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ETIOLOGY OF SCHIZOPHRENIA AND THERAPEUTIC OPTIONS

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INTRODUCTION

Schizophrenia (SCH) is a major psychiatric disease. The underlying psychopathological mechanisms are not thoroughly understood. Recent working hypotheses on the etiology of SCH discuss numerous molecular mechanisms; those hypotheses require an extensive multidisciplinary research, the results of which would either confirm or discard them. One of the hypotheses discusses the disturbance of membrane phospholipids and cytokynes in SCH that might result in anomalies of oxidative and anti-oxidative processes (Nadalin et al. 2008, Buretić-Tomljanović et al. 2008, Akyol et al. 2002, Arolt et al. 2000, Arvindakshan et al. 2003, Bakeret al. 1996). The changes of membrane phosphorlipids are related not only to the intensity of symptoms, but also to the specific clinical representations of SCH (Peet et al. 2002, Puri et al. 2000, Richardson et al. 2000). The results of numerous studies indicate the important role of lipid molecules in normal and disturbed neurotransmitter system upon which the current pharmacotherapy of SCH is established (Faroogui et al. 2000, Faroogui et al. 2000, Skosnik et al. 2003, Yao & van Kammen 2004, Sampath et al. 2005). Biochemical mechanism of the development of SCH, based on the lipid metabolism is not fully understood, although the biology of phospholipid molecules is completely established, and the genetic basis of the enzymes that regulate their metabolisms are determined and defined.

Another hypothesis suggests the disturbance in protein synthesis in SCH. The facts that could be assembled to create this hypothesis were mostly obtained from the Human Genome Project (HGP) (Lander et al. 2001), which has, following the secondary principle of Darwinism (Cziko et al. 1995), pointed out 84 important features in SCH. Genetic and epigenetic varieties of the genes involved in the processes of signal transduction, transcription, translation, all converge towards protein syntesis rate (PSR), that is being considered as common final pathway, supposedly responsible for genetic determination of SCH. CPSR hypothesis offers explanation for 96.7% of major findings in SCH, and reveals the connection of several important hypotetic models. The hypotheses implícate that SCH is easy to prevent and treat. In spite of all the advantages of CPSR hypothesis, a caution is necessary until all the findings are tested and proved.

The above mentioned hypotheses establish connection with another hypothesis of SCH as a neurodevelopmental disease. In early foetal development, the individual cerebral and craniofacial morphogenetic process occurs. Namely, documented differences in craniofacial appearance of schizophrenic patients and control group are connected to developmental disorders of cranio-facial morphogenesis, and are tightly linked with early cerebral development disorders (Arnold et al. 1999, DeLisiet al. 1999, Gharaibeh et al. 2000). By detailed study of facial dysmorphogenesis it may be possible to assemble enough information and enable the explanation of the nature and time of occurrence of this neurodevelopmental disorder. The multitude of factors influencing early cerebral development, environmental factors included, underlines the importance of regional morphometric studies (Selemon et al. 2001). There are no published data on craniofacial dysmorphology of schizophrenic patients in Croatia (Buretić-Tomljanović et al. 2009). Furthermore, volumetric changes of brain in schizophrenic patients has not been thoroughly researched worldwide, while in Croatia, these data are nonexistent (Gilbert et al. 2001, Verma et al. 2009, Win et al. 2008, Rusch et al. 2008, Zetzscheet al. 2008, Okugawa et al. 2007, Uchidaet al. 2008).

The etiology of SCH is still not fully established. The above mentioned hypotheses, as well as recent results of numerous research projects dealing with the etiology of SCH offer many new potentially beneficial therapeutic options.

DOPAMINE THEORY OF THE ETIOLOGY OF SCHIZOPHRENIA AND THERAPEUTIC POSSIBILITIES

Hyperactivity of dopamine within mezolymbic system causes positive symptoms (hallucinations and delusions), cognitive symptoms (thought disorders) and aggressive and hostile symptoms (especially if serotonin-mediated control of dopamine is also disturbed, which is the case in patients with impulse control disruption) (Natesan et al. 2006).

Theoretically, the increase of dopamine in mesocortical dopamine pathway could improve negative, cognitive and affective symptoms of SCH. However, since an abundance of dopamine already exists everywhere else within the brain, and in mesolymbic

dopamine pathway, any further increase of dopamine in that pathway would increase the intensity of positive symptoms. This gives rise to a therapeutic dilemma: is there a way to increase dopamine in mesocortical pathway, and simultaneously decrease the activity of dopamine in mesolymbic dopamine pathway. Atypical antipsychotic have provided solution of this therapeutic dilemma (Takahashi et al. 2006).

The function of dopamine in SCH might be much more complex than just „too high“ in mesolymbic areas and “too low” in mesocortical areas. Instead, it is plausible to characterize the dopaminergic neurons as “out of tune” or “chaotic”. Similar phenomenon might exist within mesolymbic dopamine system, with one group of mesolymbic dopaminergic neurons being „out of tune“ as well as hyperactive, causing thus positive symptoms, and the other set of mesolymbic dopaminergic neurons being also „out of tune“ and hypoactive, mediating some of the negative symptoms and dysfunctional reward mechanisms (reward, pleasure, motivetion, interest). This idea is supported by the observation that patients treated with antipsychotic drugs, particularly with conventional antipsychotics, might experience worsening of the negative symptoms, and might develop a state of „neurolepsy“, with the symptoms remarkably similar to the negative symptoms of SCH. Since the density of D2 receptors in prefrontal cortex isn't very high, this also implicates the possibility of deficient function within mesolymbic dopamine system which causes inadequacy of reward mechanisms that are presented as anhedonia, substance abuse, but may also be presented as negative symptoms: lack of rewarding social interactions, lack of motivation and interest.

The level of dopamine in nigrosriatal and mesolymbic pathways in SCH is normal, but the administration of D2 blockers (conventional antipsychotics) causes dopamine deficiency (Remington et al. 2006). The activity of dopamine in hypothalamic-hypophysal projections in SCH is also normal, but D2 blockers cause dopamine deficiency, therefore the inhibition of proalactin is no longer possible (Remington et al. 2006).

The theory on increased level of prolactin being the cause of SCH, was deducted through observation of the effects of antipsychotic drug phenothiazine which blocks the dopamine activity by binding to postsynaptic D2 receptors in dopamine pathways (Kessler et al. 2006). However, there are many „holes“ in this theory. It offers no explanation of the fact that the symptoms are alleviated only after several weeks, while binding to the receptors occurs immediately; neither has it provided clues regarding the fact that in order to achieve desired effect, the activity of the receptors needs to be down regulated below their normal level of activity. Those facts give rise to the question whether the problem lies in the excess of dopamine or in the hypersensitivity of the receptors. We now know that both facts are true.

Recent research indicate that dopamine activity is increased only in mid-regions of the brain (mesolymbic pathway), with the consequential dopamine hypoactivity in prefrontal cortex. This sequence of events is further supported by the observation that blocking the dopamine receptors causes regression of positive symptoms (hallucinations, disorganized speech...), but not the regression of negative symptoms (social withdrawal, apathy) that are linked to reduced activity in prefrontal cortex (Clinton et al. 2005).

The deficit of working memory, i.e. short-term memory in schizophrenic patients is yet another proof of dopamine deficiency in prefrontal cortex.

Schizophrenic patients have not only increased level of dopamine and increased number and sensitivity of their receptors within CNS, but also an increase of D3 receptors in peripheral blood. By the use of molecular biology techniques it was possible to show that human peripheral blood lymphocytes express several types of dopamine receptors in their membranes (D3, D4, and D5). It has been speculated that the lymphocytic dopamine receptors mirror the activity of brain dopamine receptors (Ilan et al. 2001).

A study had been conducted with the aim to measure by densitometry the level of mRNA for dopamine receptors in lymphocytes of schizophrenic patients and age and sex matched healthy individuals to establish whether those receptors may serve as peripheral markers of the disease. Significant increase in level of mRNA D3 receptors, but no increase of D4, was found in schizophrenic patients (the increase of D3 dopamine receptors was found also post-mortem in the brains of both treated and untreated schizophrenic patients) (Ilan et al. 2001). No antipsychotic treatment had any effect upon this finding, since there was no increase in untreated patients. The study suggests lymphocytic D3 receptors mRNA to be employed as a marker for identification and follow up for SCH. In conclusion, the results of this study suggest that the level of lymphocytic D3 receptor mRNA represents a reliable peripheral marker for SCH and an important tool in early diagnostics (Ilan et al. 2001).

THE ROLE OF GLUTAMATE IN THE ETIOLOGY OF SCHIZOPHRENIA AND NEW THERAPEUTIC POSSIBILITIES

Glutamates are the principal excitatory neurotransmitter in CNS that can excitate and activate any CNS neuron. It's an amino acid, employed as a building block in protein biosynthesis (Coyle et al. 2006).

Currently, extensive research of the hypothesis that links hypofunction of NMDA receptors in certain glutamate pathways and positive symptoms of SCH is being undertaken (Coyle et al. 2006, Bennet et al. 2005, Scarr et al. 2005). Cortex – brain stem cortical projections communicate with mesolymbic dopaminergic pathway through GABA interneurons in ventral tegmental area (VTA). Excitatory glutamate stimulation of interneuron NMDA receptors causes the release of GABA that usually mediates the inhibition of dopamine release in

mesolymbic dopamine pathway. Therefore, the descending glutaminergic pathway under normal circumstances acts as a brake in mesolymbic dopaminergic pathway. If the NMDA receptor residing on GABA interneurons becomes hypoactive, no descending effect of tonic inhibition will occur, the net result being hyperactivity of the described dopaminergic pathway. These are the outlines of the theory for the biology of mesolymbic dopamine hyperactivity that is linked to the positive symptoms of psychosis.

The cortex – brain stem projection communicates directly with the mesocortical dopaminergic pathway in VTA (therefore, there are no GABA interneurons here), and causes tonic excitation in normal circumstances (i.e., it acts as an accelerator of mesocortical dopamine neurons). If the NMDA receptors in the cortex – brain stem projection become hypoactive, the tonic excitation is lost, and mesocortical dopaminergic pathway becomes hypoactive, potentially offering an explanation for cognitive, negative and affective symptoms of SCH (Pralong et al. 2002).

Hypofunction of NMDA receptors within five glutamate pathways may potentially account for positive, negative, affective and cognitive symptoms; also, it provides an explanation for deregulation of dopamine due to hypofunciton of NMDA receptors, resulting in hyperactivity in mesolymbic dopaminergic pathway for positive symptoms and hypoactivity in mesocortical dopaminergic pathway for cognitive, negative and affective symptoms of SCH. Many of the currently standing theories founded on the genetic basis of SCH are shifting their attention upon NMDA receptors in search of new drugs for the treatment of SCH (Javitt et al. 2006).

THE ROLE OF SEROTONIN IN THE ETIOLOGY OF SCHIZOPHRENIA AND THERAPEUTIC POSSIBILITIES

Recently, a lot of attention has been given to the abnormalities of serotonin system that might be connected with the development of SCH. The discovery that hallucinogen agents like indolamine and phenetilamine that exert their actions on CNS via 5HT2 receptors, a conclusion has been made that the hallucinations in SCH might occur through similar mechanism (Reynolds et al. 2004). In the studies of the actions of hallucinogen substances, two brain regions are in focus: locus coeruleus and cortex. In these areas the hallucinogens act through 5HT2A receptors and increase the transmission of glutamate. In prefrontal cortex 5HT2A receptors also stimulate the release of glutamate. This effect can be reversed by the inhibitory group II/III metabotropic glutamate agonists that act presynaptically, and by antagonists of AMPA glutamate receptors which act postsinaptically, on non-NMDA receptors. This is a confirmation of the link between serotonin and glutamate systems.

The following observations have been made: a) serotonins receptors are involved in psychomymetic and psychotogenic properties of hallucinogens; b) there is an increase in number of cortical 5-HT2A and 5-HT1A receptors in the brain of schizophrenic patients; c) 5-HT2A and 5-HT1A receptors have major role in the onset and treatment of side-effects of atypical antipsychotics; d) there are firm evidence of the link between 5-HT2A receptors gene polymorphism and the development of SCH; e) trophic role of serotonin in neurodevelopment may be impaired in SCH; f) 5-HT2A receptor mediated activation of prefrontal cortex may be insufficient in schizophrenic patients; g) serotonergic and dopaminergic neurotransmitter pathways in the brain are intertwined and may both be impaired in SCH (Aghajanian et al. 2000).

The research showed that schizophrenic patients have significantly higher concentration of platelet serotonin than their healthy counterparts. Hyperserotoninaemia is more often seen in schizophrenic patients with predominantly paranoid than in the patients with predominantly non-paranoid symptoms. Extremely high levels of platelet serotonin in chronically ill schizophrenic patients may reflect the progression of the disease. High levels of platelet serotonin were not related either to the seasonal or diurnal variations of platelet serotonin or to the age of the patients. The study showed higher level of platelet serotonin in male than in female patients. In the course of treatment with both classical and atypical antipsychotic drugs no change of the concentration of platelet serotonin has been observed, irrespective of the type of SCH as well as of baseline pre-treatment level of platelet serotonin. The results imply the change in the peripheral serotonin system in schizophrenic patients (Muck-Šeler et al. 2005).

PET-scan study was conducted with the aim to measure the binding of serotonin to the 5-HT2A receptors in the non-treated schizophrenic patients and healthy age-matched controls. The results showed reduced density of serotonin receptors in older subjects from both groups. There were no significant differences between sexes in the group of healthy subjects. A significant decrease of serotonin binding in frontal cortex was observed in the brains of schizophrenic patients. These results show that reduced number of serotonin receptors in SCH occurs in the early stages of the disease, prior to the exposure to neuroleptic drugs (Ngan et al. 2000).

THE ROLE OF ACETILCHOLINE (ACH) IN THE ETIOLOGY OF SCHIZOPHRENIA AND THERAPEUTIC POSSIBILITIES

Post mortal and neuroimmaging studies showed reduced number of M1 and M4 muscarine receptors in schizophrenic patients in several key loci, including nucleus caudatus and putamen, hippocampus, anterior

and dorsal cingular cortex, and prefrontal cortex, while there were no changes in the number of M2 and M3 receptors. Relative hyperactivity of cholinergic system may contribute to the negative symptoms of SCH, but also to the gravity of productive symptoms (Thomas et al. 2003).

As far as the acetyl-choline metabolizing enzymes are concerned, there are proofs of reduced concentration of choline-acetyltransferase in the pons, while the concentration of the same enzyme is increased in hippocampus, caudate nuclei, putamen and nucleus accumbens in schizophrenic patients. Several pharmacological studies were very important for the understanding of the role of cholinergic system in the pathophisiology of SCH. In those studies anti-cholinergic drugs or acetyl-choline agonists were given to the schizophrenic patients, and the effects were observed and quantified. The results showed that choline-esterase inhibitors improve cognitive functions of the patients, while muscarine antagonists improve negative, but also intensify positive symptoms of SCH – this finding was interpreted as an increased cholinergic activity.

As far as cholinergic interaction with other neurotransmitter systems in SCH is concerned, there is an important discovery of muscarine receptors in dopaminergic neurons in striatum, substantia nigra and cortex; VTA also releases dopamine when stimulated by acetyl-choline. Some scientists speculate that SCH may be caused by excessive activation of neurons in pedunculopontine and latero-dorsal tegmental nuclei, followed by the activation of dopaminergic neurons.

There are proofs that schizophrenic patients have shorter REM latency, which may also be a consequence of muscarine "supersensitivity" (Thomas et al. 2003).

NEURODEGENERATIVE HYPOTHESIS OF SCHIZOPHRENIA

Neuroimmaging studies of the schizophrenic patient's brains show functional and structural abnormalities, giving rise to the assumption that the observed neurodegenerative process followed by progressive loss of neuronal functions might be ongoing, integral part of the development of SCH (Bota et al. 2005, Cavelier et al. 1995).

Neurodegenerative theories of SCH assume that the progressive loss of neuronal functions, either by the loss of dendrites, by the destruction of synapses, or by neuronal death might be the cause of the symptoms and progression of SCH. The causes of neurodegeneration might be: genetic programming of neuronal or synaptic destruction, prenatal exposure to anoxia, toxins, infections, malnutrition, resulting in foetal insults; dopamine-mediated neurodegeneration and/or glutamate-mediated excytotoxicity that may initially cause positive symptoms, but following neuronal death, residual negative symptoms pervade (Bota et al. 2005).

There are many proofs of the loss of cortical grey matter, reduction of amygdale, hippocampus, and reduction in frontal and temporal lobes in schizophrenic patients. Dopamine is a probable culprit in this case, since it is well documented that the excess of dopamine in certain conditions causes cell death. Namely, dopamine inhibits mitochondrial respiration; the reduced activity of mitochondrial cytochrome-C oxidase has been shown in schizophrenic patients. The energetic deficit may reduce the activity of DAT (dopamine transporter) and keep the neurotransmitter in extracellular liquid longer (Cavelier et al. 1995).

Yet another mechanism that contributes to the cellular oxidative stress lies in the catabolism of dopamine; with the help of MAO, hydrogen-peroxide is generated and linked to non-bound iron molecules, causing oxidative damage of the cells.

Pivotal idea that offers the explanation for neurodegeneration in SCH, as well as the explanation for resistance to the pharmacotherapy, claims that neurodegenerative events in SCH may be mediated by one kind of excessive activity of glutamate called excytotoxicity. Excytotoxic hypothesis of SCH assumes that the neurons degenerate as a result of excessive excitatory neurotransmission of glutamate neurons. The process of excytotoxicity is not exclusive for neurodegeneration in SCH, it is also employed as explanation for neurodegeneration in many different neurological and psychiatric conditions, including Alzheimer's disease and other degenerative dementias, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and even stroke (Alphs et al. 1989).

NEURODEVELOPMENTAL HYPOTHESIS OF SCHIZOPHRENIA

It is believed that early brain dysmorphogenesis may cause facial dysmorphogenesis as well. Since there is an anomaly of early brain development in SCH, it is believed that the same anomaly may be mirrored in facial dysmorphogenesis. Early anthropometric research showed minor variations of facial morphology in schizophrenic patients, but the development of digital technology and tri-dimensional lasers surface scanner enabled much more profound research of this subject. 3D MRI morphometric technique has also been successful in the research of dysmorphogenesis (Johnson et al. 2006). In a number of researches many deviations of facial morphology were established, and they were significantly more often present in schizophrenic patients: mouth, lips and chin are narrower and pushed backwards, upper portion of a face, mandible and basis of the skull are wider, palate is short and wide. Eyes, orbits and cheeks are placed laterally, while the upper orbital margin is protruding, nose is small, lips are fuller, forehead is low, middle and lower sections of the face are elongated. Some authors describe the sculls of schizophrenic patients as

brachichephalic. All the changes of facial morphology indicate towards tight relationship of facial and cerebral development. Deviant facial morphology of schizophrenic patients represents an external expression of all the changes occurring during foetal development, and results in established schizophrenic process (Arnold et al. 1999, DeLisiet al. 1999, Gharaibeh, et al. 2000, Buckley et al. 2008).

Morphometric changes of the brain show the reduction of gray matter's volume, increased volume of cerebro-spinal fluid, dilatation of brain chambers, while the results on white matter volume show no consistency. Abnormalities are more marked in frontal and temporal regions (Gilbert et al. 2001, Verma et al. 2009, Win et al. 2008, Rusch et al. 2008, Zetzscheet et al. 2008, Okugawa et al. 2007, Uchidaet et al. 2008). The brains of treated patients show increased volume of basal ganglia (Davatzikos et al. 2005). Some sex differences were also found (Davatzikos et al. 2005).

THE ROLE OF CENTRAL PROTEIN SYNTHESIS IN THE ETIOLOGY OF SCHIZOPHRENIA

Using the results obtained in Human Genome Project (HGP) (Lander et al. 2001), new insigts regarding the etiology of SCH were searched for. As previously mentioned, genetic and epigenetic varieties of the genes included in the processes of signal transduction, transcription, and translation converge towards the curve for protein synthesis (protein synthesis rate, PSR), as an expected final pathway that is supposed to be responsible for genetic determination of SCH; this model also reveals interconnection of several important hypothetic models. Hypotheses implicate that SCH is easy to prevent and treat, partly by immunization against neurotrophic viruses, partly by development of new drugs that would specifically enhance central protein synthesis (Moises et al. 2002).

It is therefore possible that SCH is caused by the reduced cerebral protein synthesis, including entire human proteome. The reduced protein synthesis may be caused by environmental (e.g. viruses) and genetic agents (Moises et al. 2002). Environmental component is explained by epigenetic variety of the genes during intrauterine development or early in life, as well as by reduction of CPSR due to reduced growth factors, hormones, ageing and latent viral infections that are known to reduce the level of PSR.

CPSR hypothesis accounts for about 96.7% of major discoveries in SCH, it reveals the relationship among previously independent discoveries, and integrates several very important hypotheses.

Depending on the rate, the reduction of CPSR expectedly causes prodromal, depressive and negative symptoms first. Severe defficiency of CPSR may further cause positive, disorganized, and finally catatonic symptoms. Reduction of CPSR that would cause schizophrenic symptoms may be the consequence of reduced quantity of growth factors or hormons, or may develop after acute, latent or re-activated viral infection. Re-activation of a latent virus is probably responsible for majority of the acute episodes of SCH. Significant deficit of CPSR causes neuronal degeneration.

Increase of CPSR during remission will initiate neural remodelling. Increase of CPSR happens either spontaneously, or is induced by some medicines, such as insulin, prolactin or by electrostimulation. Either way, the regeneration of neuronal network is incomplete and some defects persist (Moises et al. 2002).

Antipsychotic mechanisms of antipsychotic drugs are linked to CPSR. There are observations showing the common feature of all the typical and atypical antipsychotic drugs, such as clozapine, olanzapine, risperidone, amisulpride, ziprazidone and zotepine, which is increase of CPSR (Moises et al. 2002, McLaughlin et al. 2003).

Electrostimulation and electroconvulsive therapy – which has proven itself efficient in grave catatonic schizophrenia – increases the level of insulin and protein synthesis.

PHOSPHOLIP THEORY OF SCHIZOPHRENIA

Long chain polyunsaturated fatty acids (LC-PUFA) are essential for normal development of the brain structures and its functions. It is therefore plausible that a disturbance of their metabolism participates in the aetiology of SCH, depression and other mental disorders. Biochemical mechanism of SCH is based upon the metabolism of lipids, but is not fully clarified, although the biology of phospholipid molecules is well known, and the enzymes involved in the regulation of their metabolism are entirely cloned (Feldberg et al. 1976).

The reduced content of polyunsaturated fatty acids has been observed post mortem in the membranes of cerebral tissue, peripheral tissues, e.g. red blood cells (Herken et al. 2001) and skin fibroblasts and plasma (Horrobin et al. 1989) of schizophrenic patients.

Disorder of multiple neurotransmitters in SCH (dopaminergic, serotonergic, noradrenergic, glutaminergic, GABA-ergic) supports the phospholipid hypothesis which gives central role in the pathophysiology of this disease to neuronal membranes and numerous processes that take place there.

Many studies demonstrated the deficiency of arachidonic acid (AA) and fatty acids in the membranes of peripheral and central cells of schizophrenic patients, that is caused by increased activity of the PLA2 (phospholipase) enzyme. Next event is the increase in release of LC-PUFA from membrane phospholipids, increased production of anti-inflammatory cytokines (AA derivates), increased peroxidation of lipids, and creation of free radicals, and imbalance of release and

re-uptake of fatty acids in membrane phospholipid molecules (Ross et al. 1997).

The research is directed towards the potential of unsaturated fatty acids in treatment of SCH (Freeman 2006, Richardson 2006).

DISCUSSION

The cause of SCH has still not been fully elucidated. The development of new technologies has enabled important research into putative causes of this disease. In order to improve diagnostic and therapy protocols, the exact pathophysiological mechanisms are being researched. Based on the current research data, it is necessary to cluster schizophrenic patients according to their phenotypes; there are still many areas for further research, including and underlining the procedure of routine follow-up of schizophrenic patients, starting with the conception, in persons with increased risk for SCH. Prenatal, perinatal and postnatal properties of SCH may help to establish early diagnosis of the disease.

There are many different theories and hypotheses on possible links among some neurotransmitters, genes and environmental factors and SCH. In dopamine hypothesis of SCH, the disturbed level of dopamine is thought to be the main cause of SCH. It is considered that the dopamine activity is increased in mid-region of a brain (mesolymbic pathway) (Natesan et al. 2006), and reduced in prefrontal cortex (Clinton et al. 2005). The dopamine receptors are also being scrutinized, and are found to be increased not only in CNS, but also in peripheral blood lymphocytes (Ilan et al. 2001). It is well established that high level of dopamine leads to cell death by inhibition of mitochondrial respiration and by reduction of mitochondrial cytochrome-C oxidase activity in schizophrenic patients (Cavelier et al. 1995).

Glutamate hypothesis of SCH deals with a cluster of pathological mechanisms related to glutamatergic signalling. In early stages of the research, this hypothesis was based on clinical, neuropathological, later also genetic findings; all of them indicated towards hypofunction of glutamatergic signalling trough NMDA receptors (Coyle et al. 2006, Bennet et al. 2005, Scarr et al. 2005). Metabotropic glutamate receptors mGluR2 and mGluR3 are thought to play an important role in the pathophysiology of SCH. There are proofs that schizophrenic patients have a significant increase of glutamate-carboxipeptidase II and decrease of mGluR3 protein in dorsolateral prefrontal cortex, while the level of mGluR2 protein remains unchanged. Pre-clinical studies show that the activation of mGlu5 or mGlu2/3 receptors may be an efficient strategy for the alleviation of cognitive deficiencies that are caused by the NMDA receptors-mediated reduction of neurotransmission. A number of valid, genetically based theories of the etiology of SCH are shifting their focus on NMDA receptors as a likely candidate for new SCH treatment drugs (Javitt et al. 2006).

The discovery that some hallucinogenic drugs, e.g. indolamine and phenetilamine act upon CNS via 5-HT2 receptors, led to the conclusion that hallucinations in SCH might be caused by the same mechanism (Reynolds et al. 2004). The increased number of 5-HT2A and 5-HT1A cortical receptors has been observed in the brains of schizophrenic patients. The polymorohism of 5-HT2A receptor gene has also been confirmed; that may indicate insufficient 5-HT2A receptor - mediated activation of prefrontal cortex (Aghajanian et al. 2000). Current research show that schizophrenic patients have significantly increased level of platelet serotonin, compared to healthy individuals, the finding that is more pronounced in patients with predominantly paranoid symptoms of the disease (Muck-Šeler et al. 2005).

Pharmacological studies propelled the research on the involvement of cholinergic system in the pathophysiology of SCH; the anticholinergic or acetylcholine agonists were administered and the changes in the patients were studied. Postmortal and neuroimmaging studies showed reduced number of M1 and M4 muscarine receptors in schizophrenic patients in crucial loci, such as caudate nucleus, putamen, hippocampus, anterior and posterior cingular cortex, and prefrontal cortex (Thomas et al. 2003).

Neurodegenerative theory of SCH assumes that the progressive loss of neuronal function either by the loss of dendrites, by the destruction of synapses or neuronal death may be the cause of the symptoms and progression of SCH (Bota et al. 2005, Cavelier et al. 1995). The progressive course of the disease supports the neurodegenerative theory of SCH, as well as the observation that successful antipsychotic treatment may vary significantly in the course of the disease. Those hypotheses are being explained by the excessive glutamate action that causes excitotoxicity.

Neurodevelopmental hypothesis of SCH indicates that the development of the brain and face are closely connected, so that any disturbance in the brain development may be mirrored in facial morphology (Arnold et al. 1999, DeLisiet al. 1999, Gharaibeh,et al. 2000, Buckley et al. 2008). The reduction of gray matter volume and the increase of cerebrospinal fluid volume have been observed in schizophrenic patients. Also, in schizophrenic patients certain changes in facial morphology have been observed, and their appearance shows statistically significant regularity of occurrence.

New working hypotheses of the ethiology of SCH operate with a number of molecular mechanisms, the most researched being the disruption in central protein synthesis as a cause of SCH. Membrane phospholipids are also being extensively researched.

The disrupted protein synthesis hypothesis is based on the research results from human genome project. Both environmental and genetic factors can cause reduced protein synthesis. This is the only hypothesis that accounts for nearly all of the phenotypic properties of SCH, and is still being extensively tested (Moises et al. 2002, McLaughlin et al. 2003).

New studies also showed the importance of the membrane phospholipids' metabolism disorders (Herken et al. 2001, Horrobin et al. 1989). The results have defined the reduction of fatty acids incorporation and neuronal membrane catabolism enhancement. The underlying mechanism is abnormally high activity of phospholypase A2 (PLA2) enzyme which leads to increased release of LC-PUFA from membrane phospholipids; this event causes increased synthesis of inflammatory mediators, increased lipid peroxidation and release of free radicals, as well as imbalance between release and re-integration of fatty acids in membranes of phospholipid molecules.

CONCLUSIONS

There are many hypotheses on the development of SCH. None of them fully explains all of the phenotypic properties of SCH, but all of them offer new therapeutic options. The closest to elucidate all of the properties of the disease is the central protein synthesis reduction hypothesis, but it is still a subject of extensive control research. Unequivocal definition of the ethiology of SCH would contribute significantly to the diagnosis and treatment of SCH.

All the above mentioned hypotheses clearly show the necessity for collaborative efforts of genetic scientists, psychologists and psychiatrists in the treatment of schizophrenic patients. Definition of the phenotypic groups of SCH might result in the creation of type –specific diagnostic and treatment algorithms.

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