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Review

Models of schizophrenia in humans and animals based on inhibition of NMDA receptors

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ABSTRACT

The research of the glutamatergic system in schizophrenia has advanced with the use of non-competitive antagonists of glutamate NMDA receptors (phencyclidine, ketamine, and dizocilpine), which change both human and animal behaviour and induce schizophrenia-like manifestations. Models based on both acute and chronic administration of these substances in humans and rats show phenomenological validity and are suitable for searching for new substances with antipsychotic effects. Nevertheless, pathophysiology of schizophrenia remains unexplained. In the light of the neurodevelopmental model of schizophrenia based on early administration of NMDA receptor antagonists it seems that increased cellular destruction by apoptosis or changes in function of glutamatergic NMDA receptors in the early development of central nervous system are decisive for subsequent development of psychosis, which often does not manifest itself until adulthood. Chronic administration of antagonists initializes a number of adaptation mechanisms, which correlate with findings obtained in patients with schizophrenia; therefore, this model is also suitable for research into pathophysiology of this disease.

Contents

1. Introduction—*N*-methyl-D-aspartate receptor in schizophrenia

An important role of the glutamatergic neutrotransmitter system in the etiopathogenesis of schizophrenia has been supported by findings on various levels from molecular interactions up to the structural layout of neuronal network in the human brain (Goff and Coyle, 2001; Owen et al., 2004). Glutamate acts through several types of both ionotropic and metabotropic

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receptors (review Dingledine et al., 1999; Petrovič et al., 2005). In particular, the change of function of the ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptor is crucial to the research of schizophrenia. This receptor consists of several types of subunits including the obligatory NR1 subunit and the facultative NR2A–D and NR3A and B (Hollmann et al., 1994). In addition, the NMDA receptor is interconnected with a set of intracellular proteins creating postsynaptic density, such as ErbB and dysbindin-1 (Sheng and Pak, 2000). Studies have implicated genes for these proteins associated with increased risk for schizophrenia (review O'Tuathaigh et al., 2007). Neuregulins are a family of growth and differentiation factors that bind to the ErbB family of tyrosine kinase transmembrane receptors. Neuregulin-1 is expressed in central nervous system and plays main role in synapse formation, neuronal migration and synaptic plasticity (Falls, 2003). In addition, the receptor for neuregulin-1, ErbB, is colocalized with the NMDA receptor and probably regulates the kinetic properties of the NMDA receptor by phosphorylating the NR2 subunit (Moghaddam, 2003). Dysbindin-1 (dystrobrevin-binding protein) which is implicated in postsynaptic density and signaling (Benson et al., 2001). Another group of susceptibility gene for schizophrenia is the G72/G30 complex. The G72 protein is a D-amino acid oxidase activator, the enzyme degrades D-serine (coagonist of the NMDA receptor). However, a recent association study with 14 candidate genes including genes associated with the NMDA receptor did not support evidence for their association with schizophrenia (Sanders et al., 2008). It seems that polymorphisms in these genes are associated with risk of schizophrenia in some cohorts of patients.

Another approach to studying the role of the NMDA receptor in schizophrenia is assessing changes in transcript and protein expression of the NMDA receptor subunits and of the protein associated with NMDA in patients with schizophrenia postmortem. In a recent review, Kristiansen et al. (2007) summarized NMDA receptor abnormalities in schizophrenia using postmortem brain samples. Changes in transcripts of the different NMDA receptor subunits or of proteins associated with the NMDA receptor (NF-L, PSD-95, PSD-93 and SAP102) in different brain regions were either not found at all or were rather inconsistent. For instance, protein expression for NR2B was decreased in dorsomedial thalamus and, in the same region, an increase in the NR1-C2 isoform of the NR1 subunit was found without affecting the total NR1 protein expression. More changes in protein expression have been documented for proteins associated with the NMDA receptor. The expression of PSD-95 was found to be decreased in anterior cingulate cortex and hippocampus and increased in dorsomedial thalamus and in nucleus accumbens. A similar protein, PSD 93, was decreased in anterior cingulate cortex. Decreases in proteins NF-L and SAP102 were found in dorsolateral prefrontal cortex and in the hippocampus, respectively. These findings in postmortem studies show some changes in the NMDA complex in several brain regions. However, it should be mentioned that postmortem brain tissues are from patients who are not drug naive. It has been documented that antipsychotic agents (haloperidol and clozapine) have an affinity for the NMDA receptor (Zhuravliova et al., 2007; Bressan et al., 2005). Therefore, the use of imaging techniques in drug naive patients could bring a relevant finding about the role of the glutamatergic system in schizophrenia. Study by Pilowsky et al. (2006) show relative decrease of NMDA receptors in the left hippocampus in drug free patients but not in antipsychotic-treated patients with schizophrenia.

In spite of the large number of clinical observations it is still unknown and therefore subject to interpretation whether and how NMDA receptors are exactly involved in the pathogenesis of schizophrenia. Helpful tool for addressing this question is the use of substances acting as non-competitive antagonists of the NMDA glutamate receptor (phencyclidine, ketamine, and dizocilpine). The use of these substances changes the behaviour in both humans and animals and induces schizophrenia-like manifestations (review Coyle et al., 2004). Below we provide a review of up-to-date research experience with NMDA antagonists in the study of etiopathogenesis of schizophrenia.

2. Neurodevelopmental model of schizophrenia

Neurodevelopmental hypothesis of the origin of schizophrenia assumes that a disorder in pre- or perinatal development of the brain will result in manifestation of the disease in early adulthood (Weinberger, 1996). This hypothesis also includes a neurodegenerative aspect. That is to say, several studies suggest a possible assault to the brain during development, which results in schizophrenia in early adulthood (Lipska et al., 1995; Howland et al., 2004; review Deutsch et al., 2001). Neurodegeneration has even been shown to persist in some groups of patients, particularly in those with significant impairment of cognitive functions (review Pérez-Neri et al., 2006).

Neurodevelopmental model of schizophrenia based on NMDA receptor inhibition is based on the results of Ikonomidou et al. (1999) indicating that administration of the NMDA receptor antagonists dizocilpine (MK-801) and phencyclidine (PCP) in late fetal and early postnatal period of life in the rat will increase neuronal death by apoptosis. On the contrary, administration of these substances to rats at an adult age will increase neuronal damage by necrosis with subsequent gliosis (Olney et al., 1991). The time period when the inhibition of NMDA receptors increases cell damage correlates with the maximum expression of these receptors. This period corresponds in humans with the third trimester of pregnancy (Lee and Choi, 1992) and in rats with the first 2 postnatal weeks of life (Rao et al., 1997; Colwell et al., 1998). The increased death of neurons by apoptosis during the early phase of central nervous system development may result in decreased ability of neuronal damage by programmed death, which has been reported in chronic patients with schizophrenia (Jarskog, 2006).

The increased destruction of neurons by apoptosis following systemic acute and chronic administration of PCP, ketamine or MK-801 in early postnatal period (between PND 7 and PND 11) has been reported in all animal studies (Ikonomidou et al., 1999; Wang et al., 2001; Harris et al., 2003; Fredriksson et al., 2004; Stefani and Moghaddam, 2005). In addition, a decreased expression of cytoskeletal proteins MAP2 and SNAP25 has been reported (Lema Tome et al., 2006), which may result in disorganization of neuronal circuits in adulthood. The increased apoptosis was also observed after neonatal administration of *N*-acetyl-L-aspartyl-L-glutamate (NAAG) which is a partial agonist of the NMDA receptor and an agonist of the mGluR II receptor (Bubeníková-Valešová et al., 2006).

In accordance with the neurodevelopmental hypothesis, early administration of NMDA receptor antagonists changes the behaviour of rats in adulthood (Table 1). Behavioural manifestations in rats which are related to the symptoms and neurobiological markers of schizophrenia include four major dimensions: hyperlocomotion, stereotypy, deficiency in information processing, impairment of cognitive functions (working memory and attention), and impaired social interaction (Lipska and Weinberger, 2000; Bubeníková et al., 2003).

The impairment of cognitive functions is currently considered to be the primary and persistent manifestation in patients with schizophrenia (Elvevag and Goldberg, 2000; Keefe et al., 2006; Andreasen, 1999). Following early NMDA receptor inhibition, both working and reference memory in the Morris water maze are impaired in adult rats (Gorter and de Bruin, 1992; Sircar and Rudy, 1998; Wang et al., 2001; Sircar, 2003; Stefani and Moghaddam, 2005; Pehrson et al., 2007). Some studies have shown a deficiency

Table 1
Comparison of clinical symptoms of schizophrenia with the schizophrenia-like behaviour induced by NMDA antagonist (modified version from Lipska and Weinberger, 2000)

Clinical symptoms of schizophrenia	Behavioural changes in animal model of schizophrenia
Psychotic symptoms	An increase in locomotor activity
Stereotypic behaviours	A perseveration of behaviour (sniffing, face washing etc.)
Vulnerability to stress	Changes in locomotory activity or behaviour induced by stress
Information processing deficits	Deficit in prepulse inhibition of acoustic startle reaction or wave P50
Attentional deficits	Deficits in latent inhibition
Cognitive deficits	Impairment in spatial memory tests
Social withdrawal	Reduced contacts with unfamiliar partners

Table 2
Comparisons of changes in behaviour and central nervous system after acute or chronic administration of NMDA antagonist

	Acute administration	Chronic administration	Reference
Glutamatergic system	An increase of glutamate in frontal cortex	A decrease of glutamate and an increase of glutamine level in frontal cortex	Moghaddam et al. (1997), Kondziella et al. (2006) and Zuo et al. (2006)
Dopaminergic system	An increase of dopamine release in PFC and nucleus accumbens	A decrease of dopamine production and utilization	Moghaddam et al. (1997), Jentsch et al. (1997) and Jentsch et al. (2007)
GABAergic system	A decrease of GABA release	A decrease of mRNA expression of GAD67, a number of parvalbumin-positive GABAergic neurones	Yonezawa et al. (1998), Qin et al. (1994) and Keilhoff et al. (2004)
Behavioural changes	Hyperlocomotion	Increasing of locomotor activity by stress and amphetamine	Jentsch and Roth (1999), Geyer et al. (2001), Zajaczkowski et al. (2003), Hitri et al. (1993), Tiedke et al. (1991), Sams-Dodd (1995, 1998), Koek et al. (1988), Vales et al. (2006), Stefani and Moghaddam (2005), Rujescu et al. (2006), Li et al. (2003), Mandillo et al. (2003), Schulz et al. (2001), Jentsch et al. (1998), Shiigi and Casey (1999), and Stoet and Snyder (2006)
	A deficit in information processing	An impairment in cognitive tests and information processing	
	An impairment in spatial working memory, executive control	A decrease in social interaction	
	A decrease in social interaction	An increase of stereotypy behaviour	
	An increase of stereotypy behaviour		

in information processing measured by the test of prepulse inhibition of the startle reaction (PPI) in adult rats (Wang et al., 2003, 2004; Takahashi et al., 2006). On the other hand, other studies have reported no change in PPI (Harris et al., 2003; Stefani and Moghaddam, 2005; Rasmussen et al., 2007). By virtue of hyperdopaminergic condition in the mesolimbic system, the hyperlocomotion in rats can be correlated with positive symptoms in schizophrenia (McCullough and Salamone, 1992; Lipska and Weinberger, 2000). However, the presumed hyperlocomotion following neonatal exposure to NMDA receptor antagonists has not been reported in all studies (Harris et al., 2003; Stefani and Moghaddam, 2005; review Du Bois and Huang, 2006; Baier et al., 2007). On the other hand, hyperlocomotion has been reported following administration of amphetamine (Wedzony et al., 2005) or metamphetamine (Abekawa et al., 2007), an increased sensitivity to dopamine-increasing substances thus being another indicator of schizophrenia-like behaviour (Lipska and Weinberger, 2000; Bubeníková et al., 2003). Not only hyperlocomotion, but also excessive grooming of animals (a marker of stereotypy) is dependent on the dopaminergic system (DalÍOlio et al., 2000). The increased grooming in adult rats was observed after neonatal administration of NAAG (Bubeníková-Valešová et al., 2006).

Beside behavioural disorders, structural changes in CNS following early inhibition of NMDA receptors have also been detected in adult rats. An increased volume of subiculum and reduced number of hippocampal CA1 neurons has been reported in adult rats following neonatal (7 PND) acute administration of MK-801 (Harris et al., 2003). With regard to the inconsistent findings in humans, data on the change in expression (mRNA and protein) of the NMDAR subunits in adulthood following neonatal exposure to NMDA receptor antagonists are important. These results might point to likely changes in the structure of NMDA receptors in schizophrenia. A reduced expression of the NR1subunit (protein, immunoautoradiography) in ventral hilus and, conversely, an increased expression of this subunit in dorsal hilus (Harris et al., 2003), as well as a reduced expression of the NR2B subunit mRNA (Sircar et al., 1996) have been found in individual studies. Beside the change in the glutamatergic system, prenatal administration of MK-801 (E15-E18) decreases also the number of parvalbumin-positive GABAergic neurons in the medial cortex in adult rats (35 and 63 PND) (Abekawa et al., 2007). Reduction of these GABAergic neurons in the prefrontal cortex (Brodmann areas 9 and 10) has also been documented in patients with schizophrenia (Lewis et al., 2005).

The findings concerning neonatal inhibition of NMDA receptors point to a significant role of the glumatergic system in the development of cognitive functions and response of the organism to psychotomimetics such are amphetamine or apomorphine. Neonatal inhibition of the NMDA receptor is a heuristic model of schizophrenia based on the neurodevelopmental hypothesis of the origin of the disease. The use of this model in the research of schizophrenia highlights the role of the neuronal apoptosis in the pathophysiology of schizophrenia. It is interesting that through the inhibition of the NMDA system in certain vulnerable periods of development one can change the sensitivity of the mesolimbic system and induce an associated increased reactivity to amphetamine, metamphetamine and related substances. The influence of environment (stress and new environment) during adolescence on individual behaviour following neonatal inhibition of the NMDA receptor has not been studied so far. The high time demand is a main disadvantage of this model. This methodical drawback makes it

problematic to use this model in the search for new substances with antipsychotic effects.

3. Genetic model of schizophrenia based on inhibition of NMDA receptor

The genetic model inspired by a hypothetical NMDA dysfunction in schizophrenia is based on a decrease in expression of the NR1 subunit or of other NMDA receptor subunits. Mohn and colleagues showed that an insertion of a gene of resistance to neomycine into intron 20 of the *NR1* locus reduced expression of the NR1 subunit by 90% in homogenates from the cerebral cortex of mice that were genetically adjusted this way (Mohn et al., 1999). Mice with full deletion of the gene for the NR1 subunit die immediately after birth (Forrest et al., 1994). NR1 hypomorphic mice (NR1−/−) show schizophrenia-like behaviour (Table 1). These mice have also shown an increased locomotor activity, a decreased metabolic activity (autoradiographic measurement of 14C-2-deoxyglucose uptake) in medial prefrontal cortex, anterial cingulum and hippocampus (Duncan et al., 2002), decreased social interaction (Duncan et al., 2004; Mohn et al., 1999) and decreased PPI (Duncan et al., 2004, 2006). An increased sensitivity to amphetamine has been reported in these mice only in the PPI test, but not during observation of locomotor activity (Miyamoto et al., 2004).

Mouse model with a point mutation in the glycine-binding site of the NR1 subunit (*Grin1*) exhibits a fivefold reduction (mutation at position 481 Asp/Asn) or 86-fold reduction (mutation at position 483 Lys/Gln) in the receptor glycine affinity. Heterozygote mice $Grin1^{D481N/K483Q}$ exhibit NMDA receptor hypofunction, hyperlocomotion, impairment in habituation, intact PPI test with an increase in startle response and an impairment of performance in visible platform task in the Morris water maze test (Ballard et al., 2002).

Another methodological approach to decreasing the expression of the NR1 subunits in selective brain areas is application of antisense oligonucleotides. Adult rats injected with vectors expressing an antisense RNA for the NR1 subunit to dorsal hippocampus exhibited impaired learning in an avoidance task (Cheli et al., 2006). Another study applied antisense oligonucleotides against the NR1 subunit by using the HVJ-liposome-mediated gene-transfer method into both dorsal and ventral hippocampus (Inada et al., 2003). The NR1 subunit was blocked by 30% in the hippocampus and knockdown animals showed decreased PPI, but their spatial memory in the water maze task remained unaffected (Inada et al., 2003). A pilot study from our laboratory showed that a single dose of antisense oligonucleotides into the ventral hippocampus decreased expression of NR1 subunit by 20% without any effect on performance in the PPI test (Vrajová et al., 2007).

In addition, knockout mice for the NR2A subunit showed the following changes in behaviour: hyperlocomotion in novel environment, cognitive deficit in latent learning in the water finding test, impaired spatial memory in the Morris water maze test and, finally, impaired associative learning in eye blink conditioning and fear conditioning. PPI was unaffected (see review Enomoto et al., 2007; Takeuchi et al., 2001; Sakimura et al., 1995).

The genetic models of hypofunction of the NMDA receptors show constructive validity and some of them also phenomenological validity. They point to the significant role of NMDA receptors and especially of the NR1 subunit in the pathophysiology of schizophrenia.

4. Pharmacological model of schizophrenia: hypofunction of NMDA receptors in adults

This model consists in acute or chronic administration of NMDA receptor antagonists to adults (Table 2), and is based on the glutamatergic hypothesis of schizophrenia (Javitt and Zukin, 1991; Carlsson et al., 2001). This hypothesis presumes that by inhibition of NMDA receptors, the mesolimbic dopaminergic system becomes secondarily activated which in turn causes psychosis. Besides affecting the dopamine system, blockade of NMDA receptors reduces the firing rate of fast-spiking inhibitor interneurons in the frontal cortex (Homayoun and Moghaddam, 2007). Therefore, acute inhibition of the NMDA receptor causes disinhibition of neurotransmitter systems. However, long-term exposure to NMDA antagonists is followed by a decrease of brain activity (Jentsch and Roth, 1999). The first description of induction of schizophrenia-like symptoms by NMDA antagonists in humans has been reported with phencyclidine (Luby et al., 1959). Phencyclidine (PCP) is a substance originally used as a dissociative anesthetic agent, however, its administration is associated with a number of adverse effects and it may induce addiction (Baldridge and Bessen, 1990). Similar to PCP is dizocilpine (MK-801, synthesized in 1982), originally developed as neuroprotective and anticonvulsant substance (Olney et al., 1989; Kochhar et al., 1991). The last candidate substance for schizophrenia modeling is ketamine. Ketamine was synthesized in 1962, and was introduced to the market as an anesthetic agent in 1970 (White et al., 1982). Ketamine evokes nightmares, depersonalisation, derealisation and changes in emotiveness, the common complication of ketamine anesthesia (Coppel et al., 1973). Similar to the above-mentioned substances is memantine, which is clinically used for treatment of dementia and major depression (Robinson and Keating, 2006; Zarate et al., 2006). Memantine has lower affinity (>500 nmol/l) and more rapid kinetics for the NMDA receptor than MK-801, PCP or ketamine. Memantine has fast on/off kinetics with a moderate-affinity to the NMDA receptor ensures that, 15–20% of channels remain unblocked and available for physiological activation (Robinson and Keating, 2006).

4.1. Acute administration of NMDA receptor antagonists

Following acute systemic administration of NMDA receptor antagonists, an increase in extracellular level of glutamate, dopamine, serotonin and acetylcholine in the frontal area of rats and monkeys occur (Moghaddam et al., 1997; Martin et al., 1998; review Jentsch and Roth, 1999). On the contrary, local application of MK-801 into rat prefrontal cortex lacked any effect on serotonin and glutamate levels (López-Gil et al., 2007). The effects of NMDA antagonists on extracellular levels of monoamines are regulated indirectly, likely by GABAergic neurons. Reversible loss of GAD67 (glutamic acid decarboxylase) and parvalbunim GABEergic interneurons was observed in primary cortical neuronal cultures exposed to NMDA receptor antagonists (Behrens et al., 2007). In the subcortical area, the acute administration of NMDA receptor antagonists increased dopamine production (DOPAC/dopamine ratio) in nucleus accumbens (Hatip-Al-Khatib et al., 2001; Jentsch et al., 1997) and dopamine in striatum in the rat (Lillrank et al., 1994), but not in the monkey (Adams et al., 2001). Furthermore, local administration of PCP into the medial prefrontal area in the rat decreased extracellular GABA levels (Yonezawa et al., 1998), conversely, in striatum, local administration of the substance had an opposite effect (Lillrank et al., 1994). Brain metabolic activation was increased in hippocampal formation and limbic cortical regions after administration of NMDA antagonist in rats. On the other hand, reduced uptake was observed in cortical regions (layers 3 and 4) (Duncan et al., 1999). On the contrary, in unmedicated patients with schizophrenia glucose metabolic rate was decreased in thalamus, frontal and temporal lobe (Lehrer et al., 2005). In another study with patients with positive symptoms, hypermetabolic pattern was demonstrated in frontal cortex and thalamus, as well as in striatum

and in temporal cortex (Soyka et al., 2005). It is likely that the changes in metabolic pattern after acute administration of NMDA antagonists are similar to those occurring in patients with acute psychotic state. Acute administration of ketamine-induced expression of Homer1a (the candidate gene in schizophrenia) in ventral striatum and nucleus accumbens, calmodulin protein kinase II (αCaMKII) and transporter for dopamine (DAT) in substantia nigra and ventrotegmental area (Iasevoli et al., 2007). The expression of Homer1a (immediate early form of Homer, which regulates the metabotropic glutamate receptor GluR 1/5) is induced by synaptic activity and glutamate as well as by cocaine and amphetamine. The αCaMKII enzyme phosphorylates Homer1 (Iasevoli et al., 2007). The induction of expression of the above-mentioned genes following acute administration of ketamine suggests interconnection of NMDA receptors with the dopamine system and with mGluR 1/5. An increase in the activation of cfos (immediate early gene) indicates neuronal activity (Herdegen et al., 1995). Acute administrations of NMDA antagonists induce expression of cfos and fos-related antigen in the cortical areas (prefrontal and retrosplenial cortex), nucleus accumbens, amygdala, hippocampus and the hypothalamus (Imre et al., 2006; Zhang et al., 1999; Duncan et al., 1998). In addition, NMDA antagonists induced cfos expression correlates to brain metabolic activity and to psychomimetic effects of these drugs (Duncan et al., 1998). By contrast, an anesthetic dose of ketamine resulted in a robust induction of cfos in the same brain areas as observed after a subanesthetic dose (Duncan et al., 1998). High doses of NMDA antagonists produce neuronal injury in posterior cingulate and retrosplenial cortex (Olney et al., 1989). Injury of cortical neurons is manifested by vacuolization of the neuronal cytoplasm (Olney et al., 1989) and is accompanied by induction of the HSP70 heat shock protein (Sharp et al., 1991). Acute administration of PCP increases mRNA expression of NMDA associated protein SAPAP (synapse-associated protein90/postsynpatic denisty-95-associated protein1) in nucleus accumbens and hippocampus (Kajimoto et al., 2003). Acute PCP treatment did not affect phosphorylation, expression, or phosphorylation ratio of the NR1 subunit of the NMDA receptor (Mouri et al., 2007).

The excessive changes in the neurotransmitter system following acute administration of NMDA receptor antagonists result in changes in behaviour of the animals (mice, rats and monkeys). We searched the MEDLINE database back to 1990 for publications focusing exclusively on observation of the effects of selected NMDA receptor antagonists on behaviour of the mouse, rat and monkey. The studies demonstrated worsening of working memory, decreased level of prepulse inhibition of the startle reaction (PPI), impaired social interaction, hyperlocomotion and increased stereotypy (Linn et al., 2007; Zajaczkowski et al., 2003; review Geyer et al., 2001; review Jentsch and Roth, 1999; Shiigi and Casey, 1999; Hitri et al., 1993; Sams-Dodd, 1995). In monkey experiments (*Maccaca mulatta*), acute dose of ketamine impaired executive control (Stoet and Snyder, 2006), which is very similar to the results obtained in schizophrenic patients (Kravariti et al., 2005). PPI is a marker of sensorimotor gating (Table 1) and deficits in PPI were found in severe neuropsychiatric disorders such as schizophrenia (see review Geyer et al., 2001). As described earlier, administration of NMDA antagonists to rodents and monkeys produced deficit in PPI similar to that found in patients with schizophrenia (Linn et al., 2007). However, administration of ketamine in healthy humans enhances PPI and reduces startle magnitude, which is in contrast to the results seen in patients with schizophrenia (Abel et al., 2003).

4.2. Long-term administration of NMDA receptor antagonists

Long-term administration of NMDA receptor antagonists results in a decrease in extracellular glutamate in the frontal area of the brain of mice (Zuo et al., 2006). Contrarily to acute administration of NMDA receptor agonists, long-term treatment decreases production (DOPAC/dopamine ratio) and utilization (HVA/dopamine ration) of dopamine in dorsolateral prefrontal cortex and prelimbic cortex in rats and monkeys (Jentsch et al., 1997, 2007). Subchronic administration of PCP results in sensitization of the mesolimbic dopaminergic system (Jentsch et al., 1998). Similar changes in the glutamatergic and dopaminergic systems were found in patients with schizophrenia (Kim et al., 1980; Tsai et al., 1995; Breier et al., 1997). Chronic intermittent exposure to phencyclidine induced reduction in glucose utilization in the prefrontal cortex, thalamus and auditory system, structures displaying similar changes in schizophrenia (Lehrer et al., 2005; Cochran et al., 2003). Moreover, several studies have confirmed an increased level of glutamine in the prefrontal cortex, anterior cingulum and thalamus in patients during the first schizophrenic episode (Bartha et al., 1997; Théberge et al., 2002). A similar change in glutamate metabolism has been found in the frontal area of rats following repeated administration of MK-801 (Kondziella et al., 2006). Subchronic administration of ketamine induces similar changes in cfos expression in the hippocampus as acute administration of NMDA antagonists. Moreover, changes in cfos expression were observed after a 14-day washout period (Keilhoff et al., 2004). Chronic administration of PCP facilitated the NMDA synaptic current while depressing the extra-synaptic NMDA current. Postsynaptic NMDA receptors respond with larger and faster NMDA currents than those localized extra-synaptically and could increase sensitivity to subsequent damage of neurons (Yu et al., 2002). Chronic administration of NMDA receptor antagonists decreases the expression of protein RGS4 (Gu et al., 2007). The lower expression of RGS4 has been reported in the frontal area of patients with schizophrenia (Mirnics et al., 2001). Chronic administration of MK-801 increases mRNA expression of subunits NR2B and NR1, exon 5 of the NMDA receptor in rat hippocampus (Rujescu et al., 2006) and decreases NR2A (Oh et al., 2001; Rujescu et al., 2006). No significant changes in protein levels of the NMDAR subunits, such as NR1, NR2A or NR2B were observed in rats exposed to different durations of PCP (Gu et al., 2007). In another study, enhancement of NR1 expression and a decrease of NR1 phosphorylation (Ser897) in prefrontal cortex were observed after chronic PCP treatment in mice (Mouri et al., 2007). The level of phosphorylated NR1 (Ser897) is decreased in the frontal cortex in patients with schizophrenia (Emamian et al., 2004). It is suggested that the decreased phosphorylation ratio of NR1 may be associated with the impairment of cognitive function (Mouri et al., 2007).

GABAergic neurotransmission is also compromised following chronic administration of NMDA receptor antagonists. A decreased mRNA expression of enzyme GAD_{67} synthesizing GABA (Qin et al., 1994) and reduction of parvalbumin-positive interneurons (Rujescu et al., 2006; Morrow et al., 2007) have been detected. These findings correlate with post mortem findings in patients with schizophrenia (Hashimoto et al., 2003; Benes, 1998; Benes and Berretta, 2001). Subchronic administration of ketamine in mice induced an increase in NADPH oxidase activity and increased oxidative stress in the PFC, hippocampus and thalamus, which induced a loss of parvalbumin interneurons (Behrens et al., 2007). Furthermore, chronic administration decreases neurogenesis in the dentate gyrus (Maeda et al., 2007).

The above-mentioned changes in neurotransmitter systems are associated with behavioural changes reported following a long-term administration of NMDA receptor antagonists. Impairment of cognitive functions and information processing following chronic NMDA administration has been reported in several studies in different animals species (Jentsch et al., 2007; Vales et al., 2006; Stefani and Moghaddam, 2005; Rujescu et al., 2006; Mandillo et al.,

2003; Schulz et al., 2001). Moreover, the cognitive deficit is still present after withdrawal from the drug in monkeys and mice (Jentsch et al., 2007; Mouri et al., 2007). Learning is associated with phosphorylation by Ca^{2+}/CaMKII. Inhibition of NMDA receptors decreases this phosphorylation, which may explain the deficits in cognitive function induced by these substances (Mouri et al., 2007). Chronic administration of phencyclidine increases stress- and amphetamine-induced hyperlocomotion (Jentsch et al., 1998), impairs social behaviour and increases stereotyped behaviour in rats and monkeys (Sams-Dodd, 1998; Linn et al., 2007). Long-term administration of NMDA receptor antagonists results in sensitization of locomotor activity in the rat (review Jentsch and Roth, 1999).

Acute inhibition of the NMDA receptor induces schizophrenia-like behaviour in animals and shows phenomenological validity as a model. Due to its time feasibility, this model is often used to predict the effect of substances with potential antipsychotic properties (Bubeníková et al., 2005; Large, 2007). The animal model of schizophrenia based on long-term administration of NMDA receptor antagonists shows both constructive and phenomenological validity. Changes in neurotransmitter systems represent an analogy to the changes reported in selected patients with schizophrenia. The NMDA antagonist-induced cognitive dysfunction, particularly of working memory and attention, also supports the validity of this model for schizophrenia research (Table 2). Its pertinence in searching for new substances with antipsychotic effects and in elucidating the mode of action of currently available psychotropic drugs has been repeatedly demonstrated. On the other hand, it should be taken into account that repeated administration with high doses of metamphetamine produces changes similar to chronic effects of NMDA antagonists. Recently it has been found those antipsychotics are similarly effective against abnormalities in this model (Abekawa et al., 2008).

4.3. Studies with ketamine in healthy volunteers

In human studies, ketamine appears to be a useful tool for modeling schizophrenic psychosis due to its specific psychotomimetic properties (Anis et al., 1983) and excellent safety profile. The ketamine model of schizophrenia was first fully verified by Krystal et al. (1994). The study confirmed that infusion of subanesthetic doses of ketamine results in dose-dependent induction of both positive and negative symptoms of schizophrenia, and worsening of cognitive functions relevant to the activity of the prefrontal cortex. However, mini mental state examination scores are not altered by ketamine and the finding suggests a specific psychotomimetic effect of ketamine different from its potential delirogenic action. In this fundamental study, ketamine had no effect on the plasma level of 3-methoxy-4-hydroxyphenyelthylenglycol (MHPG), which argues against the role of noradrenaline in its mode of action. At the same time ketamine flattened the physiological decrease in homovanillic acid (HVA) and, according to authors, this finding confirms a mild potentiation of the dopaminergic system. In a dose-dependent manner, ketamine increased the levels of prolactine and cortisol. The induction of negative symptoms in this study in particular gives evidence for the specific modeling of schizophrenia with ketamine compared to other psychotomimetic substances that only induce simple psychosis (Bowers and Freedman, 1966; Krystal et al., 1994). Other authors have later confirmed the induction of the broad spectrum of schizophrenia symptoms by ketamine.

Summarizing the influence of ketamine on the symptom spectrum, it seems that the positive symptoms induced by ketamine in healthy volunteers are not as severe as those observed in patients with schizophrenia relapse. Furthermore, true hallucinations are relatively rare after ketamine, while symptoms related to perception distortion are more characteristic of this model (Krystal et al., 1994; Malhotra et al., 1996).

Induction of negative symptoms such as blunted affect, alogia and social withdrawal, is the main argument in favor of the ketamine model. These negative symptoms are not attributable to the anesthetic effect of ketamine and may be rather a result of its specific activity in this respect (Krystal et al., 1994; Malhotra et al., 1996). The similarities between schizophrenia and the effect of ketamine in subanesthetic doses are mostly remarkable in disorganization symptoms, i.e. formal thought disorders and behavioural disorganization (Adler et al., 1999; Krystal et al., 1998, 1999b).

Subanesthetic doses of ketamine in healthy volunteers also result in cognitive dysfunction associated with the activity of frontal and temporo-hippocampal parts of the brain. This ketamine-induced cognitive dysfunction is similar to findings in schizophrenia, and includes worsening of verbal fluency tests, interpretation of proverbs, working and semantic memory, Stroop test and Wisconsin Card Sorting Test (Ghoneim et al., 1985; Krystal et al., 1994, 1998, 1999a; Malhotra et al., 1996; Oye et al., 1992; Radant et al., 1998).

Ketamine administration to healthy volunteers has been assessed in terms of neuro-physiological changes occurring in schizophrenia. The evaluation of PPI represents a methodology which is species nonspecific and reflects an impairment of sensorimotoric gating. In the case of evaluation of ketamine effect on PPI, either minimal suppression or an increase in PPI has been reported in healthy volunteers following subanesthetic doses (Abel et al., 2003; Duncan et al., 2001; Oranje et al., 2002; van Berckel et al., 1998). These observations are in conflict with findings in schizophrenia (Braff et al., 2001). The finding of PPI increase after ketamine suggests the role of dopaminergic rather than glutamatergic dysfunction in PPI impairment in humans (Oranje et al., 2002). On the contrary, ketamine infusion causes an impairment of smooth pursuit eye movements analogous to that occurring both in schizophrenic patients and their relatives (Avila et al., 2002; Radant et al., 1998; Weiler et al., 2000).

Brain imaging studies further support this model. Ketamine administration induces metabolic changes in the brain similar to those in acute psychosis, e.g. an increase in metabolism in the frontal areas of the brain, cingulum (Vollenweider et al., 1997) and thalamus (Langsjo et al., 2003). The studies have also confirmed that the ketamine model provides a link for the glutamatergic and dopaminergic theories of schizophrenia. The acute administration of ketamine to healthy volunteers decreased binding of D_2 radioligand ^{11}C-raclopride in striatum resulting from an increased release of endogenous dopamine (Breier et al., 1998; Smith et al., 1998; Vollenweider et al., 2000). Furthermore, the changes in ^{11}C-raclopride binding correlated with the induction of schizophrenic symptoms.

4.4. Studies with ketamine in schizophrenic patients

Ketamine is experimentally used also for induction of psychotic symptoms in patients with schizophrenia. Although these studies are ethically controversial (Carpenter, 1999), adverse effects other than provocation of short-term acute symptoms have not been reported nor were there any observable effect on the long-term prognosis of the tested subjects (Lahti et al., 2001).

A comparison of the effect of subanesthetic doses of ketamine in healthy volunteers and in schizophrenic patients has brought in several significant findings. While in healthy volunteers ketamine administration only rarely induces typical hallucinations (Krystal

et al., 1999a,b), in patients ketamine provokes characteristic acoustic or visual hallucinations (Lahti et al., 1995). It has been shown that patients with schizophrenia who are exposed to psychotomimetic substances (amphetamine, tryptamines, phenylethylamines and others) experience more frequently development of psychosis which persists regardless of the elimination of the drug from the body (Lieberman et al., 1987). However, these substances do not induce symptoms which are individually specific for patients (Angrist et al., 1980; Angrist and Gershon, 1970; Tamminga et al., 1978). On the contrary, ketamine provokes individually specific symptoms similar to those that the concrete patients experienced in spontaneous relapses (Lahti et al., 1995). This is the additional argument supporting the validity of this model in healthy volunteers as well as in animal testing.

The review of studies in healthy individuals and patients suggests that ketamine administration in subanesthetic doses provokes schizophrenic symptoms in the full extent. Furthermore, in patients it induces individually specific symptoms. Studies which have induced psychotic symptoms by amphetamine (Janowsky and Risch, 1979), lysergic acid diethylamide (Freedman, 1968; Lieberman et al., 1987) and dimethyltryptamine (DMT) (Gillin et al., 1976) represent an alternative to the ketamine model. Current experience leads to consensus that although these substances induce acute psychosis, they do not model the specific symptoms characteristic of schizophrenia.

5. Conclusions

The non-competitive NMDA receptor antagonists exert potential for modeling psychotic behaviour. Models based on acute or chronic administration of these substances both in humans and rats show phenomenological validity and are usable in the testing of new substances with potential antipsychotic effect. Nevertheless, pathophysiology of schizophrenia remains unexplained. With respect to the neurodevelopmental model of schizophrenia based on early administration of NMDA antagonists it seems that increased cellular damage by apoptosis or changes in function of glutamatergic NMDA receptors in the early development of central nervous system are decisive for subsequent development of psychosis which often does not manifest itself until adulthood. Chronic administration of antagonists initializes a number of adaptation mechanisms, which correlate with findings obtained in patients with schizophrenia; therefore, this model is also suitable for research into pathophysiology of this disease.

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