REVIEW ARTICLE

Potential pathomechanisms of ADHD based on neurometabolite changes

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a most common psychiatric disorder in the childhood. The exact pathomechanisms related to ADHD core symptoms – hyperactivity, impulsivity and inattention – are still unclear. The developmental dysfunction of cortical-striatal-thalamic-cortical network combined with the dysregulation of catecholamine neurotransmitters could be responsible for symptoms of the disorder. Magnetic resonance spectroscopy is a method which allows a partial view on molecular mechanisms of biochemical and metabolic processes in human brain by in vivo measurement. We address the hypothesis of a potential pathomechanisms associated with ADHD symptoms which is based on the studies concerning magnetic resonance spectroscopy method and ADHD.

INTRODUCTION

Attention deficit hyperactivity disorder is a psychiatric disorder, which starts to develop in childhood, affecting boys in comparison with girls in the proportion 4–9:1 (Cantwell 1996). The severity and degree of expression of its core symptoms – hyperactivity, impulsivity and inattention – varies among patients. Different diagnostic criteria of DSM-IV and ICD-10 allow a distinct interception of patients with these symptoms. Since all 3 core symptoms are required for a diagnosis of hyperkinetic disorder by ICD-10, the ADHD is diagnosed in a presence of one from two symptoms (inattention or hyperactivity/impulsivity) according to DSM-IV; thus, this diagnosis includes different subtypes (ADHD inattentive subtype, ADHD hyperactive/impulsive subtype and ADHD combined subtype).

In practice, the diagnosis of hyperkinetic disorder covers more serious symptoms and is less frequent than the diagnosis of ADHD in epidemiologic studies (Paclt 2007). From this point of view the prevalence differs in children from 3 to 12% depending on sample selection and diagnostic criteria utilised (Perlov 2006). In adulthood, the clinical image changes, hyperactivity and impulsivity have the tendency to decline more than inattention (Biedermann *et al.* 2000), while the dysfunction in working performance, disruption in social functioning, low self-estimation, higher rate of traffic accidents, higher risk of drug abuse and other psychiatric disorders are present (Spencer *et al.* 2002). The patients with diagnosed ADHD in childhood are at increased risk for personality disorders in late adolescence, specifically borderline, antisocial,

avoidant, and narcissistic personality disorders. Moreover, the subjects with persistent ADHD are at higher risk for antisocial and paranoid personality disorders but not the other personality disorders when compared to those in whom ADHD remitted (Miller *et al.* 2008). However, the risk for antisocial behaviour depends on the gender – ADHD male patients were more likely to have antisocial personality disorder associated with higher rates of current drug abuse than ADHD female patients (Cumyn *et al.* 2009).

The purpose of this review is to address a hypothesis of a potential neurobiological pathomechanisms based on the studies concerning magnetic resonance spectroscopy method in children with ADHD.

ADHD AND NEUROANATOMIC STRUCTURES

The exact mechanisms responsible for ADHD symptoms are still unclear. It seems that the developmental dysfunction of cortical-striatal-thalamic-cortical network should be responsible for ADHD symptoms (Casey *et al.* 2007). The most discussed brain areas related to ADHD are prefrontal cortex covering the frontal associative cortical area, basal ganglia (nucleus caudatus and putamen forming corpus striatum; globus pallidus, which forms nucleus lentiformis with putamen), anterior cingulate cortex (included into the cortical limbic system), telencephalon white matter and centrum semiovale.

Frontal associative cortical area receiving fibres from other cortical areas sends out conducting fibres to cortical areas participating on the preparation and realization of movements and treatment. The functions of frontal associative cortical area are various: an association (integration) associated with the signal analysis from other cortical areas; regulation of motor activity, participation on higher mental functions, forming a cognizance of personality about him/herself in relations to environs, engagement in short-term memory (Cihak 1997). Additionally, prefrontal cortex regulates organization, planning and control by attention (Solanto 2002). The frontal associative cortical area dysfunction is demonstrated as the partial motor disorders, decrease of intellectual abilities and morals, pathic state of self-satisfaction, self-consciousness, self-estimation, decreasing ability of attention, short-lasting memory (Cihak 1997).

Basal ganglia are involved in the excitatory and inhibitory processes and their relations in voluntary movements. Affecting neurons of motor cortex by circuits from cortex to basal ganglia, thalamus and back to cortex and neurons of reticular formation through substantia nigra, basal ganglia influence signals before reaching alpha-motoneurons of spinal cord. They are involved in the movements realization, performance and a preparation by affecting of the premotor cortex function (Cihak 1997).

The emotional states, sexual behaviour and solicitousnes of offsprings, transmission of emotional states into the treatment, connection of emotional states with somatomotor and visceromotor reactions, regulation influence on hypothalamic centres and participation on short-term memory are regulated by limbic cortical structures with their receiving and conducting fibres from and to all the cortical associative areas (Cihak 1997). The anterior cingulate cortex as a principal area of limbic system associated with ADHD is a crucial regulator of top-down and bottom-up information processing (Posner *et al.* 1997).

ADHD AND NEUROTRANSMITTER DYSREGULATION

Two different hypotheses concerning dysregulation of neurotransmitters are offered by contemporary state of research. The first hypothesis of catecholamine deficiency and increased level of dopamine transporters is supported by the experience in ADHD patients clinical state improvement treated by stimulants (blocking reuptake of catecholamines) (Madras *et al.* 2005; Dougherty *et al.* 1999; Krause *et al.* 2000; Carrey *et al.* 2003). On the other hand, reduction of dopamine transporters demonstrated by positron emission tomography (Volkow *et al.* 2007), 18F-DOPA hyperactivity in striatum and nucleus accumbens (Ernst *et al.* 1999) and the level of homovanilic acid in cerebrospinal fluid correlating with the severity of disorder (Castellanos *et al.* 1996) support the second hypothesis of hyperdopaminergic and hypernoradrenergic state in striatum (Fayed *et al.* 2007).

Anatomic and functional abnormalities were supported by a number of studies using radiologic examinations providing a results diversity. Computed tomography and brain magnetic resonance imaging of ADHD patients showed unspecific abnormalities in prefrontal cortex, basal ganglia and corpus callosum (Bergström, Bille, 1978), reduced right prefrontal cortex, striatum, nucleus caudatus (Castellanos *et al.* 1994; Hynd *et al.*1990; Filipek *et al.* 1997), globus pallidus (Singer *et al.* 1993), corpus callosum (Baumgartner *et al.* 1996), enlarged left basal ganglia (Castellanos *et al.* 1996), reduced volumes of the white matter in the frontal regions, including the corpus callosum and globus pallidus (Castellanos *et al.* 1996). Moreover, no structural abnormalities bilaterally in prefrontal area, lentiform nucleus, posterior cingulate and centrum semiovale were found (Fayed *et al.* 2007). A reduction of glucose metabolism in prefrontal and premotor cortical area, corpus callosum and thalamus (Zametkin *et al.* 1990); and no significant differences in glucose metabolism absolute measures between ADHD adolescents and controls were showed using positron emission tomography (PET) (Zametkin *et al.* 1993).

Radiologic measures of assumed macroscopic anatomic structures abnormalities in ADHD with the great

results diversity are unclear and discussed as a crucial position to reveal the disorder etiopathogenesis.

A partial view on molecular mechanisms in the involved anatomic areas is provided by magnetic resonance spectroscopy (MRS). MRS allows to acquire until recently inaccessible information about biochemical and metabolic processes in human brain by *in vivo* measurement using NMR (nuclear magnetic resonance) spectra of some isotopes (Starcuk *et al.* 2005).

METHOD

Magnetic resonance spectroscopy in ADHD

By measuring resonant frequency of some atomic nuclei with an unpaired number of protons or/and neutrons that have nonzero magnetic moment (^{1}H, ^{13}C, ^{31}P, ^{23}Na), MRS is lineal continuator of NMR (Bloch 1946). If the nuclei are situated in a static magnetic field and high-frequency magnetic field of suitable frequency (Larmor frequency depending on the measured nucleus and magnetic field B_0) affects a sample, the effect of nuclear magnetic resonance is induced. After switching off the high-frequency emission, the nuclei of sample act as oscillating electromagnets and induce the measurable oscillating electromagnetic waves with Larmor frequency, which fade out in time. Electrons surrounding the nucleus produce low currents by their motion, forming additional magnetic field in surroundings of nucleus. The additional magnetic field forces against the principal magnetic field B_0. Since magnetic resonance of nucleus is directly proportional to the magnetic field, the nucleus resounds at various resonance frequency by the different configuration of electrons` orbits, impacted by chemical bond of atom in a considerable measure. Thus the nucleus of the same chemical element resounds at a slightly different frequency in the different chemical bonds. Moreover, the frequency difference depends on the magnitude of magnetic field B_0. The quantity of *chemical shift* of nucleus in the concrete chemical surroundings was defined as the quotient of the frequency difference and resonance frequency of nucleus in magnetic field B_0 to avoid the recalculating of frequencies in the different B_0. Thus the chemical shift is constant for the chemical compound, independent of $B_{0,}$ expressed in units *parts per million (ppm)*. 0 ppm is assigned to tetramethylsilane (TMS) due to great significance in analytic chemistry. Chemical shift is directly proportional to the resonant frequency difference of the measured compound and TMS and inversely proportional to the frequency of TMS (Weiss & Boruta 1998; De Graaf 1998).

Typical *in vivo* spectrum of human brain tissue consists of choline, creatine, N-acetyl aspartate and lactate signals measurable by long-echo time and of myoinositol, Glx signal comprising glutamine, glutamate and gama-amino-butyric acid and lipids measurable by short-echo time. Echo time (TE) is the time interval between sample excitation and a moment of measuring the highest signal of the sample. Myoinositole and Glx spectra due to spin-spin interaction do not form the simple peaks – singlets, but rather the group of peaks – multiplets. Signal of multiplets is deformed, their amplitude is decreased and signal disappears in interference in measures by longer echo time. The signal of macromolecules, impeding the quantification of spectra with short echo time as wide and low peaks, acts in the same manner. (Bittsansky 2009). The surface under the peak, not the height of the peak, is proportional to the number of atoms giving signal in measured volume. To determine the local relative concentration of the chemical compound, the surface under the peak must be divided by measured volume (De Graaf 1998; Bittsansky 2009).

In clinical conditions, two types of spatial localization of spectra are used in magnetic resonance spectroscopy in human measures – SVS (single voxel spectroscopy) and CSI (chemical shift imaging). SVS includes two basic advantages: better regulation of magnetic field homogeneity and more unambiguous spatial localization. On the other hand, CSI allows the simultaneous acquisition of a higher number of information (De Graaf 1998).

LCModel as the program of spectra postprocessing is considered to be the best technique of the measured spectra evaluation, which eliminates the possible sources of faults by rather robust manner (Bittsansky 2009).

In the majority of MRS studies of ADHD patients, single voxel ^{1}H – magnetic resonance spectroscopy evaluated by LCModel is used.

Alterations in neuronal metabolites

The highest signal of the human adult brain is produced by acetyle groups of N-acetylaspartate (NAA). The NAA signal is almost undistinguishable from signal of N-acetylaspartylglutamate (NAAG) in standard magnetic fields 1.5 Tesla. Thought NAA is mentioned in many studies, the signal often consists of tNAA (total NAA=NAA+NAAG) (Bittsansky 2009). Despite of more than 50 years of research, the role of NAA in the brain remains controversial. NAA is present almost exclusively in neurons, axons and dendrites with the diversity of concentrations in different neuronal types (Simons *et al.* 1991). The hypotheses include NAA role (but are not limited to) as an osmolite, an acetate contributor in myelin sheath synthesis, a mitochondrial energy source, a precursor for N-acetylaspartyl glutamate, fissile product of NAAG, regulator of proteosynthesis, spare substance for acetyl-CoA and aspartate and a ligand for certain metabotropic glutamate receptors (Rigotti *et al.* 2007; Barker 2001; Moffett & Namboodiri 2006). The levels of NAA change in ways that would be expected if it served as a biomarker for neuronal viability or metabolic health. (Mason & Krystal 2006). According to the research results, NAA is a sensitive indicator of irreversible damage of neurons in warrant-

able indications (Bittsansky 2009). However, the temporary reversible decrease of NAA correlated with the temporary clinical condition impairment, NAA signal is a marker of transient damage as a consequence of NAA changes in neurons (or other cells) or a manifestation of discussed brain neuroplasticity (Rakic 2002).

The resonances of glutamate, glutamine and GABA (gamma-aminobutyric acid) overlap and form the multiplet with the summary term Glx due to J-coupling in magnetic field 1.5T. Assigning the principal excitatory (glutamate) and inhibitory (GABA) neurotransmitter function, the balance of their activities substantially determines the excitatory tone of the brain. Further, glutamate and GABA are components of aminoacid metabolic cycles including cellular energy metabolism (Mason & Krystal 2006). Due to the neuronal – astrocyte high energy demanding interaction in glutamate "recycling" metabolism, alteration of its level does not have to necessarily imply abnormal neurotransmission, but may signify an impaired glial function (Magistretti *et al.* 1999; Sibson *et al.* 1998).

Myoinositol (mI) as a pentose sugar is a component of inositol phospholipids metabolism integrated in biomembranes. Furthermore myoinositole is an osmotic regulator and a partner in signalling pathways involving monophosphates and protein kinase C (Pouwels & Frahm 1998; Isaacks *et al.* 1994; Manji *et al.*1996). Due to its absence in neuronal cells, myoinositol is considered as a marker of glia (Brand *et al.* 1993).

The resonances of choline containing compounds, involving signals of glycerophosphocholine (GPC), phosphocholine (PC) and small amount of choline (Cho), are undistinguishable in "*in vivo*" clinical measures of magnetic fields 1.5 T and manifest as a peak deformation of tCho in (total choline) (Barker *et al.* 1994). These metabolites are involved in metabolism of membrane lipids phosphatidylcholine and sfingomyeline, which are continuously degraded and resynthetized. Thus the peak is generally believed to be related to membrane metabolism and provides some indication of membrane turnover, either increased membrane degradation or synthesis (Mason & Krystal 2006).

MPL (membrane phospholipids) precursor (phosphomonoesters (PMEs), phosphoethanolamine and phosphocholine) levels and MPL breakdown products (phosphodiesters (PDEs), glycerophosphoethanolamine and glycerophosphocholine) levels measurable by phosphorus 31 magnetic resonance spectroscopy (^{31}P MRS) provide the information about synthesis and degradation activity of MPLs (i.e. the density of dendrites and synaptic connections) (Vance 1988)

The resonance of tCre (total creatine) is a compound peak of creatine and phosphocreatine with the important role as an energy reserve (Bittsansky 2009). The concentration of tCre changes less in pathological conditions, thus it is mentioned as an appropriate standard to compare the modifications of other peaks. However, the concentration of tCre is sensitive to alterations of brain energy metabolism and decreases with the reduction of metabolism (Burtscher & Holtas 2001; Castillo *et al.* 1996).

DISCUSSION

We address a hypothesis of the assumed mechanisms associated with ADHD symptoms which is based on MRS studies of ADHD patients (Table 1). The 18 studies were strictly selected from information source Pubmed/Medline and assignment of the keywords: "ADHD, magnetic resonance spectroscopy, neurometabolites". Moreover, the limitations of these studies include relatively small samples of probands, wide age range, nonuniform used methodology in various studies.

Children with ADHD – combined subtype had lower NAA/Cr ratios than children with ADD and healthy children in lenticular nucleus (Sun *et al.* 2004) and lower NAA/Cr than healthy children both before and after one dose of methylphenidate (10 mg) in the globus pallidus (Jin *et al.* 2001).

We hypothesized that the NAA decreased level in ADHD children in basal ganglia could represent lower metabolic activity or decreased neuronal density. The basal ganglia are involved in the excitatory/inhibitory processes in voluntary movements including an effect of the motor cortex control. The decreased metabolic activity of basal ganglia might be responsible for the hyperactivity symptom. The NAA increased level in prefrontal cortex (Fayed *et al.* 2007; Courvoisie *et al.* 2004) might represent the compensatory increased metabolism based on "feedback mechanisms" in this area, which might introduce a neurobiological response to the dysfunction of basal ganglia through the cortical – striatal pathway. Thus the hypermetabolism might cause the dysfunction in the motor activity preparing, pursuance and short-lasting memory. Contrary, ADHD adults had decreased NAA levels in the prefrontal cortex than ADD patients and healthy controls (Hesslinger *et al.* 2001). The proposed pathomechanism of this finding might involve the lower metabolism or decreased density of neurons due to the long lasting of hypermetabolism in this area. This condition could also explain the fact that the inattention symptom has lower tendency to subside than hyperactivity and impulsivity (Biederman *et al.* 2000).

In neurons, NAA combined with glutamate forms NAAG (N-acety-aspartyl-glutamate), which blocks the presynaptic Ca^{2+} channels by affecting of presynaptic metabotropic glutamate receptors type 3. These mechanisms lead to decreasing of glutamate release (Bittsansky 2009). The NAA decrease in the ADHD adult patients thus the lower level of NAAG due to the deficiency of substrate, might lead to an increased activity of glutamatergic system resulting in mesocortical dopaminergic system activation. It leads to increased activation of GABA-ergic limbic system pathways and

Tab. 1. Neurometabolite changes in ADHD.

	Number of subjects	Age (yr)	Neurometabolite changes in ADHD	Brain region of significant changes
Stanley *et al.* (2006)	10 ADHD 15 controls	7.0–11.9 (range)	↓PME	BG, PFC bilaterally
			↓fPME/fPDE	BG (PFC)
Stanley *et al.* (2008)	31 ADHD 36 controls	6.1–10 6.1–10.4 (range)	↓fPME	BG bilaterally
			↑fPME, fPME/fPDE	Inferior parietal region
Perlov *et al.* (2007)	28 ADHD 28 controls	32.4±10.4 30.5±7.7 (mean±SD)	↓Glx/Cr	Right anterior cingulate cortex
Carrey *et al.* (2007)	13 ADHD t-naive and after 8w of t 10 controls	6–11 (range)	↑Glx, Cr (ADHD vs.controls) ↓Cr after stimulant t	Left striatum
Carrey *et al.* (2003)	14 ADHD t-free and after 13w of t	7–13 (range)	↓Glx/Cr after t (MPH, ATX, DX)	Left striatum
Sun *et al.* (2005)	10 ADHD-I 10 ADHD-C 10 controls	10–14 (range)	↓NAA/Cr in ADHD-C vs. ADHD-I and controls	Right lentiform nucleus
			↓NAA/Cr in ADHD-C vs. controls (ADHD-I)	Left lentiform nucleus
Fayed, Modrego (2005)	8 ADHD 21 autistic children 12 controls	9.1 7.3 7.7 (mean)	↑NAA/Cr in ADHD vs. autistic children and controls	Left centrum semiovale
Courvoisie *et al.* (2004)	8 ADHD-H 8 controls	6–12 (range)	↑NAA/Cr, Glu/Cr, Cho/Cr	Right frontal lobe
			↑Glu/Cr	Left frontal lobe
Yeo *et al.* (2003)	23 ADHD 24 controls	7–20 (range)	No differences in neurometabolites, ↑NAA and Cr predicted worse performance in CPT in ADHD, right DL volume correlated positively with the concentration of NAA, Cr, Cho in ADHD	Right, left dorsolateral frontal area
MacMaster *et al.* (2003)	9 ADHD 9 controls	7–16 (range)	↑Glx/Cr (positively correlated with the age of ADHD symptoms onset)	Right prefrontal cortex
			↑Glx/Cr (trend to significance)	Left striatum
Jin *et al.* (2001)	12 ADHD before and after one MPH dose 10 controls	10–16 11–15 (range)	↓NAA/Cr both before and after one MPH dose (5%↑NAA/Cr)	Striatum bilaterally
			↑Cho/Cr	Right striatum
Colla *et al.* (2008)	15 ADHD 10 controls	36.1±7.6 33.2±6.9 (mean±SD)	↑Cho CPT-IP was highly correlated to ↑choline signal	Anterior cingulate cortex
Ferreira *et al.* (2009)	10 ADHD-C 9 ADHD-I 12 controls	8–24 (range)	↓mI in ADHD vs.controls	Right VMPFC
			↑Cho/Cr in ADHD-C vs.ADHD-I	Left thalamus-pulvinar
			↑Glx/Cr in ADHD-C vs.ADHD-I and controls	Left putamen
Kronenberg *et al.* (2008)	7 ADHD t-naive before and after 5–6 w of MPH t	25–44 (range)	↑NAA, ↓ChoCC following MPH t	Anterior cingulate cortex
Fayed *et al.* (2007)	22 ADHD 8 controls	6–16 4–12 (range)	↑NAA/Cr	Right prefrontal region Left centrum semiovale
Moore *et al.* (2006)	15 ADHD 8 ADHD+BD 7 controls	6–17 (range)	↑Glx/Ino in ADHD vs. ADHD+BD and controls ↑Glx/Cr in ADHD vs. ADHD+BD (controls)	Anterior cingulate cortex
Carrey *et al.* (2002)	2 ADHD before and after MPH t (14, 16w)	9.8; 7.4	↓Glx/Cr in all subjects after t	Left striatum
	2 ADHD before and after ATX t (16, 18w)	8.2; 11.8	↓Glx/Cr in subjects treated by ATX	Right prefrontal cortex
Hesslinger *et al.* (2001)	5 ADHD 5 ADD 5 controls	27.8±3.03 27.2±3.27 27.0±2.92 (mean±SD)	↓NAA in ADHD vs. ADD and controls	Left dorsolateral prefrontal cortex

PFC - prefrontal cortex, BG - basal ganglia, t - treatment, w - weeks, MPH - methylphenidate, ATX - atomoxetine, DX - dexedrine, ADHD-I - ADHD inattentive type, ADHD-C - ADHD combined type, ADHD-H - ADHD hyperactive Type, ADD - attention deficit disorder (= ADHD-I), CPT-IP - The continuous performance test, identical pairs version, VMPFC - ventromedial prefrontal cortex, BD - bipolar disorder

to the increased inhibition of dopaminergic pathways to anterior cingulate cortex (Perlov *et al.* 2007). These mechanisms could explain decreased levels of Glx in anterior cingulate cortex found in ADHD adult patients due to the co-releasing of dopamine and glutamate (Perlov 2006). Thus the decreased metabolism of prefrontal cortex leading to decreased glutamate activity in limbic system might explain the changes in the clinical state in the adulthood and higher risk of the personality disorders, as limbic system participates in the functions mentioned above. This hypothesis is in the accordance with the studies (van Elst *et al.* 2001). NAA levels, potentionally reflecting the neuronal metabolic activity, were increased after 5-6 week`s metylphenidate therapy leading to improved clinical state (Kronenberg et al. 2007). In frontal area, increased levels of Glx resonances were found (Courvoisie *et al.* 2004; MacMaster *et al.* 2003), which cover signals from glutamate, glutamine and GABA. Thus it may predictate the complicated interpretation of the Glx resonances. However, the glutamate seems to be responsible for increased levels of this signal in the case of assumed frontal area hypermetabolism.

Glutamate as excitatory aminoacid neurotransmitter causes the decreasing of neuronal membrane resistance leading to the depolarization state and action potential threshold decline; thus, the neuronal pathways are easily stimulated. This facilitation of neuronal excitation may be the reason of the increased metabolism (Fayed *et al.* 2007; Courvoisie *et al.* 2004). As mentioned above, this condition might be the compensatory effort of brain cortex to increase the dopamine deficit in basal ganglia (glutamate increases the dopamine release). Then an inadequate regulation – "gating" of sensory information in the striatum might allow cortical input to capture and drive a self – sustaining loop as hypothesized by MacMaster, 2003. This would be in the accordance with other studies related to the hypermetabolism in the prefrontal cortex, thus the findings of increased levels of NAA (Courvoisie *et al.* 2004; Fayed *et al.* 2007), as NAA levels have been correlated with mitochondrial energy metabolism (Clark 1999) and glutamate (Courvoisie *et al.* 2004; MacMaster *et al.* 2003) as a component of amino acid metabolic cycles including cellular energy metabolism (Mason & Krystal 2006). The hyperactivation of cortical – striatal neuronal pathways could lead to the increased levels of glutamate in basal ganglia (Carrey *et al.* 2007; MacMaster *et al.* 2003; Ferreira *et al.* 2009) and glutamate decrease in basal ganglia after 13/14–18 weeks lasting therapy (Carrey *et al.* 2003; Carrey *et al.* 2002).

Higher levels of choline resonances were found in basal ganglia in both – adults and children with ADHD (Ferreira *et al.* 2009; Jin *et al.* 2001); particularly in the frontal lobe in ADHD children (Courvoisie *et al.* 2004) and in anterior cingulate cortex in ADHD adults (Colla *et al.* 2007). The hypermetabolism and increased levels of glutamate with its neurotoxic effect might explain the increased levels of choline as an indicator of membrane turnover. This would indicate an effect of 5–6 week's therapy resulting in the decreased choline levels in anterior cingulate cortex of adult ADHD patients (Kronenberg *et al.* 2007).

PME (phosphomonoesters) represents the metabolite participating in the neuronal membrane building. PDE (phosphodiesters) represents the product of membrane degradation. The PME and PME/PDE level were decreased in the prefrontal cortex and basal ganglia in ADHD children (Stanley *et al.* 2006; 2008). These findings are in the accordance with our hypothesis related to the prefrontal area increased activity leading to the hyperexcitatory condition with the glutamate neurotoxicity. As Stanley *et al.* (2006) propose, the reduction in the equilibrium of MPL turnover suggest decreased synthesis of MPLs and reduced membrane mass or a potential reduction in the dendrites proliferation and synaptic connections. This might be in the accordance with the increased glutamate in these areas due to its neurotoxic effect, thus the increased levels of choline. Another interesting findings were discovered in the inferior parietal region, which plays an important role in visual sustained attention and set shifting. This area has the function of the secondary sensitive cortical area and acts as the kinesthetic centre as well (Cihak 1997). The higher levels of PME were found in ADHD children and a stronger negative association between free-PME levels and age was observed in the healthy children compared with ADHD group (Stanley *et al.* 2008). The increased membrane synthesis could represent the compensatory effort of this brain area to balance the disturbances in the cortical-striatal-thalamic-cortical pathway in the control of attention and movements.

CONCLUSION

Our hypothesis proposes basal ganglia dysfunction associated with the dopamine/glutamate dysregulation and consequent compensatory prefrontal area increased activity leading to the hyperexcitatory condition with the glutamate neurotoxicity. The decreased metabolism/neuronal density in the prefrontal area might lead to glutamatergic and dopaminergic pathways disinhibition with the decreased dopamine level in the limbic system in adult age. These potential mechanisms could be included in clinical state conversion.

REFERENCES

1 Barker PB, Breiter SN, Soher BJ, Chatham JC, Forder JR, Samphilipo MA, *et al.* (1994). Quantitative proton spectroscopy of canine brain: in vivo and in vitro correlations. Magn Reson Med. **32**: 157–63.
2 Barker PB (2001). N-acetyl-aspartate – A neuronal marker? Ann Neurol. **49**: 423–424.

3 Baumgartner TL, Singer HS, Dencla MB, Rubin MA, Abrams MT, Colli MJ, *et al.* (1996). Corpus callosum morphology in children with Tourette`s syndrome and attention deficit hyperactivity disorder. Neurology. **4**: 477–482.
4 Bergstrom K, Bille B (1978). Computed tomography of the brain in children with minimal brain damage. A preliminary study of 46 children. Neuropediatrie. **9**: 378–384.
5 Biederman J, Mick E, Faraone SV (2000). Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. **157**: 816–8.
6 Bittsansky M (2009). O dôležitých mozgových metabolitoch viditeľných protónovou magnetickou rezonančnou spektroskopiou a ich správnej kvantifikácii v medicínskej diagnostike (Important brain metabolites distinguishable by proton magnetic resonance spectroscopy and their correct quantification in medical dianostics) (dissertation). Martin: Jessenius faculty of medicine, Commenius University in Bratislava
7 Bloch F (1946). Nuclear induction. Physical review. **70**: 460–474.
8 Brand A, Richter-Landsberg C, Leibfritz D (1993). Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. Dev Neurosci. **15**: 289–98.
9 Burtscher IM, Holtas S (2001). Proton MR spectroscopy in clinical routine. J Magn Reson Imaging. **13**: 560–567.
10 Cantwell DP (1996). Attention deficit disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry. **35**: 978–87.
11 Carrey N, MacMaster FP, Sparkes SJ, Khan SC, Kusumakar V (2002).Glutamatergic changes with treatment in attention deficit hyperactivity disorder: a preliminary case series. J Child Adolesc Psychopharmacol. **12**: 331–6.
12 Carrey N, MacMaster FP, Fogel J, Sparkes S, Waschbusch D, Sullivan S, *et al.* (2003). Metabolite changes resulting from treatment in children with ADHD: a 1H-MRS study. Clin Neuropharmacol. **26**: 218–21.
13 Carrey NJ, MacMaster FP, Gaudet L, Schmidt MH (2007). Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. **17**: 11–7.
14 Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB *et al.* (1997): Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. JAmAcad Child Adolesc Psychiatry. **36**: 374–383.
15 Castellanos FX, Giedd JN, Eckburg P, Marsh WL, Vaituzis AC, Kaysen D, *et al.* (1994). Quantitative morphology of the caudate nucleus in Attention Deficit Hyperactivity Disorder. Am J Psychiatry. **151**: 1791–1796.
16 Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, *et al.* (1996). Quantitave brain Magnetic Resonance Imaging in Attention Deficit Hyperactivity Disorder. Arch Gen Psychiatry. **53**: 607–616.
17 Castellanos FX, Elia J, Kruesi MJ, Marsh WL, Gulotta CS, Potter WZ, *et al.* (1996). Cerebrospinal fluid monoamine metabolites in boys with attention-deficit/hyperactivity disorder. Neuropsychopharmacology. **14**: 125–137.
18 Castillo M, Kwock L, Mukherji SK (1996). Clinical applications of proton MR spectroscopy. AJNR Am J Neuroradiol. **17**: 1–15.
19 Clark JB (1998). N-acetyl-aspartate: a marker for neuronal loss or mitochondrial dysfunction. Dev Neurosci. **20**: 271–276.
20 Colla M, Ende G, Alm B, Deuschle M, Heuser I, Kronenberg G (2008). Cognitive MR*1*spectroscopy of anterior cingulate cortex in ADHD: elevated choline signal correlates with slowed hit reaction times. J Psychiatr Res. **42**: 587–95.
21 Courvoisie H, Hooper SR, Fine C, Kwock L, Castillo M (2004). Neurometabolic functioning and neuropsychological correlates in children with ADHD-H: preliminary findings. J Neuropsychiatry Clin Neurosci. **16**: 63–9.
22 Cumyn L, French L, Hechtman L (2009). Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatry. **54**: 673–83.
23 Cihak R (1997). Anatomie 3 (Anatomy 3). 1st ed. Praha: Grada publishing spol.s.r.o., p.391–7.
24 De Graaf RA (1998). In Vivo NMR Spectroscopy: Principles and techniques. 1st ed. Chichester: John Wiley & sons Ltd.
25 Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ (1999). Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet **354**: 2132–2133.
26 Ernst M, Zametkin AJ, Matochilk JA, Pascualvaca D, Jons PH, Cohen RM (1999). High midbrain 18F-Dopa accumulation in children with ADHD. Am J Psychiatry. **156**: 1209–1215.
27 Fayed N, Modrego PJ (2005). Comparative study of cerebral white matter in autism and attention-deficit/hyperactivity disorder by means of magnetic resonance spectroscopy. Acad Radiol. **12**: 566–9.
28 Fayed N, Modrego PJ, Castillo J, Dávila J (2007). Evidence of brain dysfunction in attention deficit-hyperactivity disorder: a controlled study with proton magnetic resonance spectroscopy. Acad Radiol. **14**: 1029–35.
29 Ferreira PE, Palmini A, Bau CH, Grevet EH, Hoefel JR, Rohde LA, *et al.* (2009). Differentiating attention-deficit/hyperactivity disorder inattentive and combined types: a (1)H-magnetic resonance spectroscopy study of fronto-striato-thalamic regions. J Neural Transm. **116**: 623–9.
30 Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology. **48**: 589–601.
31 Hesslinger B, Thiel T, Tebartz van Elst L, Hennig J, Ebert D (2001). Attention-deficit disorder in adults with or without hyperactivity: where is the difference? A study in humans using short echo (1)H-magnetic resonance spectroscopy. Neurosci Lett. **304**: 117–9.
32 Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D (1990). Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. Arch Neurol. **47**: 919–926.
33 Isaacks RE, Bender AS, Kim CY, Prieto NM, Norenberg MD (1994). Osmotic regulation of myo-inositol uptake in primary astrocyte cultures. Neurochem. Res. **19**: 331–338.
34 Jin Z, Zang YF, Zeng YW, Zhang L, Wang YF (2001). Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a 1H-magnetic resonance spectroscopy study. Neurosci Lett. **315**: 45–8.
35 Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K (2000). Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett. **285**: 107–110.
36 Kronenberg G, Ende G, Alm B, Deuschle M, Heuser I, Colla M (2008). Increased NAA and reduced choline levels in the anterior cingulum following chronic methylphenidate. A spectroscopic test-retest study in adult ADHD. Eur Arch Psychiatry Clin Neurosci. **258**: 446–50.
37 MacMaster FP, Carrey N, Sparkes S, Kusumakar V (2003). Proton spectroscopy in medication-free pediatric attention-deficit/hyperactivity disorder. Biol Psychiatry. **53**: 184–7.
38 Madras BK, Miller GM, Fischman AJ (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry. **57**: 1397–409.
39 Magistretti PJ, Pellerin L, Rothman DL, Shulman RG (1999). Energy on demand. Science. **283**: 496–7.
40 Manji HK, Bersudsky Y, Chen G, Belmaker RH, Potter WZ (1996). Modulation of protein kinase C isozymes and substrates by lithium: the role of myo-inositol. Neuropsychopharmacology. **15**: 370–381.
41 Mason GF, Krystal JH (2006). MR spectroscopy: its potential role for drug development2for the treatment of psychiatric diseases. NMR Biomed. **19**: 690–701.
42 Miller CJ, Flory JD, Miller SR, Harty SC, Newcorn JH, Halperin JM (2008). Childhood attention-deficit/hyperactivity disorder and the emergence of personality disorders in adolescence: a prospective follow-up study. Journal Clin Psychiatry. **69**: 1477–84.
43 Moffett JR, Namboodiri MA (2006). Expression of N-acetylaspartate and N-acetyaspartylglutamate in the nervous system. In Moffett JR, Tieman SB, Weinberger DR, Coyle JT, Namboodiri MA, editors. N-acetylaspartate: A Unique Neuronal Molecule in the Central Nervous System. 1st ed. New York: Springer Science+Business Media, Inc., p. 7–26.

44 Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, *et al.* (2006). Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. Am J Psychiatry. **163**: 316–8.

45 PacIt I *et al.* (2007). Hyperkinetická porucha a poruchy chování (Hyperkinetic disorder and conduct disordres). 1st ed. Praha: Grada Publishing a.s., p.240

46 Perlov E, Philipsen A, Hesslinger B, Buechert M, Ahrendts J, Feige B, *et al.* (2007). Reduced cingulate glutamate/glutamine-to-creatine ratios in adult patients with attention deficit/hyperactivity disorder – a magnet resonance spectroscopy study. J Psychiatr Res. **41**: 934–41.

47 Posner MI, DiGirolamo GJ, Fernandez-Duque D (1997) Brain mechanisms of cognitive skills. Conscious Cogn. **6**: 267–290.

48 Pouwels PJ, Frahm J (1998). Regional metabolite concentrations in human brain as determined by quantitative localized proton MRS. Magn Reson Med. **39**: 53–60.

49 Rakic P (2002). Neurogenesis in adult primate neocortex: an evaluation of the evidence. Nat Rev Neurosci. **3**: 65–71.

50 Rigotti DJ, Inglese M, Babb JS, Rovaris M, Benedetti B, Filippi M, *et al.* (2007). Serial whole-brain N-acetylaspartate concentration in healthy young adults. AJNR Am J Neuroradiol. **28**: 1650–1651.

51 Sibson NR, Dhankhar A, Mason GF, Rothman DL, Behar KL, Shulman RG (1998). Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. Proc Natl Acad Sci U S A. **95**: 316–321.

52 Simons ML, Frondoza CG, Coyle JT (1991). Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. Neuroscience. **45**: 37–45.

53 Singer HS, Reiss AL, Brown JE, Aylward EH, Shih B, Chee E, *et al.* (1993). Volumetric MRI changes in basal ganglia of children with Tourette`s syndrome. Neurology. **43**: 950–956.

54 Solanto MV (2002). Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res. **130**: 65–71.

55 Spencer TJ, Biederman J, Wilens TE, Faraone SV (2002). Overview and neurobiology of attention-deficit/hyperactivity disorder. J ClinPsychiatry. **63** (Suppl. 12): 3–9.

56 Stanley JA, Kipp H, Greisenegger E, MacMaster FP, Panchalingam K, Pettegrew JW *et al.* (2006). Regionally specific alterations in membrane phospholipids in children with ADHD: An in vivo 31P spectroscopy study. Psychiatry Res. **148**: 217–21.

57 Stanley JA, Kipp H, Greisenegger E, MacMaster FP, Panchalingam K, Keshavan MS, *et al.* (2008). Evidence of developmental alterations in cortical and subcortical regions of children with attention-deficit/hyperactivity disorder: a multivoxel in vivo phosphorus 31 spectroscopy study. Arch Gen Psychiatry. **65**: 1419–28.

58 Starcuk Z, Krupa P, Starcuk Z jr., Horky J (2005). ^{1}H in vivo MR spektroskopie v klinické neurologii (^{1}H in vivo MR spectroscopy in clinical practice). Neurol prax. **6**: 133–138.

59 Sun L, Jin Z, Zang YF, Zeng YW, Liu G, Li Y, *et al.* (2005). Differences between attention-deficit disorder with and without hyperactivity: a 1H-magnetic resonance spectroscopy study. Brain Dev. **27**: 340–4.

60 Van Elst LT, Thiel T, Hesslinger B, Lieb K, Bohus M, Hennig J, *et al.* (2001). Subtle prefrontal neuropathology in a pilot magnetic resonance spectroscopy study in patients with borderline personality disorder. J Neuropsychiatry Clin Neurosci. **13**: 511–4.

61 Vance, J.E. (1988). Compartmentalization of phospholipids for lipoprotein assembly on the basis of molecular species and biosynthetic origin. Biochim Biophys Acta. **963**: 70–81.

62 Volkow ND, Wang GJ, Newcorn J, Fowler JS, Telang F, Solanto MV, *et al.* (2007). Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage. **34**: 1182–1190.

63 Weiss J, Boruta P (1998). Úvod do magnetickej rezonancie (Introduction to the magnetic resonancy). 1st ed. Bratislava: GOEN, s.r.o.

64 Yeo RA, Hill DE, Campbell RA, Vigil J, Petropoulos H, Hart B, *et al.* (2003). Proton magnetic resonance spectroscopy investigation of the right frontal lobe in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. **42**: 303–10.

65 Zametkin AJ, Nordahl TE, Gross J, King CA, Semple WE, Rumsey J, *et al.* (1990). Cerebral glucose metabolism in adults with hyperactivity of childhood onset. New Engl J Med. **323**: 1361–1366.

66 Zametkin AJ, Liebenauer LL, Fitzgerald GA, King AC, Minkunas DV, Herscovitch P, *et al.* (1993). Brain metabolism in teenagers with attention-deficit hyperactivity disorder. Arch Gen Psychiatry. **50**: 333–40.