Journal of Alzheimer's Disease 7 (2005) 173–180
IOS Press

Discussion

Alzheimer research forum live discussion: Brain derived neurotrophic factor and Alzheimer's disease – What is the connection?[1]

Nicole C. Berchtold and Carl W. Cotman led this live discussion on 25 November 2003.

http://www.alzforum.org/res/for/journal/cotman/cotman_transcript.asp

Participants: Carl Cotman and Nicole Berchtold (*University of California, Irvine*), *Gabrielle Strobel* (*Alzheimer Research Forum*), *Qiurong Xiao* (*Memory Pharma*), *Fulya Karaman Trakya* (*University Medical Faculty, Turkey*), *Roland Pochet* (*Université Libre de Bruxelles, Belgium*), *Volkmar Lessmann* (*University of Mainz, Germany*), *Danling Wang* (*China*), *Leigh Holcomb* (*Texas A&M University, Neuropsychiatry Research Program*), *Margaret Fahnestock* (*McMaster University, Hamilton, Ontario*), *Taihung Duong* (*Indiana University School of Medicine-Terre Haute Center*), *Jorge Busciglio* (*University of California, Irvine*), *Shunwei Zhu* (*Karolinska Institutet, Huddinge Hospital University, Stockholm*).

Gabrielle Strobel: Welcome to today's chat everyone, and hello, Carl and Nicole. It is great to have you.

Roland Pochet: Are there any BDNF knockout (KO) mice?

Gabrielle Strobel: As I recall, Roland, there are and they were extensively studied with rescue experiments to establish a role of BDNF in LTP, etc. But Nicole and Carl know much more about this.

Carl and Nicole: Yes, there are BDNF KO mice; however, the homozygotes do not survive. The heterozygotes do, and a number of studies have been published. The better approach now is the TrkB KO – TrkB being a receptor for BDNF.

Margaret Fahnestock: There are also conditional BDNF KO mice.

Gabrielle Strobel: Carl and Nicole, does the field know anything about the molecular pathways controlling BDNF expression?

Volkmar Lessmann: Of course, neuronal and physical activity are *the* major regulators of BDNF expression.

Gabrielle Strobel: I know, but how do they turn on BDNF? What is the signal transduction, transcription factors?

Carl and Nicole: Regarding molecular pathways, CREB is involved in expression of exon 3, as well as another calcium-dependent response element; also CamKinase2 is involved in regulation of exon 1 BDNF transcript. Other transcription factors are the estrogen

[1] Note: The transcript has been edited for clarity and accuracy.

ISSN 1387-2877/05/$17.00

response element. There is also an AP-1 site on BDNF; however, the precise role is not really clear.

Gabrielle Strobel: Carl and Nicole, that is interesting. I just heard a talk by Jie Shen at the Society for Neuroscience meeting in New Orleans saying that presenilin conditional knockout in adult neurons reduces CREB pathway function (and BDNF expression). And CamKinase2 levels were also down in Shen's mice [1].

Carl and Nicole: That is interesting, and relevant.

Margaret Fahnestock: We know a lot about BDNF regulation from extensive work in the rat, much of it from Dr. Cotman's group. However, how some of the other rat BDNF promoters besides 1 and 3 are regulated, and whether these regulatory sites are operable in human BDNF has not been determined. It should be noted that consensus CREB sites exist upstream of the equivalent exons in the human BDNF gene, which suggests the human BDNF gene may be regulated in a manner similar to the rat gene. My laboratory implicated transcripts 1 and 3 in reduced BDNF expression in AD [2], consistent with known activity-dependent BDNF regulation in the rat.

Carl and Nicole: Yes, that is an important point, that the human BDNF appears to be similarly constructed and regulated as the rodent gene; this is particularly relevant when trying to translate exercise research to humans.

Gabrielle Strobel: How much/frequent exercise is necessary to get an effect? I believe you had data on that in New Orleans, Nicole?

Carl and Nicole: In rodents, we have found that alternating days of activity is as effective as daily activity for increasing BDNF. Also, BDNF appears to be "primed" by exercise, so that even when there is a fairly long gap between exercise sessions (two weeks), the second period of exercise, even a short one like two days, will ramp BDNF right back up again.

Gabrielle Strobel: I read that; it sounded almost like sort of an immune response where the second response is bigger and faster.

Carl and Nicole: That is an interesting analogy. It does seem like that.

Gabrielle Strobel: Are there drugs that can exploit what is known about BDNF transcriptional regulation?

Carl and Nicole: One class of drugs that can capitalize on the glutamatergic-regulation of BDNF is the ampakines, which enhance AMPA receptor function and are investigated for benefits to cognitive function. Also, the antidepressants, different classes, all seem to converge on BDNF.

Leigh Holcomb: The antidepressant effect on BDNF is very interesting, especially given the recent data from Santarelli et al. [3] that neurogenesis is required for behavioral effects of antidepressants.

Gabrielle Strobel: Leigh, in New Orleans I saw a study saying that exercise in rodents also increases serotonin receptors and transporters. Maybe that is part of the antidepressant effect, as well.

Leigh Holcomb: Thanks for that information, Gabrielle.

Carl and Nicole: Also, it is interesting that exercise itself has antidepressant action, and enhances neurogenesis. BDNF may be one of the common regulatory mechanisms driving this (we elaborated on this in our TINS paper last year [4]).

Volkmar Lessmann: If I recall it correctly, those mice that show the strongest increase of BDNF in hippocampus in response to exercise have no benefit from it in memory tasks. How would you explain this, Carl?

Carl and Nicole: We are not sure which study you refer to; however, this has not been our experience. We must note that exercise appears to enhance the rate of learning, rather than the final performance, so if the effect was assessed too late in the learning protocol, no effect will be seen.

Volkmar Lessmann: Thanks, Carl and Nicole for the information. I cannot recall the citation at the moment, but this was observed in rats selected for high motivation of voluntary wheel-running. It was discussed that maybe these rats are so much interested in performing the exercise itself, they do not care where they are going, for example, in a memory task.

Carl and Nicole: Volkmar, that is a good point. I do vaguely recall this study.

Taihung Duong: Is the increase in BDNF with exercise specific to certain brain cell types (pyramidal, granular, Purkinje)?

Shunwei Zhu: In which brain region do you see increased BDNF after exercise?

Carl and Nicole: The most robust and sustained increase is in the hippocampus; however, other regions where changes were seen early on (several days of exercise) are the cerebellum, caudal cortex region, and there is recent evidence that there is induction in the basal ganglia. Regarding cerebellar BDNF: We did this with nuclease protection assay and do not know about cellular specificity.

Danling Wang: Does BDNF also have a role in antioxidative stress?

Volkmar Lessmann: I have recently heard about transgenic mice models trying to exploit BDNF activity by means of GFP reporter under the different BDNF promoters. I am not aware of any published results by now, but wanted to know whether anybody else is using this approach.

Gabrielle Strobel: Regarding neurogenesis: Brian Christie from University of British Columbia compared neurogenesis in the dentate gyrus of running and sedentary rats and found increased BDNF and glutamate receptors in the running animals, so there is more corroboration, as presented in New Orleans.

Roland Pochet: What is known about BDNF expression in spinal cord?

Carl and Nicole: BDNF and TrkB appear to increase in the spinal cord with exercise [5].

Fulya Karaman: Do you have any knowledge about induction in basal ganglia after exercise in patients with Parkinson disease (PD)? Are these results familiar to anyone?

Carl and Nicole: That would be an autopsy study; we are not actually familiar with the details there. However, a recent study by John Marshall shows exercise enhances behavioral recovery from 6-OHDA lesion.

Gabrielle Strobel: I do not know anything about BDNF in PD, but recall studies showing some benefit of exercise. Nicole, are you in contact with AD care facilities about exercise in patients? Is this being "translated"?

Carl and Nicole: Many AD care facilities do use exercise. The recent Teri paper [6] demonstrated that exercise reduced depression and improved quality of life in mild to moderate AD. However, the underlying basic science rationale for using exercise for AD benefits is not widely known to the AD care facilities.

Fulya Karaman: What kind of exercises should we advise for patients, and how frequently?

Carl and Nicole: Most of the studies have found benefits of mild aerobic exercise, such as walking or something a little more strenuous, for 30 minutes four or more times per week. Art Kramer has published a nice meta-analysis covering this issue [7] that would probably be useful for you.

Gabrielle Strobel: I wonder, too, how much of an effect exercise can really have to stem such a serious disease. (Not that there is much competition from powerful drugs, unfortunately.) What do you think? Fair skepticism?

Margaret Fahnestock: Carl, how much is BDNF elevated by exercise? We showed that it is reduced to 25 percent of normal in AD. Could exercise counteract this?

Carl and Nicole: Margaret, exercise may, assuming that pathology does not interfere with the induction mechanisms for BDNF. BDNF protein is increased around 1.5- to twofold in the hippocampus, and this effect can be seen even after three months of exercise in rodents.

Margaret Fahnestock: I would like to be able to analyze a cohort of early AD patients for whom activity levels are known.

Qiurong Xiao: You mean that the high-level BDNF would stay for three months?

Carl and Nicole: Qiurong, yes.

Danling Wang: Three months – so if the exercise ceases, will the level of BDNF drop back soon?

Carl and Nicole: Danling, you ask about the decay rate of BDNF. BDNF drops gradually back to reach baseline after about seven days of sedentary lifestyle. A second exercise period, though (even just a few days or maybe even hours), makes BDNF rise back to the previous high levels.

Danling Wang: What is the protective function of BDNF in the pathology of AD? To reduce the neurotoxin of amyloid-β, or prevent tau phosphorylation, or protect oxidative stress and only benefit behavioral change in some sense?

Carl and Nicole: Danling, those are excellent questions and need to be investigated.

Gabrielle Strobel: To pick up Danling's point about BDNF expression and oxidative stress: A poster by Fernando Gomez-Pinilla in New Orleans said that a diet high in fats and sugars decreases BDNF, synapsin, and CREB expression in the hippocampus, and causes cognitive impairment. They modeled this in rats and said that vitamin E supplementation reversed all this.

Volkmar Lessmann: Actually, one could try 6-hydroxydopa (6-OHDA) lesions in BDNF knockout mice and look at whether exercise of the mice still improves outcome. Is anybody aware of such a study?

Carl and Nicole: Most BDNF conditional KOs focus on BDNF loss in the hippocampus, though, so this model is not really relevant to PD and 6-OHDA lesion.

Margaret Fahnestock: Some studies show cognitive impairment in BDNF heterozygotes. It would be interesting to study exercise in these mice, and to see how much the BDNF could be elevated.

Carl and Nicole: Margaret, definitely.

Volkmar Lessmann: Yes, but heterozygous BDNF knockouts survive well, although they show similar defects in plasticity to homozygous. Maybe homozygous KOs are not necessary here as well?

Margaret Fahnestock: Homozygotes are not viable, unless you go to the conditional BDNF KOs.

Shunwei Zhu: Carl, what is the relationship between BDNF and other neurotrophins (like NGF) with regard to exercise?

Carl and Nicole: Shunwei, most studies find that the most robust increases are in BDNF, though our early work shows that NGF and FGF are also induced in the hippocampus, but only early on, and are not sustained.

Shunwei Zhu: And what is the pathway of BDNF when it is expressed following external or environmental stimulations in brain regions?

Carl and Nicole: Shunwei, BDNF activates TrkB receptors, and sets off a number of intracellular signaling pathways including MAP kinase, phosphatidylinositol-3 kinase and phospholipase C?

Gabrielle Strobel: What exactly is the learning benefit from exercise? Is it known if it is applicable/relevant to human AD? Is it learning speed, or better retrieval, for example?

Carl and Nicole: Gabrielle, Colcombe and Kramer's work suggests that the main benefits are on executive function, the same aspects of cognition that decline with age. This includes multitasking, decision-making, set-shifting, etc.

Gabrielle Strobel: Thanks, that is informative. How well-established is the direct action of BDNF on synaptic plasticity? Early papers by Erin Schuman, Tobias Bonhoeffer, and Bai Lu, I believe, made waves about seven years ago, but I have not followed how well this has been substantiated with a mechanism. Because otherwise, BDNF's effect would lie more in signaling and changing gene expression. Wrong?

Carl and Nicole: BDNF has become well-accepted to be a critical modulator of plasticity, and a recent paper even listed BDNF effects on plasticity as a new class of plasticity effects along the ranks of LTP and LTD.

Margaret Fahnestock: When injected directly into rat brain, BDNF has an effect on excitability, but does not cause sprouting.

Gabrielle Strobel: To be more precise: I know BDNF is important for LTP, etc. I understand BDNF gets expressed and secreted in response to neuronal activity. But how does BDNF, in turn, act on synapses to change their electrophysiological function? That is the part I do not understand.

Volkmar Lessmann: Gabrielle, the first reports of BDNF action in excitatory synapses were by M. M. Poo

and our laboratory. In developing cultures, it is now well-established by several groups that BDNF raises release probability. It is not sure whether this effect is retained in older tissue, or whether the approaches of exogenous BDNF application simply tend to fail to make BDNF reach the synapses.

Carl and Nicole: Gabrielle, BDNF appears also to affect downstream genes, including ones specific to the synapse, that can increase synaptic efficacy, as well as increase presynaptic neurotransmitter release.

Fulya Karaman: What can be the reason for the long-lasting high levels of BDNF in rodents?

Carl and Nicole: Fulya, it could be that the daily (daylight hours) inactivity allows the next exercise session to be a sustaining and possibly new stimulus. It is an interesting question to which we do not really know the answer.

Shunwei Zhu: So does BDNF level in all brain regions increase at the same time and to the same extent?

Taihung Duong: How closely related genetically are the human BDNF and the rat BDNF?

Carl and Nicole: BDNF is extremely well-conserved across species. But the human form has more splice variants than does the rodent, and the rodent does not seem to have the polymorphisms that the human does.

Margaret Fahnestock: Human and rat BDNF are virtually identical at the protein sequence level. However, it appears that the genes are different. For example, the numbers of upstream exons and transcripts in the human brain are different than in rat.

Danling Wang: Where is BDNF synthesized, what is the secretion pathway, and how is it regulated?

Volkmar Lessmann: Danling, our recent studies using BDNF-GFP show targeting of BDNF to glutamate synapses and release upon tetanic synapse stimulation.

Carl and Nicole: Danling, BDNF is principally synthesized by glutamatergic neurons, and can be retrogradely and anterogradely transported. There are a lot of nice reviews out on this.

Jorge Busciglio: Carl and Nicole, is increased cerebral blood flow (CBF) relevant to the mechanism of exercise-induced BDNF upregulation?

Carl and Nicole: Jorge, increased CBF might be a factor, though neurotransmitter release and hormone changes induced with exercise are certainly also important.

Volkmar Lessmann: Regarding BDNF secretion: Is there anybody in the chat who was able to reproduce the fast current induced by BDNF application, as seen by Kafitz and coworkers?

Gabrielle Strobel: Does anyone know if a new generation of neurotrophic/neuroprotective drugs is under development? It has been a decade since initial clinical trials with CNTF and similar proteins failed.

Carl and Nicole: Gabrielle, we suggest a "new generation" drug for increasing neurotrophic and neuroprotective factors in the brain: It is called exercise. . .

Gabrielle Strobel: Carl and Nicole, I am with you. But that is a lifestyle change, and those are hard to implement, like getting people off burgers and fries.

Shunwei Zhu: Is there any literature describing the correlation of BDNF level in blood and brain extract with exercise?

Carl and Nicole: Shunwei, we are currently investigating this. We do not think there is anything published on blood/brain BDNF correlation.

Danling Wang: How about CSF? Could BDNF be detected there?

Taihung Duong: Dr. Fahnestock, is BDNF reduced in all regions of the brain in AD?

Margaret Fahnestock: We have only looked at basal forebrain cholinergic targets – cortex and hippocampus – and it is reduced in both areas.

Fulya Karaman: Is there any reduction in the temporal lobe, Dr. Fahnestock?

Margaret Fahnestock: We have mostly looked at frontal and parietal cortex; I do not think we looked at temporal cortex.

Carl and Nicole: BDNF and CSF – I do not think this has been reported either. I doubt there would be much BDNF in CSF, because even in tissue, it is quite low, so

it may be below the detection threshold. Also, BDNF is a sticky molecule, and might not be "free-floating" in CSF.

Leigh Holcomb: Has anyone developed an aerobics tape for AD patients?

Carl and Nicole: Leigh, there are exercise tapes for older people with disabilities, but we are not sure if there are ones specifically directed for AD.

Volkmar Lessmann: To my knowledge, AD drugs mainly influence acetylcholine function. What is the possible connection to BDNF release or function?

Gabrielle Strobel: Volkmar, good question (though memantine acts on NMDA receptors).

Margaret Fahnestock: Cholinergic agonists should increase the drive on hippocampal neurons, inducing BDNF. I do not know if this has been shown, though.

Volkmar Lessmann: But memantine is an NMDAR blocker, right? Our studies show that synaptic NMDA receptor activity is likely to enhance synaptic BDNF secretion. But, of course, such a connection is not always that straightforward.

Carl and Nicole: Ampakines are probably a better alternative to memantine. There was a recent report that memantine reduced performance in rodents. Unfortunately, ampakines are still under development. Acetylcholinesterase inhibitors should increase BDNF, but we are not familiar with any studies demonstrating this.

Gabrielle Strobel: Carl and Nicole, I believe ampakines are sort of the "cognitive enhancer" drugs developed by companies like Saegis? Who else is doing this?

Qiurong Xiao: Can you recommend a good BDNF antibody for immunoblots?

Carl and Nicole: Qiurong, there are a number of BDNF antibodies, but the problem is that they do not all show the same thing on immunoblots. Santa Cruz has a good one, as does Chemicon.

Gabrielle Strobel: Do I understand this right, that the only link between BDNF and AD specifically (as opposed to age-related neurodegeneration, in general) is its decrease in hippocampus? (Many things go wrong in the AD hippocampus.) What have I missed?

Carl and Nicole: Gabrielle, actually a more important link of BDNF to AD is the polymorphisms that increase incidence of AD. These polymorphisms interfere with normal intracellular trafficking and release of BDNF in response to stimuli.

Gabrielle Strobel: Carl and Nicole, yes, that is fascinating. I hope more groups will replicate those in their samples.

Qiurong Xiao: If the patient has the "bad" polymorphism of BDNF, does exercise help to reduce the risk for AD?

Carl and Nicole: Qiurong, excellent question. This absolutely needs to be investigated.

Danling Wang: Except for your KO mice, are there other animal models to reduce BDNF?

Margaret Fahnestock: The Ts65Dn mouse exhibits downregulation of neocortical BDNF correlating with memory impairment [8]. This mouse is a trisomy 16, equivalent to trisomy 21 in humans.

Shunwei Zhu: Because as you have said that exercise has some antidepressive effect, does BDNF stimulate endorphin production?

Carl and Nicole: No link yet has been made between BDNF and endorphins.

Gabrielle Strobel: Carl, I only just discovered you are working with a colony of aging dogs. That is interesting. Have you done any BDNF-related work with them? Or else, what are you studying with them?

Carl and Nicole: In aging dogs, we showed reduced amyloid with antioxidants and behavioral enrichment, but the BDNF work is still in progress.

Taihung Duong: Is there any correlation between BDNF levels and the age of the rat? Do younger rats have increased levels of BDNF compared to older rats?

Margaret Fahnestock: We see no correlation between age and BDNF mRNA or protein levels in human cortical samples [9,10]. Aging rats do not show decreases

in BDNF [11], and the only animal studies in which BDNF decreases are reported with age, to my knowledge, are complicated by various interventions such as drug treatments, lesions, or behavioral testing.

Fulya Karaman: Are there any studies about exercise levels in patients with AD – I mean about their exercise levels before they got the disease, or in other words, is it true to say that people who do some exercise after an age level have a lower risk for getting AD?

Carl and Nicole: Fulya, a dose-response study has not been done yet; almost all are descriptive/retrospective except for Richards's recent paper [12].

Gabrielle Strobel: Margaret, that is interesting. Does the memory impairment in that mouse resemble what is seen with AD models?

Margaret Fahnestock: I am not sure. I would have to check the paper again.

Leigh Holcomb: BDNF polymorphism has also been linked to schizophrenia.

Carl and Nicole: Leigh, yes, BDNF polymorphisms are linked to schizophrenia, obsessive-compulsive disorder, anorexia, possibly bipolar disorder. . . not Parkinson's.

Volkmar Lessmann: I think that to judge the molecular consequences of human BDNF polymorphisms, one should be cautious when testing hypotheses in mice or rats. Of course, this is the only way to make it. But when a single amino acid can change BDNF physiology as much as shown in the Egan paper [13]), how can you be sure that other species-dependent substitutions would not do similar things.

Carl and Nicole: Volkmar, that is definitely a good observation. The rat and human genomes are not identical, so it will require many studies before the relationship becomes clear.

Gabrielle Strobel: Clearly, this line of investigation bears watching. If anyone would like to make a closing statement, perhaps on a favorite question to solve next, now would be the time. Margaret and Volkmar, what to you is the most pressing open question at this point?

Margaret Fahnestock: That is a tough one. I would really like to be able to study BDNF levels in a cohort of AD patients grouped by the amount of exercise they get.

Volkmar Lessmann: I wonder whether the fast actions of BDNF, which have received so much attention recently, are physiologically relevant. I am talking about the fast currents induced by application of BDNF to single neurons [14,15]. Although this might not yet be relevant for AD, this story seems to change a lot in the BDNF field, as the authors claim.

Gabrielle Strobel: Volkmar, I do not know about this. What does it change?

Volkmar Lessmann: These authors claim that the most important cellular effects of BDNF are mediated via BDNF-induced synaptic-like excitation, rather than BDNF being a molecule working on the long range.

Margaret Fahnestock: Volkmar, how would you measure these fast currents in a living person?

Volkmar Lessmann: Margaret, no, of course not, but I am just talking about recent new concepts of BDNF action in more general terms, which nevertheless might be relevant for BDNF physiology in AD.

Gabrielle Strobel: Volkmar, that is exactly what I find confusing about BDNF.

Volkmar Lessmann: I do not feel long-range and short-term actions are confusing. Certainly both types of effects exist, but it is not easy to know which are at work in memory or AD in a specific experiment.

Margaret Fahnestock: We are currently working on trying to reliably detect BDNF protein in blood and CSF, but the operative word is "reliably."

Gabrielle Strobel: Margaret, you would need to understand transport and degradation dynamics in the different pools. This is a problem that besets the use of CSF Aβ/tau as biomarkers, as well.

Margaret Fahnestock: I know; it is not a likely avenue. But there are instances where BDNF levels from blood have been measured and conclusions drawn without thorough investigation of tissue BDNF levels. We would like to at least see if we can correlate these.

Gabrielle Strobel: Can one study BDNF in living people? Any way to image it?

Volkmar Lessmann: Regarding imaging of BDNF: We think knocking BDNF-GFP into the endogenous BDNF gene would be a fancy way to study BDNF targeting and secretion, at least in rodents.

Gabrielle Strobel: We have come to the end of our hour. Let me thank Nicole and Carl for this session, and everyone for contributing to such an informative and lively discussion.

References

[1] New Orleans: Symposium Probes Why Synapses Are Suffering (http://www.alzforum.org/new/detail.asp?id=914).

[2] D. Garzon, G. Yu and M. Fahnestock, A new brain-derived neurotrophic factor transcript and decrease in brain-derived neurotrophic factor transcripts 1, 2 and 3 in Alzheimer's disease parietal cortex, *J Neurochem* **82** (2002), 1058–1064.

[3] L. Santarelli, M. Saxe, C. Gross, A. Surget, F. Battaglia, S. Dulawa, N. Weisstaub, J. Lee, R. Duman, O. Arancio, C. Belzung and R. Hen, Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants, *Science.* **301** (2003), 805–809.

[4] C.W. Cotman and N.C. Berchtold, Exercise: a behavioral intervention to enhance brain health and plasticity, *Trends Neurosci* **25** (2002), 295–301.

[5] F. Gómez-Pinilla, Z. Ying, P. Opazo, R.R. Roy and V.R. Edgerton, Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle, *Eur J Neurosci* **13** (2001), 1078–1084.

[6] L. Teri, L.E. Gibbons, S.M. McCurry, R.G. Logsdon, D.M. Buchner, W.E. Barlow, W.A. Kukull, A.Z. LaCroix, W. McCormick and E.B. Larson, Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial, *JAMA* **290** (2003), 2015–2022.

[7] S. Colcombe and A.F. Kramer, Fitness effects on the cognitive function of older adults: a meta-analytic study, *Psychol Sci* **14** (2003), 125–130.

[8] H.A. Bimonte-Nelson, C.L. Hunter, M.E. Nelson and A.C. Granholm, Frontal cortex BDNF levels correlate with working memory in an animal model of Down syndrome, *Behav Brain Res* **139** (2003), 47–57.

[9] R.M. Holsinger, J. Schnarr, P. Henry, V.T. Castelo and M. Fahnestock, Quantitation of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease, *Brain Res Mol Brain Res* **76** (2000), 347–354.

[10] B. Michalski and M. Fahnestock, Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease, *Brain Res Mol Brain Res* **111** (2003), 148–154.

[11] P.A. Lapchak, D.M. Araujo, K.D. Beck, C.E. Finch, S.A. Johnson and F. Hefti, BDNF and trkB mRNA expression in the hippocampal formation of aging rats, *Neurobiol Aging* **14** (1993), 121–126.

[12] M. Richards, R. Hardy and M.E. Wadsworth, Does active leisure protect cognition? Evidence from a national birth cohort, *Soc Sci Med.* **56** (2003), 785–792.

[13] M.F. Egan, D.R. Weinberger and B. Lu, Schizophrenia, III: brain-derived neurotropic factor and genetic risk, *Am J Psychiatry* **160** (2003), 1242.

[14] K.W. Kafitz, C.R. Rose, H. Thoenen and A. Konnerth, Neurotrophin-evoked rapid excitation through TrkB receptors, *Nature* **401** (1999), 918–921.

[15] Y. Kovalchuk, E. Hanse, K.W. Kafitz and A. Konnerth, Postsynaptic Induction of BDNF-Mediated Long-Term Potentiation, *Science* **295** (2002), 1729–1734.