoms of Brunner syndrome are strikingly similar to the aberrant phenotypes of MAO-A KO mice (Cases et al., 1995; Scott et al., 2008). In these animals, MAO-A deficiency leads to high levels of brain 5-HT and norepinephrine (NE), as well as a spectrum of abnormal behavioural responses, including high levels of inter-male aggression (Bortolato and Shih, 2011; Cases et al., 1995; Scott et al., 2008), social and communication deficits (Bortolato et al., 2012a), poor exploratory behaviour towards novel contexts and objects (Godar et al., 2011), reduced depression-like responses (Cases et al., 1995), greater retention of aversive memories (Dubrovina et al., 2006; Kim et al., 1997), reduced risk assessment and maladaptive stress reactivity (Godar et al., 2011; Popova et al., 2001), repeated and perseverative responses as well as low learning reversal (Bortolato et al., 2012a). While the neurobiological bases of the behavioural changes observed in MAO-A KO mice are still incompletely understood, several findings suggest that they may be

underpinned by early developmental mechanisms. In fact, chronic pharmacological MAO-A inhibition in adult rodents does not result in aggressiveness, but rather in decreased defensive behaviour (Griebel et al., 1998), enhanced exploratory activity (Steckler et al., 2001) and reduced aggression (Isel et al., 1988). Conversely, treatment with the MAO-A selective inhibitor clorgyline and other MAO inhibitors induces behavioural alterations similar to those documented in MAO-A KO mice (Mejia et al., 2002; Whitaker-Azmitia et al., 1994). Recent studies have also shown that the overt aggression exhibited by MAO-A KO mice reflects alterations in the composition and biophysical properties of NMDA glutamate receptors of the prefrontal cortex (Bortolato et al., 2012b). This finding is particularly interesting in consideration of the key role of this region in the emotional appraisal of social and environmental contexts, as well as the well-documented function of NMDA receptors in information processing.

In addition to the characterization of Brunner syndrome, abundant clinical evidence on the role of MAO-A in aggression has come from genetic studies of the functional polymorphisms of *MAOA* gene and its promoters. In particular, the *MAOA-uVNTR*, a 30-bp VNTR polymorphism located 1.2 kb upstream of the MAO-A coding sequence (Sabol et al., 1998), has been associated with different levels of transcriptional activity of the *MAOA* gene. Of the six *MAOA-uVNTR* variants characterized to date (with 2, 3, 3.5, 4 and 5 repeats) (Huang et al., 2004a), the 3-repeat and 4-repeat (4R) alleles have been respectively associated to lower and higher transcriptional efficiency and catalytic activity (Deckert et al., 1999; Denney et al., 1999; Sabol et al., 1998).

In several studies, the 3R variant has been repeatedly associated with antisocial personality, maladaptive responsiveness to stress, deficits in affective processing and lower cognitive functioning (Brummett et al., 2008; Buckholtz and Meyer-Lindenberg, 2008; Cohen et al., 2003; Contini et al., 2006; Orelan et al., 2007; Samochowiec et al., 1999; Williams et al., 2009); but see (Koller et al., 2003) for contrasting results).

Notably, the link between genotypes and aggression has been recently found to be dependent on a gene \times environment interaction, with male 3R-carriers developing aggressive behaviour only when they had a history of abuse and neglect during childhood (Caspi et al., 2002; Edwards et al., 2010; Foley et al., 2004; Frazzetto et al., 2007; Huang et al., 2004b; Kim-Cohen et al., 2006; Weder et al., 2009).

Functional brain imaging studies have shown that, in males, the 3R variant is associated with changes in the volume of OFC, as well as hyperreactivity of amygdala and hippocampus during aversive recall (Meyer-Lindenberg et al., 2006). These findings have led Buckholtz and Meyer-Lindenberg (Buckholtz and Meyer-Lindenberg, 2008) to theorize that the 3R haplotype may interfere with the ontogenesis of the prefrontal cortex and other regions of the corticolimbic circuit, facilitating the emergence of negative socio-cognitive bias. In support of this hypothesis, Eisenberger and colleagues (Eisenberger et al., 2007) showed that low-activity variants may enhance the sensitivity of negative social experiences like social rejection. Thus, it is likely that early traumatic experiences, in association with low-activity MAO-A variants, may result in persistent alterations of socio-emotional appraisal, which could facilitate the insurgence of aggressive responses, particularly in the presence of high-provocation contingencies (McDermott et al., 2009) and threat-related situations (Williams et al., 2009).

The association between *MAOA-uVNTR* variants and MAO-A brain activity has been challenged by post-mortem (Balciuniene et al., 2002) and PET studies (Fowler et al., 2007); however, self-reported aggression in men was found to be inversely correlated to the brain activity of MAO-A irrespective of the genotype (Alia-Klein et al., 2008). Collectively, these

lines of evidence suggest that polymorphic variants may confer higher or lower “baseline” MAO-A activity levels during early life stages (critical for the development of corticolimbic circuitry); however, enzymatic function may be subsequently altered by a broad set of environmental elements throughout life (Bortolato and Shih, 2011).

The majority of association studies have failed to detect a significant correlation between *MAOA-uVNTR* variants and suicidal behaviour [(De Luca et al., 2008a; De Luca et al., 2006; De Luca et al., 2005a; Hung et al., 2012; Kunugi et al., 1999; Ono et al., 2002); but see (Lung et al., 2011) for contrasting evidence]. Nevertheless, one study has indicated that the frequency of 2R and 3R alleles is significantly higher in men who had attempted suicide by violent means compared to men who had committed suicide by non-violent means (Courtet et al., 2005); this finding suggests that the endophenotype associated with low MAO-A activity may only affect the modality of execution, rather than the intention of suicidal actions.

Other functional polymorphisms, Fnu 4HI and Eco RV, have also been investigated for the association with aggression and suicide. Ho et al. (Ho et al., 2000) reported an association of the FnuHI allele 1 - which is responsible for the lower activity of MAO-A (Hotamisligil and Breakefield, 1991) - with a history of suicide attempts in female bipolar patients. Conversely, Du et al. (Du et al., 2000) found a significant association between high-activity related allele (allele 2) and suicide in depressed male suicide victims. The significance of these findings awaits further studies to be clarified.

3. CONCLUSIONS AND RESEARCH DIRECTIONS

The evidence overviewed in the previous sections, albeit fraught with inconsistent results, is in support of a pivotal role of 5-HT-ergic system (and its multiple molecular components) in the pathophysiology of IABs and other intermediate phenotypes underlying the association between reactive aggression and suicide (such as negative bias in the interpretation of ambiguous social cues, deficits in social recognition etc.). In particular, recent studies underscored that, while alterations in 5-HT-ergic homeostasis may signal different degrees of vulnerability to violent aggressiveness and suicidal behaviours, their translation into pathological conditions occurs only in the presence of other critical environmental and gender-related variables. The convergence of these factors is posited to lead to enduring abnormalities of the socio-affective scaffolding (with respect to the connectivity between prefrontal cortex, limbic areas and raphé nuclei), which may ultimately result in higher proclivity to exhibit violent outbursts and engage in self-harmful behaviours in response to psychosocial stress or other contextual triggers.

One of the most important limitations in human studies, particularly in suicide completers, lies in the intrinsic difficulty in recognizing the distinctive contribution of diverse psychological characteristics (and their neurochemical correlates) to multifaceted behavioural phenomena such as aggression and suicidality. The pursuit of this critical goal would enable to distinguish “neurobiological signatures” relevant to IABs from complex profiles of 5-HT-ergic dysfunctions that may reflect the influence of comorbid disturbances, such as depression or anxiety.

On the other hand, the translational value of most animal studies on the neurobiological relationship between aggression and suicidal conducts is greatly limited by the lack of suicidal activity in animal models, as well as the relatively poor characterization of the differences between reactive and proactive elements of aggression in experimental preparations. The refinement of ethological criteria to distinguish diverse subtypes of aggression in

The acknowledgment of the critical importance of gene \times environment \times gender interactions in aggression promises to lead to the development of new, highly isomorphic animal models of this disorder. Current translational perspectives call for a greater interface between these innovative experimental strategies and genetic association studies with more refined assessment criteria. It is expected that the combination of this perspective with complementary epigenetic, transcriptomic, proteomic and brain-imaging approaches will help develop a heuristic translational platform to identify reliable biomarkers for the early diagnosis and prevention of reactive aggression and suicidal behaviours.

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ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
5-HTT	5-HT transporter
5-HTTLPR	5-HTT-linked promoter region
AAAH	aromatic amino acid hydroxylase
AADC	L-aromatic amino acid decarboxylase
AP2	Activator Protein-2
BDHI	Buss-Durkee Hostility Inventory
CB	calbindin
CNS	central nervous system
DDC	dopa decarboxylase
DGGE	denaturing gradient gel electrophoresis
DOPA	3,4-dihydroxyphenylalanine
DRN	dorsal raphe nucleus
EPSPs	excitatory postsynaptic potentials
FAD	flavin-adenosine-dinucleotide
GI	gastrointestinal
His	histidine
IAB	Impulsive-aggressive behaviours
IBTs	Impulsive behavioural tendencies
INS/DEL	insertion/deletion
IPSP	inhibitory postsynaptic potentials
ir	immunoreactive

KO	knockout
MAO	Monoamine oxidase
mPFC	medial prefrontal cortex
MRN	median raphe nucleus
NAc	nucleus accumbens
NMDA	N-methyl-Daspartate
NPY	neuropeptide Y
NRM	nucleus raphe magnus
NRO	nucleus raphe obscurus
NRP	nucleus raphe pallidus
NUDR/Deaf-1	nuclear deformed epidermal autoregulatory factor-1
OFC	orbitofrontal cortex
PAG	periaqueductal gray
PET	positron emission tomography
PV	parvalbumin
SNPs	single nucleotide polymorphisms
SSRIs	serotonin selective reuptake blockers
TPH	tryptophan hydroxylase
Tyr	tyrosine
VNTR	variable number tandem repeat
VTA	ventral tegmental area
WT	wild-type

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Highlights

- Implications of 5-HT-ergic dysfunctions in aggression and suicide
- Review of the anatomical distribution of the 5-HT-ergic system in brain
- Review of 5-HT receptors, transporter, synthesis and metabolic enzymes
- Interaction of genetic, environmental and gender on aggression and suicide

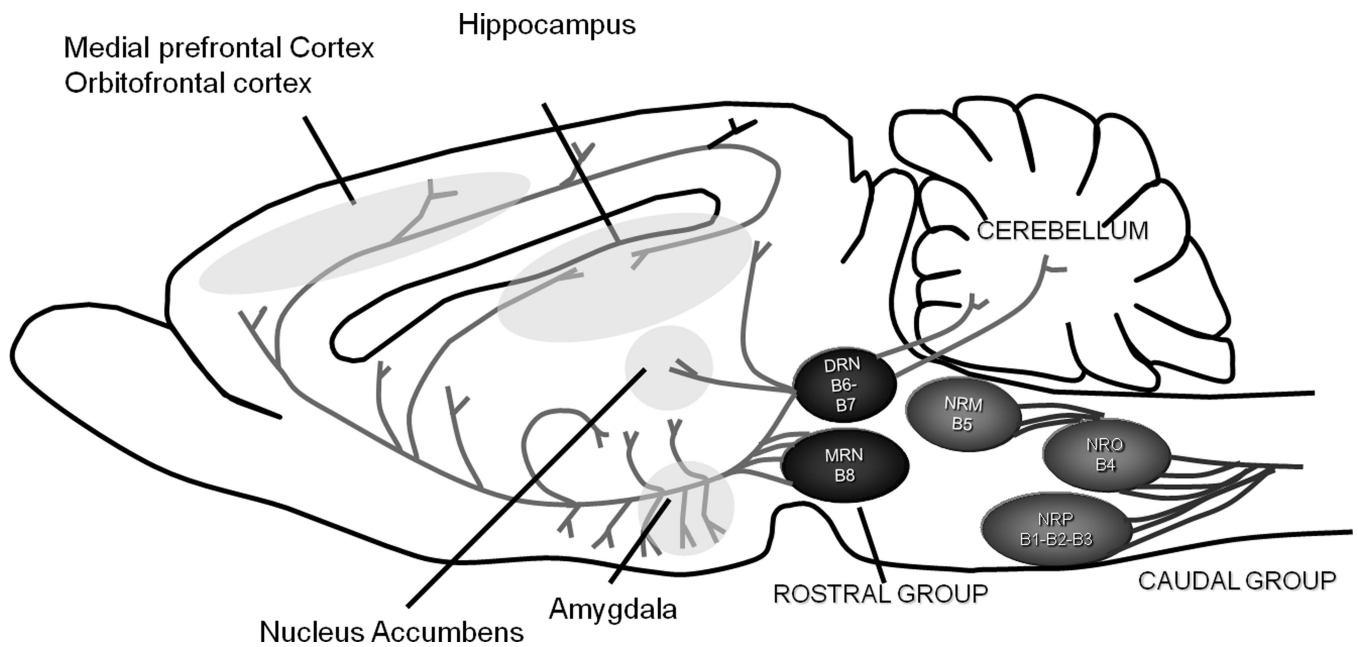
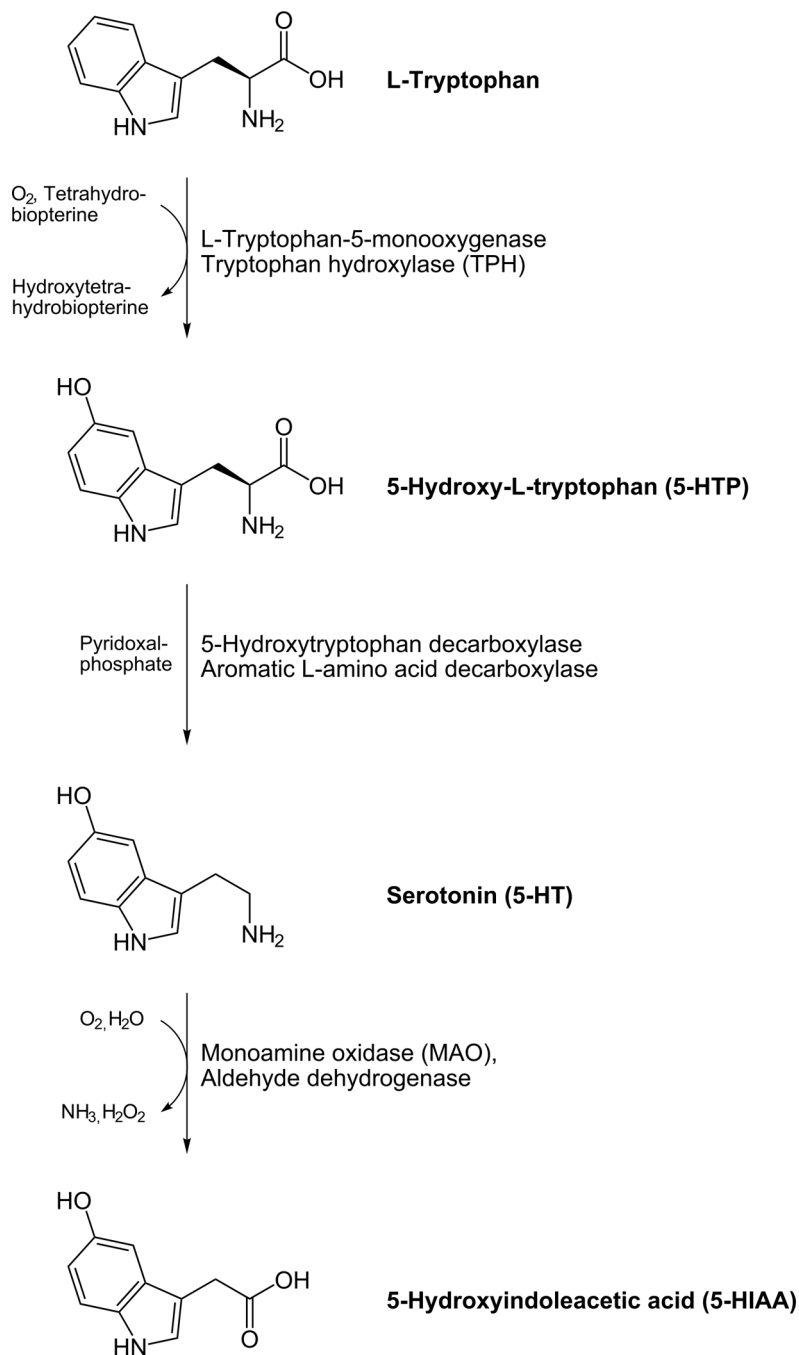


Figure 1. Midsagittal view of the rat brainstem with serotonin-immunoreactive cell body groups. The ovals encompass the two major subdivisions of the brain serotonergic system. Abbreviations: DRN, dorsal raphe nucleus; MRN, medial raphe nucleus; NRM; nucleus raphe magnus; NRO, nucleus raphe obscurus. Cell groups B1 to B9 according to the terminology of Dahlstrom and Fuxe (Dahlstrom and Fuxe, 1964). 5-HT innervations of the areas involved in aggression and suicide are depicted.

**Figure 2.**

The biosynthesis of serotonin. Tryptophan hydroxylase (TPH) catalyzes the first and rate-limiting step in the synthesis of serotonin (5-hydroxytryptamine) using tetrahydrobiopterin and dioxygen as co-substrates and producing water and dihydrobiopterin as byproducts. The second and final reaction in the biosynthesis of serotonin is catalyzed by the aromatic amino acid decarboxylase. Monoamine oxidase (MAO) catalyzes the oxidative deamination of 5-HT.

Table 1

Gene structure and regulation of key serotonergic genes in humans

	Gene Organization	Key transcription factors
5-HT _{1A}	Single exon (intronless)	Sp1, Deaf-1, Freud-1, NRSF, AP-1, CREB, MAZ (Pur-1, Zif87), NFkB, c-Jun
5-HT _{1B}	Single exon (intronless)	GR, c-Fos, c-Myc
5-HT _{2A}	3 exons	Sp1, PEA3, AP-1, STAT-3
5-HT _{2C}	4 exons	CUTL-1
5-HT _{3A}	9 exons	GR, NRSF
5-HT _{3B}	8 exons	IRF-7A, POU2F2, Meis-1, Oct-B1
5-HT ₄	At least 10 exons (multiple splice variants)	POU2F1, POU2F2, GCNF, Oct-B1
5-HT ₆	3 exons	NRSF1, NRSF2, CREB
5-HT ₇	4 exons (multiple splice variants)	Sp1, CREB
TPH ₁	11 exons	NF-Y, Sp1, TBP, TFIID
TPH ₂	11 exons	POU3F2, NRSF, GR
5-HTT	14 exons	YB-1, CTCF, GR, NFkB
MAOA	15 exons	Sp1, R1, GR, Egr-1, c-Jun, AP-1

Table 2

Polymorphisms of 5-HT2A		References
Promoter region	A-1438G, C-1420T, A-1273G, A-1182G, A-783G, G-561A, C-559T, G-400A, A-311G	Myers et al., 2007
Coding region	Thr25Asn, Ile197Val, Ser421Phe, Ala447Val, His452Tyr	Davies et al., 2006
Silent	T102C, C516T	Spurlock et al., 1998

Table 3

The two tryptophan hydroxylase isoforms, their location and corresponding physiological and pathological function of central or peripheral serotonin systems

Tryptophan hydroxylase isoform	
TPH1	TPH2
Location	
Enterochromaffin cells, pineal body	Brain
Physiological functions of serotonin	
Melatonin synthesis	Food intake and body weight
Vasoconstriction	Sleep
Haemostasis	Behavior
Immune system	Mood
Intestinal motility	Thermoregulation
Serotonin in pathology of diseases	
Migraine	Migraine
Carcinoid	Neuropsychiatric disorders
	Obesity