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Glutamate related metabolism in animal models of schizophrenia

Thesis for the degree of philosophiae doctor

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Glutamat-relatert metabolisme i dyremodeller for schizofreni

Schizofreni er en alvorlig psykisk lidelse som preges av psykotiske symptomer som vrangforestillinger, hallusinasjoner og andre symptomer som sosial tilbaketrekning og svekket sosial fungering. Epidemiologiske studier har vist at livstidsrisikoen er 0,5-1% i det meste av verdens befolkning.

Etiologien og patofysiologien til schizofreni er ikke kjent. De to viktigste patofysiologiske teoriene for schizofreni har vært den såkalte dopaminteorien og glutamatteorien. Disse predikerer henholdsvis økt aktivitet i dopaminerge systemer og redusert aktivitet i visse glutamaterge systemer. Resultater fra studier i den senere tid tyder også på at det finnes forandringer i cytoskjellettet ved schizofreni, for eksempel i mikrotubuliassosierte proteiner. De fleste schizofrenisymptomer er unike for menneskelig atferd. Å kunne reprodusere schizofreni i en dyremodell er derfor vanskelig. Dyremodeller er likevel et viktig verktøy for å identifisere patofysiologiske mekanismener bak schizofreni, og for å komme fram til nye medisiner.

Denne avhandlingen inneholder fire publikasjoner hvor vi studerte dyremodeller for schizofreni. I tre av dem ble NMDA-reseptorantagonisten MK-801 brukt til å redusere glutamaterg nevrotransmisjon i rotter. Tre forskjellige forsøksoppsett ble brukt: En enkelt injeksjon av en høy dose MK-801, daglige injeksjoner med høy konsentrasjon i til sammen seks dager, og daglige injeksjoner med en lavere dose MK-801 i seks dager. Den fjerde studien beskriver glutamatrelatert metabolisme ved ustabile mikrotubili. Dette gjorde vi ved å undersøke "knock out" mus hvor genet for det mikrotubiliassosierte proteinet STOP (Stable Tubule Only Peptide) var satt ut av funksjon.

Vi undersøkte glutamatrelatert metabolisme i alle disse modellene. Hjerneekstrakter fra flere hjerneområder ble analysert med HPLC (High Performance Liquid Chromatography), ^{13}C- og ^{1}H-magnetisk resonansspektroskopi. Ved å injisere 1-^{13}C merket glukose og 1,2-^{13}C merket acetat kunne vi se forskjell på nevron- og astrocyttmetabolisme. En enkelt dose med 0,5 mg/kg kroppsvekt MK-801 skapte flest metabolske forskjeller i temporal lappen. Her var det økte totale mengder av glutamat og glutamin, og dessuten økt innmerkning fra [1-^{13}C]glukose. Vi så liknende forskjeller da vi injiserte 0,1 mg/kg MK-801 i flere påfølgende dager. Da rottene derimot ble injisert med 0,5 mg/ MK-801, fant vi metabolske forskjeller i cingulate-, retrosplenial- og frontalcortex. Her var det også en økt totalmengde av glutamat, men innmerkning fra både [1-^{13}C]glukose og [1,2-^{13}C]acetat var redusert i flere metabolitter sammenlignet med kontrolldyrene. Reultater i artikkel 4 viser reduserte mengder av både totalglutamin og glutamin merket fra [1,2-^{13}C]acetat i cerebrum til STOP "knock out" mus.

Når vi sammenligner resultatene våre med data fra studier av pasienter med schizofreni, ser det ut til at repeterte injeksjoner av en høy dose MK-801, kan være en god dyremodell for schizofreni i et tidlig stadium. STOP "knock out" modellen viser lignende metabolske forskjeller som hos pasienter med kronisk schizofreni, og derfor kanskje en god dyremodell for mer langtkommen schizofreni. Resultatene fra studiene i denne oppgaven viser at både blokkering av NMDA-reseptoren og ustabile mikrotubili, forstyrrer glutamat-glutamin syklus, og det er fristende å påstå at interaksjonen mellom astrocytter og nevroner er undervurdert i schizofreniforskning.

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I also wish to show my appreciation to Bente Urfjell for her technical assistance.

Abbreviations

acetyl-CoA	acetyl coenzym A
AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid
ATP	adenosine triphosphate
CNS	central nervous system
DA	dopamine
EAAT	excitatory amino acid transporter
FAD	flavin adenine dinucleotide
FCR	cingulate and the retrosplenial cortices
FID	free induction decay
GABA	γ-amino-butyric acid
GAD	glutamate decarboxylase
GDH	glutamic acid dehydrogenase
Gln	glutamine
Glu	glutamate
GLUT	glucose transporter
GS	glutamine synthetase
GSH	glutathione
GTP	guanosine triphosphate
HPLC	high performance liquid chromatography
KA	kainic acid
KO	knock out
MAP	microtubule-associated protein
MCT	monocarboxylate transporter
MK-801	dizocilpine
NAA	N-acetylaspartate
NAD	nicotinamide adenine dinucleotide
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance
NMRS	nuclear magnetic resonance spectroscopy
NO	nitric oxide
nOe	nuclear Overhauser effect
NOS	Nitric oxide synthase
PAG	phosphate activated glutaminase
PC	pyruvate carboxylase
PCP	phencyclidine
PCP	phencylidine
PDH	pyruvate dehydrogenase
PFC	prefrontal cortex
SAT1	system A amino acid transporter 1
SN	system N amino acid transporters
STOP	stable tubule only polypeptide
TCA	tricarboxylic acid
TL	temporal lobe
TL	temporal lobe

Summary

Schizophrenia is a clinical syndrome of variable psychopathology, which involves thought, perception, emotion, movement and behavior. The cumulative effect of the illness is always severe and usually long lasting. Epidemiologic studies indicate that the lifetime expectancy is 0.5-1% worldwide.

The etiology and pathophysiology of schizophrenia are unknown. The two predominant pathophysiological hypotheses of schizophrenia are the dopamine hypothesis and the glutamate hypothesis. The former hypothesis states that dopamine neurotransmission is hyperactive in schizophrenia, the latter – that there is a hypofunction of glutamatergic neurotransmission in some areas of the brain. Recent studies also suggest that schizophrenia is associated with cytoskeletal alterations in neuronal architecture, e.g. differences in micro tubule associated proteins (MAP). The symptoms of schizophrenia are mostly unique to human behavior. Consequently, the exact reproduction of schizophrenia in an animal is not possible. However, animal models are important tools for exploring the underlying mechanisms of schizophrenia and for designing new therapies.

The present thesis is based on four publications on animal models of schizophrenia. We used the NMDA receptor antagonist MK-801 to induce a state of hypoglutamatergia in rats in the three of them. Three different designs were used: injection of a single high dose, repeated high dose injections over several days and repeated injections of a lower dose. The fourth study was designed to investigate glutamate related metabolism in a state of microtubule instability. Knock out mice were used as a model, in which the gene coding for the microtubule associated protein STOP (Stable Tubule Only Peptide) was deleted.

Glutamate related metabolism was investigated in these models by analyzing brain extracts from multiple brain areas, using HPLC (High Performance Liquid Chromatography) and ^{13}C and ^{1}H nuclear magnetic resonance spectroscopy. By injecting animals with 1-^{13}C labeled glucose and 1,2-^{13}C labeled acetate, the preferential substrates of neurons and astrocytes, respectively, it was possible to follow metabolic interactions between astrocytes and neurons.

A single dose of 0.5 mg/kg MK-801 produced predominantly changes in the temporal lobe with increased total amounts of glutamate and glutamine, and increased labeling from [1-^{13}C]glucose. Similar changes were observed when MK-801 was administered repeatedly at 0.1 mg/kg for 6 consecutive days and all the metabolic alterations were confined to the temporal lobe. However, while 0.5 mg/kg MK-801 was used repeatedly instead of 0.1 mg/kg MK-801, changes were found in the cingulate, retrosplenial and frontal cortices. The total amount of glutamate increased in those areas together with a decrease in labeling from both [1-^{13}C]glucose and [1,2-^{13}C]acetate in several metabolites. In Paper 4 decreased levels of both total glutamine and labeled [4,5-^{13}C]glutamine were reported in the cerebrum of STOP knock out mice.

Compared to data from studies of schizophrenic patients, our results indicate that repeated injections of MK-801 in high doses may be a good model for first episode schizophrenia and the STOP KO mouse model show similarities to and may be a good model chronic schizophrenia. Results show that both the NMDA receptor hypofunction and the loss of microtubule stability seem to disrupt the glutamate-glutamine cycle, and it can be stated that astrocytic-neuronal interactions probably are underestimated in schizophrenia research.

List of Publications

The thesis is based on the following papers:

Paper 1

BRENNER, E., KONDZIELLA, D., HABERG, A. & SONNEWALD, U. 2005. **Impaired glutamine metabolism in NMDA receptor hypofunction induced by MK801**. Journal of Neurochemistry, 94, 1594-1603.

Paper 2

EYJOLFSSON, E. M., BRENNER, E., KONDZIELLA, D. & SONNEWALD, U. 2006. **Repeated injection of MK801: An animal model of schizophrenia?** Neurochemistry International, 48, 541-546.

Paper 3

KONDZIELLA, D., BRENNER, E., EYJOLFSSON, E. M., MARKINHUHTA, K. R., CARLSSON, M. L. & SONNEWALD, U. 2006. **Glial-neuronal interactions are impaired in the schizophrenia model of repeated MK801 exposure**. Neuropsychopharmacology, 31, 1880-1887.

Paper 4

BRENNER, E., SONNEWALD, U., SCHWEITZER, A., ANDRIEUX, A. & NEHLIG, A. 2007. **Hypoglutamatergic activity in the STOP knockout mouse: a potential model for chronic untreated schizophrenia**. Journal of Neuroscience Research, 85, 3487-3493.

Table of contents

1 Introduction

1.1 Brain structure and metabolism

1.1.1 Cell types of the brain

Neurons are the cells responsible for the brain's primary functions and are characterized by their ability to send signals over shorter or longer distances. Inter neuronal signals are sent mainly via chemical signals, whereas the intracellular signal of the neuron is an electric impulse caused by ion movement across the cell membrane, primarily influx of Na^+ and efflux of K^+. The action potential runs down the axon and depolarizes the membrane of the synapse. This causes opening of voltage gated ion-channels and an increase in intracellular Ca^{2+} causing release of vesicular neurotransmitters, such as glutamate, GABA (γ-aminobutyric acid) and dopamine. The neurotransmitters cross the synaptic cleft and binds to specialized receptors on the post-synaptic membrane, where this will change the potential of the postsynaptic membrane. Each neuron in the brain can be innervated by thousands of synapses, the postsynaptic effects of each active synapse can be added together in space and time, and determines whether the postsynaptic neuron will generate a new action potential.

However, the neurons cannot do the job alone. They have three main types of helper cells (glial cells): astrocytes, oligodendrocytes and microglia. In short, oligodendrocytes create the myelin around the axons of neurons, whereas microglia have phagocytic properties and act as a part of the central nervous system's immune system (Brodal, 2001).

The role of astrocytes in the central nervous system is slowly gaining more focus. Traditionally astrocytes have been considered to only have a supportive role for neuronal structure (glia = glue), but in recent years far more complex functions with regard to for example neurotransmitter and water homeostasis have been unraveled (Nedergaard et al., 2003).

Astrocyte morphology is different in distinct areas of the brain. The protoplasmic astrocyte has many small processes that spread out in different directions contacting neuronal bodies and synapses. Some of these processes have endfeets which line the capillaries in the brain. Others line the pia and the ependymal cells bringing the astrocytes in close contact to the cerebrospinal fluid. Consequently, the astrocytes are well-suited to perform substance exchange between glial cells and neurons, different glial cells and glial cells, and blood or cerebrospinal fluid (Brodal, 2001).

It is well established that astrocytes maintain the extracellular concentration of K^+ and H^+ which are important for neurotransmission (Brodal, 2001). Moreover the astrocytes effectively remove several neurotransmitters from the synaptic cleft (Danbolt, 2001). Astrocytes also synthesize precursors for neurotransmitters (Sonnewald et al., 1993). More recent studies indicate that astrocytes provide energy substrates to neurons (e.g. lactate (Magistretti and Pellerin, 1999)) and are important in brain water homeostasis (Nedergaard et al., 2003) and in the maintenance of the blood-brain barrier. There are also emerging proofs that they are involved in synaptic modulation and regulation of both synaptogenesis and neurogenesis (Ransom et al., 2003).

1.1.2 Neurotransmitters

Chemical neurotransmission is the main way in which a signal is communicated from one neuron to another. However, electrical synapses are also present in the brain. In an electrical synapse, an ionic current may flow passively through gap junctions, and in that way alter the postsynaptic potential. In contrast, chemical synapses enable intercellular communication via the release of neurotransmitters. These are chemical agents that are stored in vesicles in the presynaptic nerve terminal and released by exocytosis into the synaptic cleft upon an action potential. The transmitters diffuse across the synaptic cleft and bind to specific receptor molecules on the postsynaptic neuron, usually altering the membrane potential by opening or closing ion channels. Neurotransmitters are often divided into classical and non-classical transmitters. The classical neurotransmitters are all synthesized in the general vicinity of where they are released. Release is calcium

dependent and they are inactivated either by a specific reuptake mechanism or by specific enzymes, or both. The classical neurotransmitters include the biogenic amines, such as serotonin and the catecholamines (dopamine, epinephrine and norepinephrine) and the amino acid transmitters (glutamate and GABA). Non-classical neurotransmitters include peptides (eg. substance P), growth factors and gases (eg. nitric oxide (NO) and carbon monoxide) (Deutch et al., 1999).

1.1.3 Neurotransmitter receptors

There are two main types of neurotransmitter receptors: ionotropic receptors and metabotropic receptors. The ionotropic receptors are ion channels that will open rapidly when a neurotransmitter binds to the binding site. The metabotropic receptors are coupled to ion channels via second messengers. Transmitters that activate metabotropic receptors produce a postsynaptic response of slower onset and longer duration than that of transmitters acting on ionotropic receptors (Waxham et al., 1999).

Glutamate receptors are responsible for mediating most of the excitatory synaptic transmission in the central nervous system. There are three main types of ionotropic glutamate receptors: AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid), kainate and NMDA (N-methyl-D-aspartate) receptors. Six gene families, with two to six genes in each family coding for glutamate receptors, are known. When it comes to the ionotropic receptors, each gene codes for a subunit. Different subunits are put together to form a receptor heteromer. AMPA receptors are formed from subunits from the GluR1-GluR4 family, and kainate receptors from the GluR5-R7, KA1 and KA2 genes. The AMPA/Kainate receptors are permeable to Na^+ and to some extent K^+ (Waxham et al., 1999).

The far most studied glutamate receptor is the NMDA receptor. Six genes coding for NMDA receptor subunits are known (NR1, NR2A-2D and NR3). The subunits are distributed differently and only the NR1 subunit is distributed throughout the brain. In contrast to the AMPA/kainate receptors, the NMDA receptors are permeable to both Ca^{2+} and Na^+. They are also voltage dependent. During normal membrane resting potentials

the channel is blocked by a magnesium ion. Accordingly, the channel may only open when binding of glutamate and depolarization of the postsynaptic membrane happens at the same time. Influx of Ca^{2+} activate a variety of intracellular processes, therefore NMDA receptors appear to be more directly responsible for aspects of learning and memory than other receptors (Waxham et al., 1999). The binding site for glutamate/NMDA is also the site where competitive NMDA receptor antagonists bind, whereas non-competitve NMDA receptor antagonists like PCP (Phencyclidine), Ketamine and MK−801 (Dizocilpine) bind inside the ion channel (Zukin et al., 1987).

Dopamine receptors are metabotropic and are found both pre- and postsynaptically. There are five dopamine receptor subtypes which are grouped into the D1-like (D1 and D5) and D2-like (D2-D4) receptors. D1-like receptors activate adenylate cyclase, whereas D2-like receptors inhibit adenylate cyclase (Waxham et al., 1999).

1.1.4 Glucose metabolism in the brain

Compared to other tissues, the brain is a high energy demanding organ. Although the brain accounts for only 2% of the bodyweight, the energy required to maintain brain function is almost 20% of an individual's resting metabolic rate (Attwell and Laughlin, 2001).

Glucose is the main energy substrate for the brain, but in some circumstances other substrates can be utilized. Monocarboxylic acids including lactate and the ketone-bodies are important energy-yielding substrates in some instances, especially in neonates.
The blood-brain-barrier is the interface between the brain tissue and capillary blood. It consists of a semipermeable membrane lining either side of the endothelial cells. Substrates for energy are taken up by facilitated transport. There are specialised transporter for glucose, GLUTs, and monocarboxylic acids, MCTs.

After uptake into brain cells metabolism of glucose is similar to that in other tissues and there are three principal pathways: glycolysis, tricarboxylic acid and the pentose phosphate pathway. Glycolysis, which takes place in the cytosol, is the metabolism of

glucose to pyruvate. It results in the net production of two molecules of ATP. Under anaerobic conditions, pyruvate is converted to lactate allowing regeneration of NAD^+. Under aerobic conditions NADH will be reoxidized in the electron transport chain and pyruvate can be converted to Acetyl Co-A by the pyruvate dehydrogenase enzyme complex (PDH). Acetyl-Co-A condenses with oxaloacetate to produce citrate. This is the first step of the TCA-cycle taking place inside the mitochondria of the cell. Three pairs of electrons are transferred from NAD+ to NADH in the cycle, and one pair from FAD to $FADH_2$. In addition, 1 GTP is formed. The cycle ends with the formation of oxaloacetate from malate (for a review see (Hertz and Dienel, 2002)).

Electrons from the reducing agents NADH and $FADH_2$ are transferred through the electron transport chain, which is also called the respiratory chain, to molecular oxygen. This process is coupled to H^+ translocation across the inner mitochondrial membrane forming an electrochemical gradient. The electrochemical gradient drives the ATP synthase forming ATP. The quantity of ATP generated from this process is dependent upon coupling between O_2 consumption and ATP formation. Since every FADH2 or NADH molecule oxidized in the respiratory chain, produces essentially two or three molecules of ATP, respectively, the complete oxidation of one glucose molecule in a neural cell generates up to 34 ATP molecules. This represents a vast improvement over the two ATP molecules produced by anaerobic metabolism in glycolysis, a circumstance that makes the TCA cycle the most efficient cerebral bioenergetic process under aerobic conditions (Smith and Morowitz, 2004).

Besides being the main energy yielding metabolic pathway in the brain, the TCA cycle also has an important role in providing intermediates for many cerebral biosynthetic processes and neurotransmitters such as glutamate and GABA. (Gruetter, 2002; Owen et al., 2002) Loss of TCA cycle intermediates occurs when a-ketoglutarate is converted into glutamate and hence into GABA (in GABAergic neurons) and used in neurotransmission. To compensate for the loss of TCA cycle intermediates due to release of glutamine to the blood or decarboxylation of a four carbon unit, synthesis from precursors that are not TCA cycle intermediates themselves are needed. This kind of reaction is called

anaplerosis. The main anaplerotic enzyme in the brain is pyruvate carboxylase (PC). Anaplerotic carboxilation can also be carried out by phosphoenolpyruvate carboxykinase and malic enzyme, though they function mostly in the decarboxylation mode(Patel, 1974, Salganic.L and Koeppe, 1968). Pyruvate carboxylase is a mitochondrial enzyme and catalyzes the formation of oxaloacetate from pyruvate and HCO_3^- . PC has been shown by both biochemical and immune cytochemical methods to be expressed by cultured astrocytes, but not by cultured neurons(Shank et al., 1985, Yu et al., 1983)

1.1.5 Glutamine-glutamate cycle and compartmentation of brain metabolism

In the 1960s, after intracerebral administration of radiolabeled ^{14}C-acetate, a higher specific radioactivity in glutamine than in its precursor glutamate was found(Berl, 1965, Berl and Clarke, 1969, Waagepetersen et al., 2003). These findings could only be explained through the existence of two slowly exchanging pools of glutamate, denoted then as ‘‘large’’ and ‘‘small,’’ which exchanged radioactivity with ‘‘small’’ and ‘‘large’’ glutamine pools, respectively (Rodrigues and Cerdan, 2007). Soon, the ‘‘large’’ and ‘‘small’’ glutamate and glutamine pools were associated with the operation of the ‘‘energy’’ and ‘‘synthetic’’ TCA cycles, proposed to represent the neuronal and glial compartments, respectively. Subsequently, both cycles were connected by transfers of glutamate from the neuronal to the glial cycle, and glutamine in the opposite direction. The ‘‘glutamate–glutamine cycle’’ was conceived as a mechanism to replenish glutamate losses in the neurons during neurotransmission (van den Berg and Garfinkel, 1971).

Glutamate must be removed from quickly from the entire extracellular space. This is required for a high signal-to-noise ratio in synaptic transmission. Furthermore, excessive activation of glutamate receptors is toxic (so-called exitotocxicity) and glutamate receptors are found on most of the cellular elements (dendrites, nerve terminals, neuronal cell bodies as well as glial cells (Choi, 1992). The only rapid way of removing glutamate from the extracellular fluid surrounding the receptors is by cellular uptake (Danbolt, 2001). Glutamate uptake is accomplished by means of glutamate transporter proteins

which use the electrochemical gradients across the plasma membranes as a driving force for uptake (Danbolt, 2001). Both neurons and glial cells express glutamate transporters.

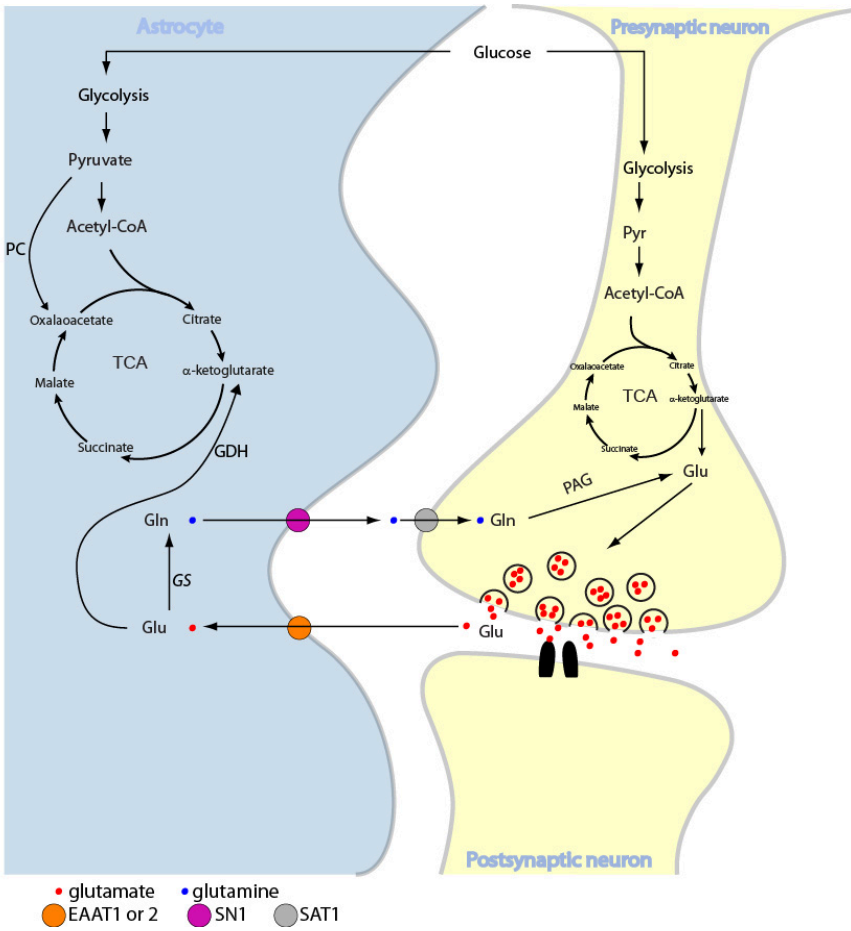

Figure 1 The glutamate-glutamine cycle. Glutamate is formed from α-ketoglutarate. After vesicular release from presynaptic nerveendings and binding to glutamate receptors on the postsynaptic membrane, glutamate is predominantly taken up by astrocytes via specialized transporter proteins. Here glutamate can be converted into glutamine, wich is not neuroactive and transported to neurons where it is converted back to glutamate and can be packed into vesicles for reuse as neurotransmitter. Also notice that the enzymes pyruvate carboxylase and glutamine synthetase are not present in neurons. Abbreviations:Gln, glutamine; Glu, glutamate; GS, glutamine synthetase; PAG, phosphate activated glutaminase; GDH, glutamic acid dehydrogenase; TCA, tricarboxylic acid cycle; EAAT, excitatory amino acid transporter; SN1, system N amino acid transporter 1; SAT1, system A amino acid transporter 1

Reuptake and reuse of glutamate as neurotransmitter is important because glutamatergic neurons, in contrast to astroglia, do not express pyruvate carboksylase as outlined above. Thus neurons cannot synthesize glutamate de novo from metabolites in the TCA cycle without causing a net loss of these metabolites. After uptake to presynaptic nerve endings, the reuse is straightforward as glutamate can be directly transported into vesicles. The first step in the recovery of glutamate uptake in astroglia is mediated by glutamate transporters EAAT (excitatory amino acid transporter) 1 and 2. (Danbolt, 2001). After uptake into astrocytes, glutamate may be transformed to glutamine by the ATP-dependent, astrocyte-specific enzyme glutamine synthetase (Martinez-Hernandez et al., 1977, Laake et al., 1995). Glutamine can be released from astroglia to extracellular fluid via the glial glutamine transporter SN1 (system N amino acid transporter 1). Glutamine is then taken up by the presynaptic neuron through the neuronal glutamine transporter SAT1 (system A amino acid transporter 1) and converted back to glutamate by phosphate-activated glutaminase (PAG) (Kvamme et al., 2001, Chaudhry et al., 2002).

1.1.6 Cytoskeleton, Microtubuli and MAPs

The cytoskeleton is the "backbone" of the cells and helps maintain cell shape. It is formed by three different structural proteins in all eukaryotic cells: actin (micro) filaments, intermediate filaments and microtubules. In the neurons, actinfilaments are found the axons and are especially important for neurogenesis during development of the nervous system. High concentration of the intermediate filaments is also found in the axons. Microtubules are important in neurogenesis and synaptogenesis, and are found in all neural projections. They are involved in both anterograde and retrograde transport of organelles, proteins and neurotransmitters. Moreover, actin filaments and microtubules are involved in moving vesicles in presynaptic nerve terminals close to the cell membrane, and in this way are essential to neurotransmitter release (Brodal, 2001). Microtubules, the main cytoskeletal components, are long protein polymers assembled from subunits formed by alpha and beta tubulins. They maintain a dynamic equilibrium between polymers and dimers through polymerization–depolymerization cycles. Microtubule-associated proteins (MAPs) that bind along the sides of microtubules regulate these processes (Shimizu et al., 2006).

1.2 Schizophrenia

Schizophrenia is a clinical syndrome of variable psychopathology, which involves thought, perception, emotion, movement and behavior. The expression of these symptoms varies across patients and over time, but the cumulative effect of the illness is always severe and usually long-lasting. Epidemiologic studies indicate that the lifetime expectancy of schizophrenia is 0.5-1% worldwide. The morbidity often persists throughout life, and has devastating consequences for both the afflicted individuals and their families. The symptoms of schizophrenia are commonly categorized into positive, negative and cognitive. Positive symptoms are those symptoms that involve an excess of normal experiences and behavior. The senses may operate at a heightened and excessive state, which can result in hallucinations and delusions. Negative symptoms, on the other side, reflect a loss of normal functions and in consequence can lead to flattened affect, impaired attention, social withdrawal and poverty of speech.

1.2.1 Neurotransmitter hypothesis of schizophrenia

1.2.1.1 Dopamine hypothesis

The most studied hypothesis of schizophrenia is the dopamine hypothesis. In 1952 it was discovered that the drug chlorpromazine, which was at that time used by surgeons, had an antipsychotic effect. Within a few years, chlorpromazine became widely used as an antipsychotic. During the 1960s and -70s, the scientists found out that the effect of chlorpromazine and other antipsychotics was due to the blockade of dopamine receptors, or more specific the D_2 receptor subtype (Carlsson and Lindqvist, 1963). This led to the dopamine hypothesis which in its simplest form proposes that dopamine neurotransmission is hyperactive in schizophrenia (Carlsson, 1978). The hypothesis was further supported by the fact that exposure to amphetamine, which is an indirect dopamine (DA) agonist, produces psychosis.

Although psychosis can be very effectively treated by dopamine antagonists, the negative and cognitive symptoms of the illness are generally resistant to treatment by antipsychotics. Functional brain imaging studies suggested that these symptoms may be

associated with a dysfunction of the prefrontal cortex (PFC) (Weinberger, 1987). This led from a theory of exclusive hyperdopaminergia to a theory of combined subcortical hyper- and prefrontal hypodopaminergia. The so-called revised dopamine hypothesis of schizophrenia predicts that subcortical mesolimbic DA projections may be hyperactive, resulting in increased stimulation of D_2 receptors and positive symptoms, while mesocortical DA projections to the PFC may be hypoactive, resulting in reduced stimulation of D_1 receptors and cognitive impairment (Moghaddam et al., 2003). The dopamine hypothesis has for a long time only been based on indirect evidence . Only in the last decade has it received more direct support. Neuroimaging studies have now shown that amphetamine-induced dopamine release is elevated in drug-naive schizophrenic patients compared to healthy volunteers (Abi-Dargham et al., 1998, Breier et al., 1997). However, the dopamine hypothesis alone has not made it possible to explain the patophysiology of schizophrenia.

1.2.1.2 Glutamate hypothesis

Another hypothesis of schizophrenia arose in the early 1980s: It was found that the psychotomimetic drug PCP, first developed as a general anesthetic in the 1950s, was a potent antagonist of the NMDA subtype of glutamate receptors (Anis et al., 1983, Lodge and Anis, 1982). Subanesthetic doses of PCP produce symptoms in healthy persons that closely resembles those seen in schizophrenia. The symptoms include both positive, negative and cognitive aspects (Luby et al., 1959). On the basis of these findings, a theory of hypoglutamatergic neurotransmission in schizophrenia was proposed (Javitt and Zukin, 1991). Studies showing abnormal expression of glutamate receptors in some brain areas of schizophrenic patients provided further support for a hypoglutamatergic theory of schizophrenia. Reductions of NR1, NR2B and NR2CR subunits of the NMDA receptor in the thalamus were reported (Ibrahim et al., 2000). Down-regulation of NR1 was also reported in the superior temporal gyrus and hippocampus (Gao et al., 2000, Sokolov, 1998). Reduced expression of AMPA- and kainate receptor subunits were also found (For a review see (Meador-Woodruff and Healy, 2000)). Moreover, the most known susceptibility genes for schizophrenia act on glutamatergic synaptic transmission (Harrison and Weinberger, 2005). A selective metabotropic glutamate 2/3 receptor

agonist has shown antipsychotic potential in animal studies (Rorick-Kehn et al., 2007, Moghaddam and Adams, 1998). Recently, the substance has been tested on schizophrenic patientst in a phase 2 clinical trial. Improvements in both positive and negative symptoms have been found, providing further strength to the glutamate hypothesis (Patil et al., 2007).

1.2.1.3 Integrative hypothesis of dopamine and glutamate

It has been suggested that the dysregulation of dopamine transmission in schizophrenia may be secondary to alterations in glutamatergic NMDA receptor-mediated transmission (Carlsson et al., 2004, Olney and Farber, 1995). A SPECT (single photon emission computed tomography) study showed that healthy volunteers who received ketamine, the amplitude of amphetamine-induced dopamine release was significantly enhanced compared to control conditions (Kegeles et al., 2000). Thus the elevated dopamine release seen in schizophrenic patients after amphetamine administration may well be secondary to a failure in glutamatergic control of dopamine neurons. This hypothesis is supported by experimental studies in rats (Miller and Abercrombie, 1996).

1.2.2 Metabolic and mitochondrial dysfunction in schizophrenia

Brain metabolism can be measured directly by fluorodeoxyglucose (FDG)-PET or indirectly by blood-flow or haemoglobin oxygen saturation. Already in 1974, a relative decrease of cerebral blood flow in the frontal cortex was found in patients with schizophrenia. The phenomenon was termed hypofrontality (Ingvar and Franzen, 1974, Cantorgraae et al., 1991). At a later time, several studies, in which different techniques were used, showed alterations in cerebral blood-flow and brain metabolic rates, and confirmed the relative hypofrontality (For a review see (Buchsbaum and Hazlett, 1998)) Several authors also observed alterations in brain metabolic rates in other brain regions, which led to the suggestion of impairment in the frontostriatal-thalamic circuitry in schizophrenia rather than only prefrontal or frontal dysfunction (Buchsbaum and Hazlett, 1998, Chua and McKenna, 1995).

Brain energy metabolism in patients with schizophrenia was also evaluated by using ^{31}phosphorous magnetic resonance spectroscopy (^{31}P-NMRS) to measure phospholipids and high-energy phosphates. A decrease in phosphodiester values and an increased ratio of phosphomonoesters/ phosphodiesters was observed in the frontal cortex of subjects with schizophrenia compared to control subjects (Volz et al., 2000). Decreased levels of ATP in the basal ganglia and the temporal lobes of subjects with schizophrenia were also observed with the help of ^{31}P-NMRS (Kegeles et al., 1998).

These findings has led to the hypothesis of impaired energy metabolism and impaired mitochondrial function in schizophrenia (Ben-Shachar, 2002, Ben-Shachar, 2009, Rezin et al., 2009, Scaglia, 2010). Mitochondrial morphological abnormalities in schizophrenia were demonstrated by microscopic analysis of autopsy specimens. Electron microscopic analyses of post-mortem specimens from the anterior limbic cortex and the caudate putamen nucleus showed mitochondrial deformation and reduced density throughout the neuropil in schizophrenic patients (Uranova and Aganova, 1989). Ultra structural studies in the caudate nucleus and the prefrontal cortex showed decreased volume density of mitochondria in oligodendrogliocytes in subjects with schizophrenia(Uranova et al., 2001) Later the same group suggested a progressive disturbance in astrocytes due to deficits in mitochondria (Kolomeets and Uranova, 2010).

Both studies of enzyme activity and genetic studies implicate abnormalities in oxidative phosphorylation in schizophrenia. Several studies have suggested that decreased activity of complex I and complex IV of the electron transport chain could underlie the pathological mechanism of schizophrenia (Ben-Shachar, 2002, Cavelier et al., 1995, Mulcrone et al., 1995, Scaglia, 2010). Altogether there is substantial evidence for a disrupted brain energy metabolism in schizophrenia.

1.2.3 Animal models of schizophrenia

1.2.3.1 General

Schizophrenia is a complex syndrome of unknown etiology, which is defined by its clinical symptoms. Most of these symptoms are unique to human behavior. Consequently, it is not possible to exactly reproduce schizophrenia in an animal. However, animal models are important tools in exploring the underlying mechanisms of schizophrenia and in designing new therapies. There are three different criteria that are important when establishing and evaluating an animal model of any disease:

1) Construct validity: The model reconstructs the etiology and pathophysiological mechanisms of the disease.

2) Face validity: The model mimics phenomenology e.g. symptoms of schizophrenia.

3) Predictive validity: The model predicts responsiveness to available treatments for that disease in humans (e.g. antipsychotic drugs) (Lipska et al., 2003).

Traditionally, most animal models of schizophrenia, on the basis of the dopamine hypothesis of schizophrenia, have focused on the dopamine neurotransmitter. The focus has recently shifted and the novel models can be categorized into three different approaches:

1) Neurodevelopmental models which test the hypothesis that schizophrenia is caused by a defect in cerebral development.

2) Glutamatergic hypofunction models which are based on the glutamate hypothesis of schizophrenia.

3) Genetic models which use targeted gene deletion or gene transfer techniques to investigate susceptibility genes, that is genes that are associated with a higher risk for developing schizophrenia in humans (Lipska et al., 2003).

1.2.3.2 The MK-801 model of schizophrenia

The glutamate hypothesis has been one of the most studied and promising hypothesis of schizophrenia in the recent years. As described above, the hypothesis is based on the observation that PCP causes schizophrenia like-symptoms in humans. Not only does PCP

mimic the positive symptoms of schizophrenia, but also produce the whole spectrum of symptoms including negative and cognitive symptoms. PCP was found to be a non-competitive NMDA receptor antagonist binding to a binding site inside the ion channel (Zukin et al., 1987). It was later shown that other NMDA receptor antagonists also had psychotomimetic properties. The PCP psychosis is therefore not a PCP-specific phenomenon, but rather a phenomenon resulting from the effective NMDA receptor blocking (Olney and Farber, 1995). One of the best characterized non-competitive NMDA receptor antagonists that binds to the PCP binding site, is MK-801 (Dizocilpine; [5R, 10S]-[+]-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine). It is a more selective and a more potent NMDA receptor channel blocker than PCP (Carlsson et al., 2001), and therefore a good tool to study hypoglutamatergia or more specific NMDA receptor hypofunction in animals (Olney and Farber, 1995) MK-801 causes behavioral changes in rodents such as hypermobility, head weaving and ataxia (Loscher et al., 1991). MK-801 also induces social withdrawal (Rung et al., 2005). The model also possesses predictive validity, as it distinguishes between atypical and typical antipsychotics based on their ability to suppress abnormal pre frontal cortex activity (Homayoun and Moghaddam, 2007).

1.2.3.3 STOP(MAP 6) knock out mouse

Cumulative evidence suggests that schizophrenia is associated with cytoskeletal alterations in neuron architecture. Affected neurons lose synaptic connectivity and the ability to transmit incoming axonal information to the somatodenritic domain (Shimizu et al., 2006). An increasing number of studies have reported altered expressions of MAPs, particularly of MAP2, in brains of schizophrenic patients (Anderson et al., 1996, Cotter et al., 2000, Rioux et al., 2003, Jones et al., 2002).

MAP6, also called STOP (Stable Tubule only Polypeptide) protein, is a MAP involved in the cold stability of microtubules, synaptic plasticity and neurotransmission (Andrieux et al., 2002). Knockout (KO) mice of STOP protein have been proposed to be a “meaningful model for the study of the pathophysiology of schizophrenia” (Brun et al., 2005). The deletion of the STOP protein leads to a decrease in synaptic vesicle density in

hippocampal CA1 terminals, impaired long term potentiation and depression at the level of Schaffer collaterals-CA1 pyramidal cell synapses (Andrieux et al., 2002). STOP KO mice are also characterized by disorganized activity with frequent shifts between hyperlocomotion and prostration, anxiety-related behavior, inability to perform object recognition tasks and social withdrawal. These behavioral disorders can be alleviated by long-term treatment with antipsychotics (Andrieux et al., 2002, Begou et al., 2008, Powell et al., 2007). STOP KO mice exhibit in addtion increased dopaminergic neurotransmission and increased efflux of dopamine in the nucleus accumbens upon stimulation (Brun et al., 2005). Interestingly, the human *STOP* gene, located at position 11q14, lies within a region which has been linked to major mental diseases including schizoid disorders (Brzustowicz et al., 2000, Holland and Gosden, 1990)and a recent study indicates that STOP gene is upregulated in the prefrontal cortex of patients with schizophrenia (Shimizu et al., 2006).

1.3 Nuclear magnetic resonance spectroscopy

1.3.1 Basic principles of NMRS(Hornak, 1997-2008, Derome, 1987)

Spin is a fundamental property of elementary particles like electrical charge or mass and protons, electrons, and neutrons possess spin. Two or more particles with spins having opposite signs can pair up to eliminate the observable manifestations of spin. Only nuclei that possess a net spin and charge, i.e. a net magnetic moment, can be studied by NMRS. This includes ^{1}H, ^{13}C, ^{7}Li, ^{19}F, ^{23}Na, ^{31}P. The present thesis is based on the work in which both ^{1}H- and ^{13}C-spectroscopy were used.

When a nucleus with a net spin is subjected to an external magnetic field, it will be aligned either with or against the magnetic field. It will also precess about the magnetic field. This is called the Larmor precession, and the frequency of this precession is called the Larmor frequency. The nuclei that are oriented parallel to the magnetic field exist in a lower energy state than the nuclei aligned against the magnetic field. According to Boltzmann statistics the number of spins at the lower energy level slightly outnumber

those at the higher energy level. A nucleus can undergo a transition between the two energy states by absorbing electromagnetic radiation. The radiation (which is in the radio frequency range) has to match the energy difference of the energy levels in order for it to happen. This takes place when the radio frequency is the same as the Larmor frequency. After the transition to the higher energy state, the nuclei will make a transition from the higher to the lower energy state and thus emit energy. This emission is the NMR signal.

The phenomenon of nuclear magnetic resonance as described above is utilized in an NMRS(nuclear magnetic resonance spectroscopy) experiment by applying a large external magnetic field, $B_{0,}$ to the sample. In addition to this static magnetic field, another magnetic field (B_1) in the form of electromagnetic waves is applied perpendicular to B_0. When $B_{1,}$ which is a radio frequency pulse with the Larmor frequency, is applied to the sample, a transition between the two energy states is induced. When B_1 is switched off, relaxation to equilibrium occurs. The relaxation is characterized for each nucleus by two time constants T1 (longitudinal relaxation) and T2 (transverse relaxation). The nuclei emit energy in the form of radiofrequency during the relaxation process. The emitted energy is detected as a signal called the free induction decay (FID) by a detection coil. To be able to analyze the data the FID is converted into an NMR spectrum by a Fourier transform, which is an operation that converts functions from time to frequency domains.

The resonance frequency of the nucleus is dependent on the magnetic field. The electrons of the atom will also circulate in the applied magnetic field and this circulation causes small magnetic fields. The total magnetic field experienced by a nucleus includes these local magnetic fields induced by electrons in the chemical bonds. This will slightly change the resonance frequency of the nucleus. The variations in the nuclear magnetic resonance frequencies of the same kind of nucleus are due to variations in the electron distribution. This phenomenon is called the chemical shift. The chemical shift makes it possible to distinguish between different molecules, and also between different atoms in the same molecule, in an NMR-spectrum. Nuclei with net spin that are close to one another exert an influence on one another's effective magnetic field. If the distance between non-equivalent nuclei is less than or equal to three bond lengths, this effect is

observable. This effect is called spin-spin coupling or J-coupling and is visible in the NMR spectrum as multiplets. For an example of homonuclear (between the same type of nuclei) spin-spin coupling see Figure 1 which depicts a ^{13}C NMR spectrum. The singlet of peak 8 represents [4-^{13}C]glutamine where only the carbon in the fourth position is ^{13}C and the doublets represents [4,5-^{13}C]glutamine where the carbons in both fourth and fifth position are ^{13}C. There can also be spin-spin couplings between a ^{13}C nucleus and its neighboring ^{1}H nuclei (heteronuclear coupling), which consequently produces multiplets in the spectrum. This makes the spectrum hard to analyze. To avoid this, proton decoupling is applied. Proton decoupling is done by using a small powered B_1 pulse with the Larmour frequency of the ^{1}H nuclei. Due to the nuclear Overhauser effect (nOe), which has not been explained here, proton decoupling will make peaks in the ^{13}C spectra higher. While analyzing the spectra, the nOe is corrected for.

1.3.2 ^{13}C NMRS and ^{13}C labeling patterns

^{13}C has a natural abundance of only 1.1 %, which makes detection difficult. ^{13}C NMRS is of limited use in studies of endogenous metabolites unless the compounds occur in large amounts. However, the low natural abundance can be used as an advantage in the study of metabolic pathways (for review, see (Bachelard and Badar-Goffer, 1993)). ^{13}C labeled metabolic precursors can be added to cell cultures or injected into research animals and humans. As a result, detection by NMRS and quantification of ^{13}C atoms and their position in different metabolites is possible. ^{13}C NMRS is in this way a very good tool to study metabolic pathways and trafficking of metabolites between different compartments of brain metabolism. In the studies that constitute this thesis, ^{13}C labeled glucose and acetate were injected into rats and ^{13}C NMRS was done on brain extracts from different brain regions. In order to interpret the NMRS-spectra and understand the results obtained from these spectra, it is necessary to know the relevant metabolic conversions of [1-^{13}C]glucose and [1,2- ^{13}C]acetate.

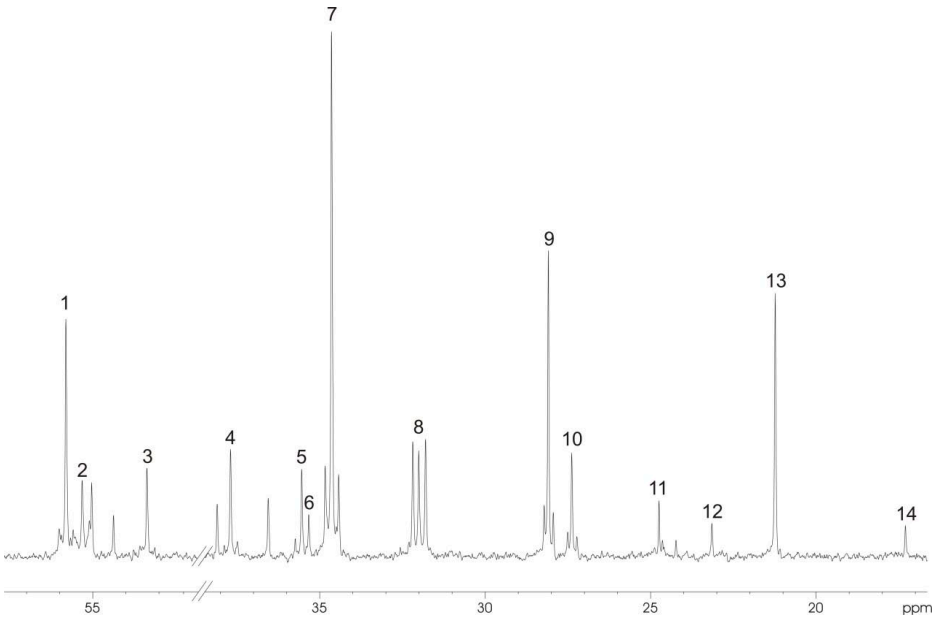

Figure 2: Example of part of a ^{13}C NMR spectrum of cerebrum extract from mice injected with [1,2-^{13}C]acetate and [1-^{13}C]glucose. Peak assignments; 1: glutamate C-2; 2: glutamine C-2; 3: aspartate C-2; 4: aspartate C-3; 5: GABA C-2; 6: succinate C-2/C-3; 7: glutamate C-4; 8: glutamine C-4; 9: glutamate C-3; 10: glutamine C-3; 11: GABA C-3; 12: N-acetylaspartate C-3; ^{13}: lactate C-3; 14: alanine C-3. Note that the singlets are mostly derived from [1-^{13}C]glucose and the doublets in the spectrum from [1,2-^{13}C]acetate.

Acetate is selectively taken up by astrocytes, through a specialized transport system (Waniewski and Martin, 1998), which is absent or less active in neurons, whereas glucose is thought to be metabolized more in the neuronal tricarboxylic acid cycle. By using ^{13}C NMRS, it has been calculated that 65% of acetyl CoA derived from glucose is predominantly metabolized in the neuronal TCA cycle (Qu et al., 2000). Thus, by simultaneous injection of [1-^{13}C]glucose and [1,2-^{13}C]acetate followed by NMRS analysis of brain extracts, information about neuronal and astrocytic metabolism can be obtained in the same animal.

Injection of ^{13}C labeled glucose and acetate leads to efficient labeling of many metabolites in the brain. They are visible in the spectrum of Figure 2. Label from [1-^{13}C]glucose can be quantified by analyzing the singlet peaks in the spectra. The doublets are mostly derived from [1,2-^{13}C]acetate and thus astrocytic metabolism. [1-^{13}C]glucose is converted to pyruvate *via* glycolysis and can form [3-^{13}C]alanine and [3-^{13}C]lactate. Pyruvate can enter the TCA cycle *via* [2-^{13}C]acetyl CoA. This will lead to the formation of [4-^{13}C]glutamate and glutamine or [2-^{13}C]GABA. Alternatively, pyruvate can be carboxylated by pyruvate carboxylase (PC) to oxaloacetate, which will lead to the synthesis of [2-^{13}C]glutamate and glutamine or [4-^{13}C]GABA. [1,2-^{13}C]acetate can also be converted to acetyl CoA. However, the product, i.e. [1,2-^{13}C]acetyl CoA, will have two ^{13}C atoms (Figure 3), which will result in doublet formation. Thus [4,5-^{13}C]glutamate and glutamine or [1,2-^{13}C]GABA are formed. Since both acetyl CoA and oxaloacetate can be labeled or unlabeled, the number of possible isotopomers of the metabolites derived from the TCA cycle is large. Only compounds derived from the first turn are represented in Figure 2. By comparing the doublets with singlets, it can be shown that glutamine is labeled more from [1,2-^{13}C]acetate (doublet) than [1-^{13}C]glucose (singlet). The opposite is the case for glutamate and GABA. Lactate, alanine, N-acetylaspartate (NAA) and succinate are mainly labeled from glucose.

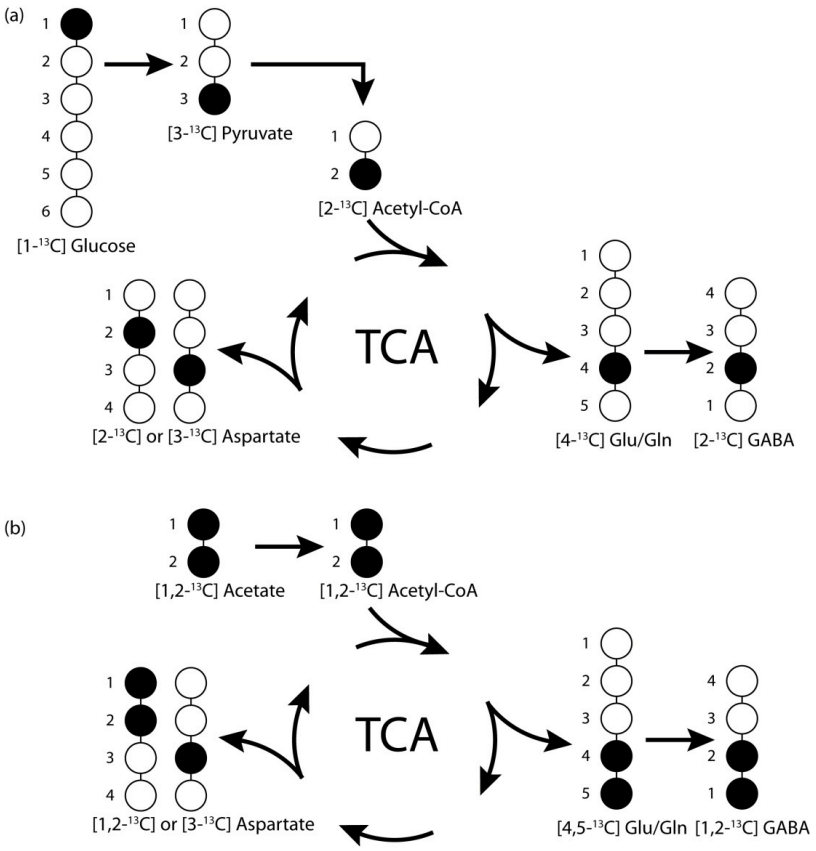

Figure 3: Schematic representation of ^{13}C labeling of glutamate, glutamine, GABA and aspartate originating from [1-^{13}C]glucose (a) or [1,2-^{13}C]acetate (b). Filled circles represent ^{13}C and empty circles ^{12}C. TCA, tricarboxylic acid cycle; Glu, glutamate; Gln, glutamine.

1.4 High performance liquid chromatography (Greibrokk et al., 1998)

High-performance liquid chromatography is a technique that can separate a mixture of compounds. It utilizes a mobile phase and a stationary phase. The analytes are dissolved in the mobile phase which is a liquid. A pump moves the analyte and the mobile phase through the stationary phase which in the case of HPLC is contained in a column. The different compounds will be separated according to their chemical properties. The time it takes for each compound to be moved through the column is dependent on the relative affinity towards the column material and the mobile phase. On the other side of the column, the compounds are detected by a detector at their specific retention times. There are several methods for detecting the compounds. In the four studies presented in the thesis, aminoacids were detected by a fluorescence detector after derivatization with o-phthalaldehyde. An electrochemical detector was used for the analysis of catecholamines.

2 Aims of study

The aims of the studies were to answer the following questions:

1. What is the effect of a single dose of the NMDA receptor antagonist MK-801 on glutamate related metabolism, and is it a good animal model of schizophrenia?
2. Do repeated injections of MK-801 over a longer period of time model schizophrenia better than a single dose of MK-801?
3. What is the effect of microtubule instability on glutamate related metabolism? Is the STOP knock out mouse a good schizophrenia model?

3 Methods

3.1 Experimental Procedures with Animals

3.1.1 Rats injected with MK-801

Three different studies were performed using systemic injections of MK-801 as an animal model of schizophrenia. All experiments were performed in accordance to internationally accepted guidelines and permission from the Norwegian Animal Reasearch Authority was obtained. Prior to experiments and between each procedure, the animals had free access to food and water and were kept at a light/dark cycle of 12 h, humidity 60%, temperature 22ºC. In the first study (Paper 1) the animals in the treatment group received a solution consisting of MK-801 (0.5 mg/kg), [1-^{13}C]glucose (543 mg/kg) and [1,2-^{13}C]acetate (504 mg/kg), the control animals were given a solution with the same concentration of [1-^{13}C]glucose and [1,2-^{13}C]acetate in sterile water, but without MK-801. Animals in both groups were injected intraperitoneally with 10 ml/kg of the respective solutions. Twenty minutes after the injection the animals were killed by decapitation and the heads snap frozen in liquid nitrogen, and later stored at -80ºC. Brains were removed, and two different areas of each hemisphere were dissected. The first area consisted of both the cingulate and the retrosplenial cortices (this is from now on referred to as FCR). The second area, which will be referred to as the temporal lobe (TL), was dissected using a horizontal cut from the most lateral point of the hemisphere extending approximately 3 mm medially and a second sagittal cut extending ventrally through the whole brain. This resulted in a sample including the temporal cortex, the piriform cortex, the entorhinal cortex, the amygdala and parts of the hippocampus. The dissection lasted max. 3 min and was performed on ice with the brains still frozen. After dissection, brain tissue was homogenized in 7% (w/v) perchloric acid and centrifuged at 4.000 g for 5 min. The procedure was repeated with distilled H_2O. The supernatants were pooled and neutralized with 1 M KOH followed by lyophilization.

In the two studies with repeated MK-801, saline or MK-801 (0.5 mg/kg body weight in Paper 3 and 0.1 mg/kg in Paper 2) were injected intraperitoneally once a day for six days. Hyperlocomotion was assessed by observing rats for 30 minutes after injection and counting how often rats passed completely one of the two imaginary lines dividing the cage in four equal quarters. The last MK-801 injection was given together with [1-^{13}C]glucose and [1,2-^{13}C]acetate and twenty minutes later animals were decapitated. The rest of the procedures were performed as described for the first study.

3.1.2 STOP KO mice

STOP KO male mice (STOP-/-), heterozygous (STOP+/-) and control wild type littermates (STOP+/+), 15 week-old, were used. Mice were housed eight per cage and maintained in quiet, uncrowded facilities (room temperature of 22ºC ± 1°C) on a 12 hour light-dark schedule (7:00 a.m., lights on), humidity 60%, and given unlimited access to lab chow and water. All animal experimentation was performed in accordance with the rules of the European Committee Council Direction of November 24, 1986 (86/69/EEC) and the French Department of Agriculture (License N°67-97).

The animals (10 in each group) were injected intraperitoneally with [1-^{13}C]glucose (543mg/kg, 0.3 M solution) and [1,2-^{13}C]acetate (504mg/kg, 0.6 M solution) followed by decapitation fifteen minutes later. The heads were immediately frozen in liquid nitrogen and stored at -80ºC. The brains were removed from the slightly thawed skull, and, because of their small size and limitations of sensitivity of the method, the forebrain/midbrain (cerebrum) including cerebral cortex and subcortical regions was used. The brainstem and the cerebellum were discarded. The tissue was homogenized in 7% (w/v) perchloric acid and centrifuged at 4,000 g for 5 min. The procedure was repeated, the supernatants pooled and neutralized with 1 M KOH followed by lyophilization.

3.2 High Performance Liquid Chromatography

Amino acids in cell extracts and medium were quantified by HPLC on a Hewlett Packard 1100 system (Agilent Technologies, Palo Alto, CA, USA). The amino acids were pre-column derivatized with *o*-phthaldialdehyde (Geddes and Wood, 1984) and subsequently separated on a ZORBAX SB-C18 (4.6 × 250 mm, 5 μm) column from Agilent by use of a phosphate buffer (50 mM, pH = 5.9), a solution of methanol (98.75 %) and tetrahydrofurane (1.25 %) as eluents. The separated amino acids were detected with fluorescence and quantified by comparison to a standard curve derived from the standard solutions of amino acids which were run after every twelfth sample.

Quantification of monoamines was done by collaborators from another laboratory. See Paper 3 for details.

3.3 ^{13}C NMR Spectroscopy

A Bruker DRX-600 spectrometer or Bruker DRX-500 (BRUKER Analytik GmbH, Rheinstetten, Germany) was used to obtain proton decoupled 150.92 MHz ^{13}C NMR spectra. For this procedure the samples were redissolved in 400 or 200 μL D_2O containing ethylene glycol 0.1% as an internal standard. Scans were obtained with a 30^{o} pulse angle and 30 kHz spectral width with 64K data points. The acquisition time was 1.08 s, the relaxation delay 2.5 or 0.5 s and the number of scans was typically 10 000. The relevant peaks in the ^{13}C and ^{1}H NMR spectra were identified and integrated using XWINNMR software. The amounts of metabolites and ^{13}C were quantified from the integrals of each relevant peak, using ethylene glycol as an internal standard. A correction factor for nOe and T_1 was determined for each peak using the inverse gated decoupling experiment (Derome, 1987). The factor was applied to all spectra.

3.4 ^{1}H NMR Spectroscopy

A Bruker DRX-600 spectrometer was used to obtain ^{1}H NMR spectra with a sweep width of 12 kHz with 32K data points. The pulse angle was 90°, the acquisition time 1.36 s and the relaxation delay was 10 s. The number of scans was 400. Water suppression was set at the residual H_2O resonance.

4 Results

4.1 Paper 1

Sprague-Dawley rats received either a single injection of MK-801 (0.5mg/kg) or saline i.p. together with [1-^{13}C]glucose (543mg/kg) and [1,2-^{13}C]acetate (504mg/kg). After decapitation the temporal lobe (TL) and the cingulate, retrosplenial and frontal cortices (FCR) were prepared and examined by HPLC, ^{1}H NMRS and ^{13}C NMRS. Hypofunction of the NMDA receptor induced similar changes in both brain areas investigated. However, the changes were most pronounced in TL. Generally, only labeling from [1-^{13}C]glucose was affected by MK-801. The only change in labeling from [1,2-^{13}C]acetate was in an isotopomer of glutamine derived from the second turn of the TCA cycle. In FCR and TL amounts of both labeled and unlabeled glutamine were increased, whereas those of aspartate were decreased. The amount of lactate, formed from unlabeled glucose or other unlabeled substrates, was also increased in both areas. In TL, not in FCR, increased concentrations of glutamate, GABA, succinate, glutathione and inositol were detected together with increased labeling of GABA and succinate from [1-^{13}C]glucose and glutamine from [1,2-^{13}C]acetate. ^{13}C enrichment was increased in succinate and decreased in glutamate. Whereas labeled and unlabeled glutamine was increased both in FCR and TL, this was only the case for unlabeled glutamate in TL.

4.2 Paper 2

Rats were given i.p. injections of MK-801 (0.1 mg/kg) or saline on 6 consecutive days, the last dose together with [1-^{13}C]glucose and [1,2-^{13}C]acetate. Analyses of extracts from FCR and TL were performed using ^{13}C and ^{1}H NMRS. Increases in amounts and labeling of glutamate and glutamine from [1-^{13}C]glucose and [1,2-^{13}C]acetate were confined to

TL. The amounts of [2-^{13}C]aspartate, derived from [1-^{13}C]glucose, and succinate were elevated in TL as well.

4.3 Paper 3

Saline or MK-801 (0.5mg/kg) were injected i.p. every day for six days and hyperlocomotion and ataxia measured semi-quantitatively for half an hour after each injection. The last dose was given together with [1-^{13}C]glucose (543mg/kg) and [1,2-^{13}C]acetate (504mg/kg) followed by decapitation 20 minutes later. TL and FCR extracts were studied by HPLC, ^{13}C and ^{1}H NMRS. Five controls and three MK-801 animals underwent cardiac perfusion. Hematoxilin-Eosin- and Nissl-stained histological slices from FCR, TL and hippocampus were examined by light microscopy and no morphological changes were found. Significant behavioral alterations such as head waving, hyperlocomotion, abducted hind limbs and ataxia were seen and exhibited considerable variability. MK-801 affected the FCR to a much greater extent than the temporal lobe with significant increases in the levels of glutathione, glutamate and taurine, but, at the same time, unchanged amounts of and turnover rates for dopamine, noradrenaline and serotonin in cortex. [4,5-^{13}C]glutamate and [4,5-^{13}C]glutamine, derived from [1,2-^{13}C]acetate, were significantly decreased in FCR. Label from [1-^{13}C]glucose was affected in the same brain region with decreases of [4-^{13}C]glutamate, [2-^{13}C]GABA and [4-^{13}C]GABA, whereas in the temporal lobe both [1,2-^{13}C]acetate- and [1-^{13}C]glucose-derived metabolites remained unchanged. Glutamate cycling from [1-^{13}C]glucose was enhanced in both brain areas investigated and an increase of the cycling ratio for ^{13}C from [1,2-^{13}C]acetate was found for glutamine in the FCR. Acetate/glucose utilization ratios of glutamate and glutamine were decreased in the FCR.

4.4 Paper 4

We examined potential disturbances in energy metabolism and interactions between neurons and glia in 15 week-old STOP KO, wild type and heterozygous mice. Animals received [1-^{13}C]glucose and [1,2-^{13}C]acetate, the preferential substrates of neurons and astrocytes, respectively. Extracts from the whole forebrain and midbrain excluding the brainstem and the cerebellum were analyzed by HPLC, ^{13}C and ^{1}H NMRS. Amounts and

labeling of most metabolites were unchanged. However, glutamine concentration and amount of [4,5-^{13}C]glutamine derived from [1,2-^{13}C]acetate were significantly decreased by 17% and 18%, respectively, in STOP KO compared to wild type mice. The amount of [4-^{13}C]glutamate was decreased in STOP KO and heterozygous mice compared to wild type. However, levels of [4-^{13}C]glutamine were unchanged.

5 Discussion

Analyses of brain metabolites from MK-801-treated rats using ^{13}C NMR spectroscopy in Paper 1-3 have substantially increased knowledge of impairments of neurotransmitter metabolism in NMDA receptor hypofunction. A single dose of 0.5 mg/kg, MK-801 produced predominantly changes in the temporal lobe with increased total amounts of glutamate and glutamine and labeling from [1-^{13}C]glucose (Paper 1). Similar changes were observed when MK-801 was administered repeatedly at 0.1 mg/kg for 6 consecutive days and all metabolic alterations were confined to the temporal lobe (Paper 2). However, changes were found in FCR when MK-801 was administered repeatedly at 0.5 mg/kg (Paper 3) instead of 0.1 mg/kg repeatedly. In vivo NMR spectroscopy studies of patients with schizophrenia showed that first-episode schizophrenic patients have
elevated glutamine levels in the medial prefrontal and the left anterior cingulate cortex (Bartha et al., 1997, Theberge et al., 2002), whereas decreased glutamine and glutamate levels were found in the anterior cingulate of patients with chronic schizophrenia (Theberge et al., 2003). The FCR in our studies includes both the medial prefrontal and the anterior cingulate cortex. Accordingly, repeated injections of high doses of MK-801 cause similar alterations to those from first-episode patients. In paper 4, a decreased level of glutamine is reported in the cerebrum of STOP KO mice compared to wild type mice. It appears that the 15-week-old STOP KO mice mimic chronic schizophrenia but not first-episode schizophrenia. Consequently, the STOP KO mice may be a good model for chronic schizophrenia and the model of repeated injections of high doses of MK-801 may be a good model for first-episode schizophrenia.

As shown in Paper 1 and Paper 2, the total amounts of glutamine and glutamine labeled from [1-^{13}C]glucose and hence from neuronal metabolism were increased. Such an

increase could be due to the increased activity of glutamine synthetase. However, no changes were observed in [4,5-^{13}C]glutamine and [4,5-^{13}C]glutamate from [1,2-$_{13}$C]acetate, which accordingly demonstrated the unperturbed metabolic flux from astrocytes to neurons. These observations both indicate that not all GS was affected by MK-801 and reveals s compartmentation of glutamine metabolism, where glutamine labeled from neuronal glutamate ([4-^{13}C]glutamate) is handled in a different compartment than glutamine from astrocytic glutamate.

As it comes to Paper 4, decreased levels of both total glutamine and labeled [4,5-^{13}C]glutamine were reported in the cerebrum of STOP KO mice. In contrast to the MK-801 experiments, this indicates a decreased glutamine synthesis by glutamine synthetase in the STOP KO mice. Interestingly, in the fourth study, there were no changes found in the [4-^{13}C]glutamine levels and , as a result, a compartmentation of glutamine metabolism in the STOP KO mouse also has to be proposed. A hypoglutamatergic state is present in both the MK-801 model and in the STOP KO mouse: In MK-801 injected rats, the state was caused by the MK-801 blocking the NMDA receptor, while in the STOP KO mouse, a reduction of the glutamatergic synaptic vesicle pool shown in some brain areas (Andrieux et al., 2002, Andrieux et al., 2006). Both these cases would cause a decreased influx of Ca^{2+} into the postsynaptic neuron through the NMDA receptor ion channel. Ca^{2+} entry into the postsynaptic neuron activates NO-synthase (NOS) through a second messenger system involving calmodulin (Kosenko et al., 2003). Nitric Oxide (NO) synthesized in the postsynaptic neuron does not only affect the post- and presynaptic neuron, but also shows effects in the nearby astrocyte. One of the effects is a tonic inhibition of GS (Kosenko et al., 2003). Reduced influx of Ca^{2+} can then, through disinhibition of astrocytic GS, cause increased glutamine production in the astrocyte. This hypothesis is able to explain the compartmentation of glutamine metabolism in both the MK-801 single dose model and in the STOP KO mouse. In the STOP KO mice, GS activity in general is decreased, There is however an increased GS activity caused by reduced activation of postsynaptic NMDA receptors in the parts of the astrocytes in absolute vicinity of the postsynaptic spines. In the MK-801 treated rats (single injection with high dose), the GS activity in general is normal, but in

the synaptic parts of the astrocyte, it is increased (See Figure 4). The finding that the activity of glutamine synthetase is decreased in brains of schizophrenic patients (Burbaeva et al., 2003) further strengthens the assumption that the glutamate-glutamine cycle is disrupted in schizophrenia. It also gives support to the STOP KO mouse as an animal model of schizophrenia.

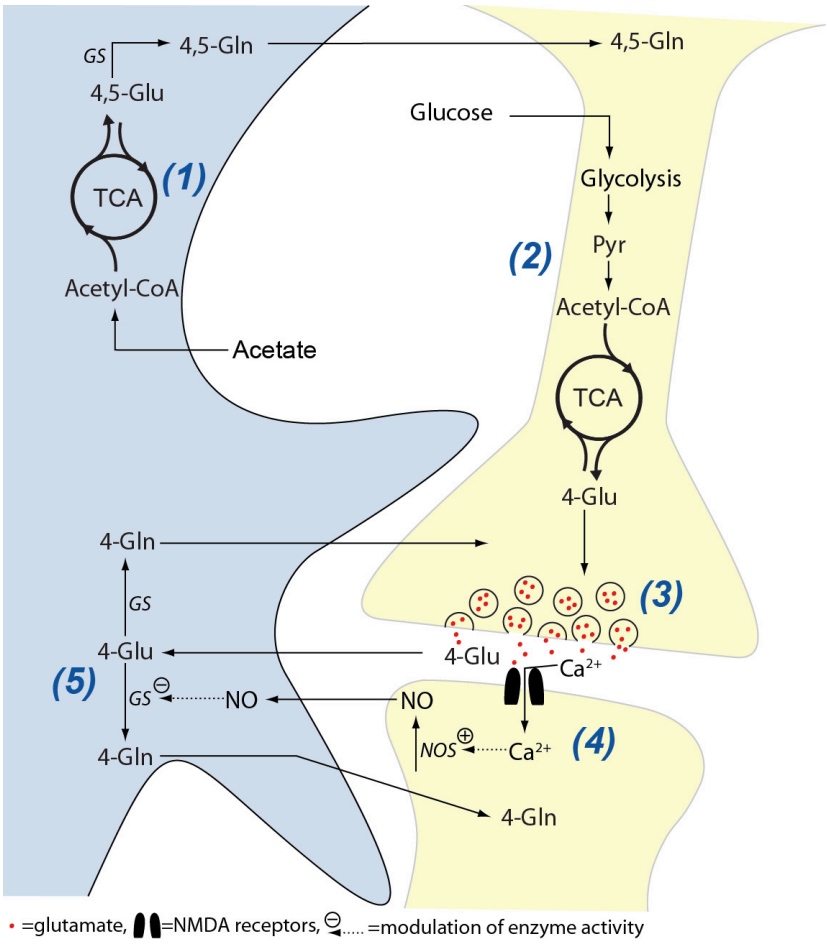

Figure 4: Schematic representation of the glutamate-glutamine cycle related interactions of an astrocyte with a pre- and postsynaptic neuron. (**1**) [1,2-^{13}C]Acetate is taken up by astrocytes, but not by neurons. Through the tricarboxylic cycle (TCA), [1,2-^{13}C]acetatyl CoA is converted to [4,5-^{13}C]glutamate. Glutamine synthetase (GS) converts [4,5-^{13}C]glutamate to [4,5-^{13}C]glutamine. (**2**) Glucose is mostly taken up by neurons. [1-^{13}C]glucose is after several steps converted to

[4-^{13}C]glutamate. (**3)** Synaptic glutamate release. (**4**) NMDA receptors are activated by synaptic glutamate and allow influx of Ca^{2+} into the postsynaptic dendrite. Ca^{2+} activates the enzyme nitric oxide synthase (NOS). (**5**) NO may diffuse into the astrocyte where it normally inhibits GS. Reduced activation of NMDA receptors by glutamate leads to reduced NO production resulting in less inhibition of GS. This will only be the case in the part of the astrocyte close to the synapse. Abbreviations: 4,5-Gln, [4,5-^{13}C]glutamine; 4,5-Glu, [4,5-^{13}C]glutamate; 4-Gln, [4-^{13}C]glutamine; 4-Glu, [4-^{13}C]glutamate; GS, glutamine synthetase; NO, nitric oxide; NOS, nitric oxide synthase; Pyr, pyruvate; TCA, tricarboxylic acid cycle.

Why do different doses of MK-801 impair brain metabolism in the different brain regions? Possibly, the clue to this mystery lies in the diversity of neuronal pathways. Thus, blocking the release of glutamate from glutamatergic neurons which act on inhibitory GABAergic interneurons, might be neurotoxic.yThe reason for that might be the indirect increase of glutamate release at a second glutamatergic neuron behind the interneuron (Farber et al., 1995). In contrast, NMDA receptor blockade, at the second glutamatergic neuron at the end of this chain might have a neuroprotective effect. Whereas a single high dose and repeated low doses of MK-801 evoked metabolic changes in the TL, repeated high doses had almost no effects on the temporal lobe, but led to significant impairment in the FCR. It is very noteworthy in this context that MK-801, when directly injected into the FCR, does not induce the neurotoxic reactions seen with comparable systemic doses (Farber et al., 2002). Thus, NMDA receptor blockade is probably required at one or more sites outside the FCR to generate these neurotoxic effects. In other words, we are probably dealing with polysynaptic network disturbances. Different doses of MK-801 may cause the same local reactions in the FCR, but may have different outcome in non-FCR areas. Thereby high doses of MK-801 will probably change polysynaptic chains in such a way that metabolism will mostly be impaired in FCR. Low doses of MK-801, on the other hand, affect other polysynaptic chains and provoke alterations in the temporal lobe. One may argue that the relevant polysynaptic changes have to be sensitized, since only repeated doses, but not a single dose, of 0.5 mg/kg MK-801 lead to alterations in the FCR.

6 Conclusions

Repeated injections of the NMDA receptor antagonist MK-801 (0,5 mg/kg body weight) in rodents may be a good model of first-episode schizophrenia, whereas the STOP KO mouse model show similarities to, and may be a good model of chronic schizophrenia.

A single high dose injection of MK-801 is an important tool to get the insights into hypoglutamatergia per se. Both NMDA receptor hypofunction and loss of microtubule stability seem to disrupt the glutamate-glutamine cycle. It can be stated that astrocytic-neuronal interactions are probably underestimated in schizophrenia research. Future drugs, designed to stabilize astrocytic-neuronal interactions, may have potent antipsychotic properties.

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Repeated injection of MK801: An animal model of schizophrenia?

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Abstract

Glutamate-induced neurotoxicity plays an important role in neurological and psychiatric diseases. Thus, much attention has been given to the potential neuroprotective role of glutamate receptor antagonists, especially to those acting on the *N*-methyl-D-aspartate (NMDA) subtype. However, in addition to their neuroprotective potential, these compounds have also neurotoxic and psychotogenic properties. In the present study we used repeated injections of MK801 to examine if this non-competitive NMDA receptor antagonist could be used to produce schizophrenia-like alterations in behavior and brain metabolism in animals. Rats were given injections of MK801 (0.1 mg/kg) on six consecutive days, the last dose together with [1-^{13}C]glucose and [1,2-^{13}C]acetate, to probe neuronal and astrocytic metabolism, respectively. Analyses of extracts from parts of the frontal cortex plus cingulate and retrosplenial cortices and temporal lobes were performed using ^{13}C and ^{1}H magnetic resonance spectroscopy. Changes in glutamate and glutamine were restricted to the temporal lobe, in which amounts and labeling from [1-^{13}C]glucose and [1,2-^{13}C]acetate were increased compared to control. Locomotor activity was slightly higher in rats treated with MK801 compared to untreated animals. Metabolic changes did not resemble the alterations occurring in schizophrenia and those after repeated high dose (0.5 mg/kg) [Kondziella, D., Brenner, E., Eyjolfsson, E.M., Markinhuhta, K.R., Carlsson, M., Sonnewald, U., 2005. Glial–neuronal interactions are impaired in the schizophrenia model of repeated MK801 exposure. Neuropsychopharmacology, Epub ahead of print] but rather those caused by MK801 seen after a single high dose (0.5 mg/kg) [Brenner, E., Kondziella, D., Haberg, A., Sonnewald, U., 2005. Impaired glutamine metabolism in NMDA receptor hypofunction induced by MK801. J. Neurochem. 94, 1594–1603.].

Keywords: [1-^{13}C]glucose; [1,2-^{13}C]acetate; MK801; NMDA; GABA; Glutamate; Metabolism; NMR spectroscopy

1. Introduction

In order to establish new treatments, *N*-methyl-D-aspartate (NMDA) and other glutamate receptor antagonists have been tested clinically in many CNS disorders (Bensimon et al., 1994; Bullock et al., 1999; Davis et al., 2000). The principal therapeutic strategy is to reduce the neurotoxicity of excessive glutamate release. Some authors reported on the neuroprotective potential of glutamate antagonists (for review see Himmelseher and Durieux, 2005) some on lack of effect (Muir and Lees, 2003) and some revealed additional neurotoxic potential of glutamate/NMDA antagonism (Olney and Farber, 1994; Farber et al., 1996, 1998, 2002; Kim et al., 1999). Results of clinical studies using NMDA antagonism have been quite disappointing, although with increasing knowledge about the complexity of NMDA receptor subtypes this might change in the future. For a review on "the enormous potential of NMDA receptor antagonists" see Smith (2003).

NMDA antagonists have found use as tools to produce schizophrenia-like symptoms in animals. Several transmitter systems have been implicated in the pathogenesis of schizophrenia and combined dysfunction of the glutamate and dopamine systems has been suggested (Javitt and Zukin, 1991; Olney and Farber, 1995; Carlsson and Carlsson, 1999; Flores and Coyle, 2003). Disturbed glutamatergic neurotransmission is especially relevant in patients with significant negative symptoms and cognitive impairment (Goff and Coyle, 2001; Tsai and Coyle, 2002; Harrison and Weinberger, 2005). Furthermore, lower glutamate levels in the cerebrospinal fluid of schizophrenia patients have been reported as well as changes in the metabotropic and the ionotropic glutamate receptors in postmortem brain tissue (reviewed by Tamminga, 1998).

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In addition to the prefrontal cortex, the bulk of the data concerns the hippocampus (Heckers and Konradi, 2002; Harrison et al., 2003). Interestingly, all the known susceptibility genes for schizophrenia act on glutamatergic synaptic transmission (Harrison and Weinberger, 2005). However, reduced GABA synthesis has also been reported in schizophrenic patients (Lewis et al., 2005).

Animal models can help to better understand and find ways to cure human diseases. We have investigated the use of MK801 as a model of schizophrenia using different protocols (Brenner et al., 2005; Kondziella et al., 2005). Neurometabolite concentrations and turnover were assessed by high field ^{13}C and ^{1}H NMR spectroscopy and analyzed with special emphasize on glial–neuronal interactions. Due to the close connection of astrocyte metabolism and the synthesis of glutamate and GABA in neurons, there are good reasons to hypothesize an astrocytic role in the pathophysiology of schizophrenia and glutamate dysfunction (Kondziella et al., 2005). Earlier we have injected a single, relatively high dose of MK801 (0.5 mg/kg) and observed distinct behavioral abnormalities and increased levels of glutamate, glutamine and GABA combined with increased labeling of these amino acids mostly in temporal lobe (Brenner et al., 2005). After repeated injections of the same dose, increased levels of glutamate were found in the frontal cortex plus cingulate and retrosplenial cortices (FCR) but not in temporal lobe (Kondziella et al., 2005). To determine whether also a lower dose would produce schizophrenia-like alterations, rats were injected with 0.1 mg/kg MK801 every day for six consecutive days. Metabolite composition was analyzed by ^{13}C and ^{1}H NMR spectroscopy.

2. Materials and methods

2.1. Materials

Male Sprague Dawley rats (with an average weight of 250 g) were obtained from Möllegaard Breeding centre, Copenhagen, Denmark. Animals were housed in individual cages at a constant temperature of 22 °C with a 12 h light/dark cycle and a humidity of 60%. Animals had free access to food and water. [1-^{13}C]glucose, [1,2-^{13}C]acetate and D_2O (99.9%) were purchased from Cambridge Isotopes Laboratories (Woburn, MA, USA); ethylene glycol from Merck (Darmstad, Germany); MK801 (Diozocilpine; [5*R*,10*S*]-[+]-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclopheten-5,10-imine), from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals were of the purest grade available from local commercial sources.

2.2. Dosing and experimental design

The experimental design was approved by the Norwegian Animal Research Authorities Welfare and the local ethics committee. Animals were injected with saline or MK801 (0.1 mg/kg body weight) intraperitoneally every day for six days. The last dose of saline or MK801 was given together with [1-^{13}C]glucose (543 mg/kg, 0.3 M solution) and [1,2-^{13}C]acetate (504 mg/kg, 0.6 M solution). Twenty minutes later animals were decapitated, heads were snap frozen in liquid nitrogen and stored at −80 °C. Brains were removed, and two areas of each hemisphere were dissected. The first area included the cingulate, the retrosplenial and parts of the frontal cortices (FCR). The second area, the temporal lobe, was dissected by a horizontal cut from the most lateral point of the hemisphere extending approximately 3 mm medially and a second sagittal cut extending ventrally through the whole brain. The resulting sample consisted of the temporal cortex, piriform cortex, entorhinal cortex, amygdala and parts of the hippocampus. The dissection was performed on ice while the brains were still frozen. Thereafter, brain tissue was homogenized in 7% perchloric acid and centrifuged at 4000 × *g* for 5 min. The procedure was repeated, the supernatants pooled and neutralized with 1 M KOH followed by centrifugation and lyophilization.

2.3. Evaluation of behavior

Cages were divided into four equally large areas by imaginary lines. After each drug administration locomotor activity was scored by counting how often the animals crossed the lines during a specific time interval.

2.4. ^{13}C NMR spectroscopy and ^{1}H NMR spectroscopy

Samples were dissolved in 200 μl D_2O (deuterated water) containing ethylene glycol 0.1% as an internal standard.

Proton decoupled ^{13}C NMR spectra were obtained using a BRUKER DRX-600 spectrometer (BRUKER Analytik GmbH, Rheinstetten, Germany). Scans were accumulated with a 30° pulse angle and 30 kHz spectral width with 64 K data points. The number of scans was 10,000. The acquisition time was 1.08 s, the relaxation delay 0.5 s. Factors for the nuclear Overhauser and relaxation effects were applied to all spectra.

^{1}H NMR spectra was obtained using the same spectrometer. Scans were accumulated with a pulse angle of 90° and a spectral width with 32 K data points. The number of scans was 400. Acquisition time was 1.36 s and relaxation delay was 10 s. Water suppression was achieved by applying a low-power presaturation pulse at the water frequency.

2.5. Data analysis

The amounts of ^{13}C and ^{1}H in the different metabolites were quantified from integrals of the relevant peaks obtained from NMR spectra with ethylene glycol as an internal standard. Some spectras were not included in the analysis due to methodological error. All results are given as mean ± standard deviation. Statistics were performed using Student's *t*-test, $p < 0.05$ was regarded as significant.

3. Results

Repeated low dose injections of MK801 altered the behavior of some animals. Locomotor activity was slightly increased in 3–4 animals at any given time point compared to control (results not shown). Successive injections did not lead to increased activity of the individual animal.

A typical ^{1}H NMR spectrum is depicted in Fig. 1A, whereas Fig. 1B shows a ^{13}C NMR spectrum from an extract of temporal lobe from a MK801 injected rat. ^{13}C labeled amino acids and other small molecules derived from [1-^{13}C]glucose or [1,2-^{13}C]acetate are clearly detected. In order to interpret the ^{13}C NMR spectra it is necessary to analyze the metabolic pathways for [1-^{13}C]glucose (Fig. 2A) and [1,2-^{13}C]acetate (Fig. 2B).

When [1-^{13}C]glucose and [1,2-^{13}C]acetate are administered simultaneously, metabolic interactions between astrocytes and neurons can be studied in the same animal. This is due to the fact that acetate is exclusively taken up by astrocytes, while the major part of acetyl-CoA derived from glucose is used in neurons. Label from [1-^{13}C]glucose and thus neuronal metabolism can be quantified by analyzing the singlet peaks in the spectrum. In contrast, the doublets seen in the spectra are mainly derived from [1,2-^{13}C]acetate and thus astrocytic metabolism. In neurons [1-^{13}C]glucose is converted to [3-^{13}C]pyruvate which can be transformed to [3-^{13}C]lactate

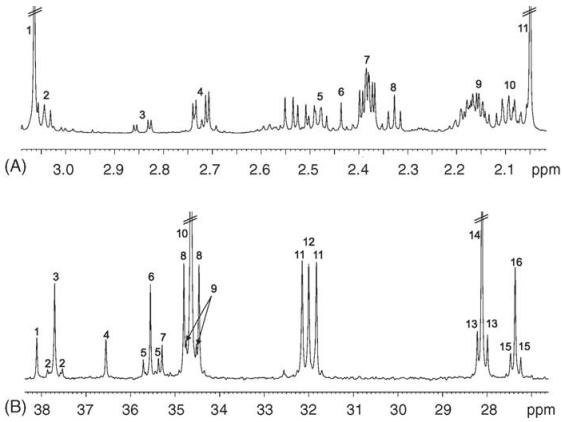

Fig. 1. (A) ^{1}H NMR spectrum of temporal lobe extract from rat injected with MK801. Peak assignments; protons on 1, creatine C-3; 2, GABA C-3; 3, aspartate C-3; 4, NAA C-3; 5, glutamine C-4; 6, succinate C-2 or C-3; 7, glutamate C-4; 8, GABA C-2; 9, glutamine C-3; 10, glutamate C-3; 11, NAA C-6. (B) ^{13}C NMR spectrum of temporal lobe extract from rat injected with MK801 together with [1-^{13}C]glucose and [1,2-^{13}C]acetate. Peak assignments; 1, creatine C-3; 2, aspartate C-3 (doublet); 3, aspartate C-3 (singlet); 4, taurine C-2; 5, GABA C-2 (doublet); 6, GABA C-2 (singlet); 7, succinate C-2 or C-3; 8, glutamate C-4 (doublet); 9, glutamate C-4 (doublet); 10, glutamate C-4 (singlet); 11, glutamine C-4 (doublet); 12, glutamine C-4 (singlet); 13, glutamate C-3 (doublet); 14, glutamate C-3 (singlet); 15, glutamine C-3 (doublet); 16, glutamine C-3 (singlet). The singlets in the spectrum are mostly derived from [1-^{13}C]glucose and the doublets from [1,2-^{13}C]acetate.

or [3-^{13}C]alanine or enter the TCA cycle as labeled [2-^{13}C]acetyl-CoA. The latter will lead to formation of [4-^{13}C]glutamate, [4-^{13}C]glutamine and [2-^{13}C]GABA. In addition, in astrocytes [1-^{13}C]glucose can be converted to [3-^{13}C]oxaloacetate by pyruvate carboxylase (PC). This will lead to labeling of [2-^{13}C]glutamate and [2-^{13}C]glutamine, and [4-^{13}C]GABA. [1,2-^{13}C]acetate can be converted to [1,2-^{13}C]acetyl-CoA. Labeled acetyl-CoA enters the TCA cycle and can lead to formation of [4,5-^{13}C]glutamate, [4,5-^{13}C]glutamine or [1,2-^{13}C]GABA.

Table 1
Amounts of metabolites (μmol/g) in extracts from the temporal lobe of controls and rats treated with MK801

	Control[a]	MK801
Glutamate	10.0 ± 1.2	11.5 ± 1.4*
Glutamine	3.6 ± 0.5	4.3 ± 0.6**
GABA	2.0 ± 0.4	2.3 ± 0.6
Aspartate	2.6 ± 0.4	2.9 ± 0.5
Succinate	0.7 ± 0.2	0.9 ± 0.2*

Animals were injected with saline ($n = 8$) or 0.1 mg/kg MK801 ($n = 10$) intraperitoneally every day for six days. Amounts of metabolites were analyzed with ^{1}H NMR spectroscopy. Metabolites were quantified using the protons on; glutamate C-4; glutamine C-4; GABA C-2; aspartate C-3; succinate C-2/3 (for details see Section 2). The results are expressed as mean ± S.D. and were analyzed with the Student's t-test.

[a] Values from Kondziella et al. (2005).

* $p < 0.05$ significant difference between control and MK801.

** $p < 0.02$ significant difference between control and MK801.

Injection of MK801 lead to metabolic changes in temporal lobe only. Thus, no results from FCR are shown. In temporal lobe there was an increase in the labeling of glutamate and glutamine from both [1-^{13}C]glucose and [1,2-^{13}C]acetate, compared to controls (Fig. 3A and B). Aspartate labeling from [1-^{13}C]glucose was increased in the MK801 treated rats, whereas GABA labeling was unaltered.

As can be seen in Table 1, MK801 administration resulted in an increase in the amounts of glutamate, glutamine and succinate in temporal lobe. The amounts of GABA and aspartate were unaffected (Table 1).

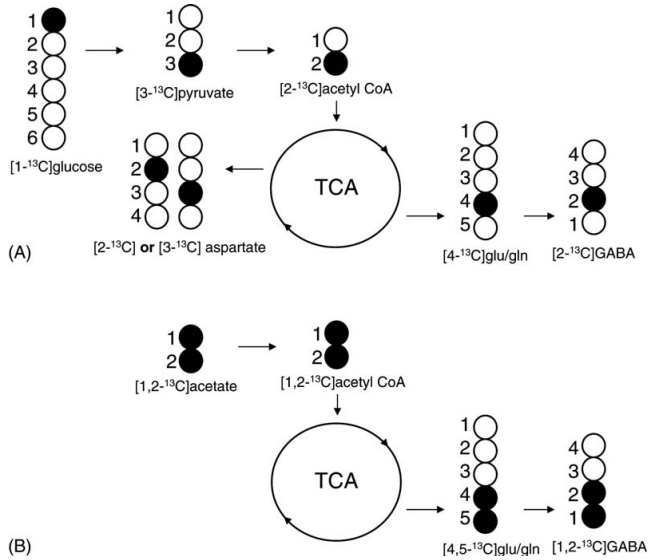

Fig. 2. Schematic presentation of isotopomers of glutamate, glutamine, GABA and aspartate derived from [1-^{13}C]glucose (A) and [1,2-^{13}C]acetate (B).

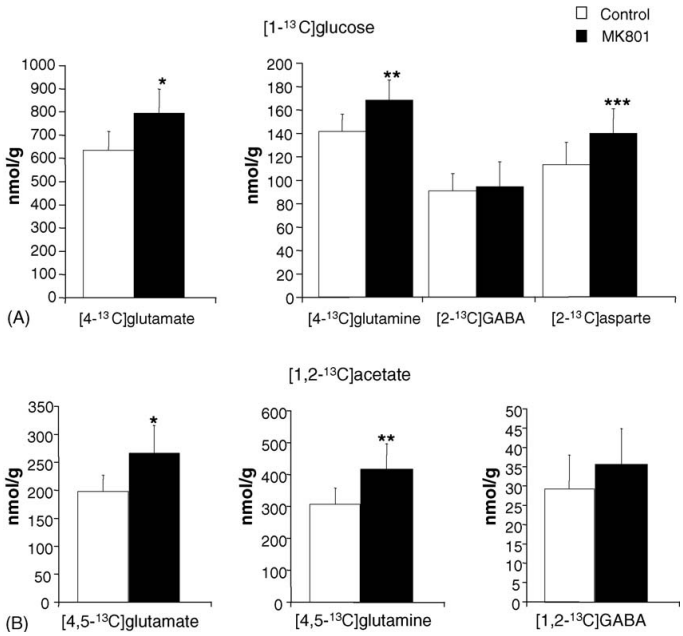

Fig. 3. Amounts (nmol/g brain tissue) of metabolites derived from (A) [1-^{13}C]glucose and (B) [1,2-^{13}C]acetate in extracts from the temporal lobe of rats treated with MK801 and controls. Animals were injected with saline ($n = 5$) or 0.1 mg/kg MK801 ($n = 7$) intraperitoneally every day for six days, the last day animals received [1-^{13}C]glucose and [1,2-^{13}C]acetate. Analyses were performed using ^{13}C NMR spectroscopy (for details see Section 2). The amount of ^{13}C in a metabolite was not corrected for natural abundance. The results are expressed as mean ± S.D. and were analyzed with the Student's *t*-test, control values from Kondziella et al. (2005). $^{*}p < 0.02$, $^{**}p < 0.03$, $^{***}p < 0.05$ significant difference between controls and MK801.

4. Discussion

NMR spectroscopy analyses of neurometabolites in brain from MK801 injected rats, a model of NMDA/glutamate-hypofunction and schizophrenia have provided valuable information about disturbances in amino acid neurotransmitter metabolism. Given once at 0.5 mg/kg, MK801 produced mainly changes in the temporal lobe with increased glutamate and glutamine concentrations and labeling from [1-^{13}C]glucose (Brenner et al., 2005). Similar changes were detected in the present study, when MK801 was injected repeatedly at 0.1 mg/kg every day for six days and changes were restricted to the temporal lobe. However, using 0.5 mg/kg repeatedly (Kondziella et al., 2005) instead of 0.1 mg/kg, resulted in changes in the FCR, thereby mimicking alterations observed in patients with schizophrenia (Bartha et al., 1997; Theberge et al., 2002; Tebartz van et al., 2005).

4.1. Glutamate and glutamine concentrations

Repeated injection of 0.1 mg/kg MK801 increased glutamate and glutamine concentrations and labeling in the temporal lobe, but not in the FCR. However, with repeated high doses (0.5 mg/kg) of MK801 no differences were found in the temporal lobe, but glutamate was increased in the FCR (Kondziella et al., 2005). In order to evaluate the significance of these findings for the understanding of glutamatergic function in schizophrenia it is important to compare with results obtained from patients. The latter analyses have to be done in vivo, where assessment of glutamatergic neurotransmission is difficult. Recent developments in NMR spectroscopy offer the opportunity to quantify a number of signals, including glutamate and glutamine. To our knowledge, there are four in vivo studies published in which absolute glutamate and glutamine concentrations were measured using NMR spectroscopy technology (Bartha et al., 1997; Theberge et al., 2002, 2003; Tebartz van et al., 2005). In an early study Bartha et al. (1997) reported increased glutamine levels in the medial prefrontal cortex of never-treated schizophrenia patients. Theberge et al. (2002) confirmed this observation for the left anterior cingulate and thalamus in a group of first-episode schizophrenia patients. In a second study, the same investigators reported significantly lower levels of glutamate and glutamine in the left anterior cingulate of patients with chronic schizophrenia, whereas Tebartz van et al. (2005) detected higher glutamate and glutamine concentrations in dorsolateral prefrontal cortex and hippocampus. However, the latter authors found an unusually low glutamate concentration in control patients and thus the relevance of this study is doubtful. Taken together the first three reports indicate that first-episode patients have an increased glutamine level in different areas of the brain, whereas chronic patients have decreased glutamate and glutamine levels in anterior cingulate. Animal models of schizophrenia should mimic this. In the present study,

increases were found in glutamate and glutamine in the temporal lobe but not in the FCR. Thus, it appears that this model does not show the same pattern as seen in schizophrenia patients and mimics more the toxic effects of MK801 possibly caused by increased glutamate in the extracellular space. In line with this is the fact that low doses of MK801 in the present study lead only to moderate hyperlocomotion alterations compared with high doses (data not shown). Repeated injection of the high dose (0.5 mg/kg) does, however, show very similar results to those from first-episode patients (Kondziella et al., 2005) and might thus be a good model for schizophrenia.

4.2. Astrocyte–neuron interactions

In the present study, labeling of glutamate and glutamine was increased in the temporal lobe, whereas GABA labeling was unchanged. It is possible to study astrocyte–neuronal interactions by analyzing the labeling patterns from [1-^{13}C]-glucose and [1,2-^{13}C]acetate in metabolites. A major role of astrocytes in the adult brain is to support neurons metabolically and the glutamate–glutamine cycle is well established (Sonnewald et al., 1997). Astrocytes are essential in maintaining the low glutamate levels in the synaptic cleft needed for precise receptor-mediated functions (Danbolt, 2001). Extracellular glutamate is taken up by astrocytes, in which it is converted to glutamine. Glutamine is then transported to the presynaptic neuron and converted to glutamate again. This process appears to be enhanced in our study, since labeling of both glutamate and glutamine from glucose, and thus mostly neurons, is increased in the temporal lobe. Labeling from [1,2-^{13}C]acetate was also increased in glutamate and glutamine in this area after repeated injection of 0.1 mg/kg MK801. Since the transport system for acetate is mostly on astrocytes such labeling originates from astrocytes (Waniewski and Martin, 1998). Taken together, these observations might be an indication of increased glutamatergic function, which could cause the neurotoxic effects of NMDA antagonism reported by several authors (Olney and Farber, 1994; Farber et al., 1995, 1996, 1998). A similar increase in labeling of glutamate and glutamine in the temporal lobe was reported by Brenner et al. (2005) after injection of a single dose of 0.5 mg/kg MK801. However, repeated high dose injections had no effect on labeling in the temporal lobe but lead to a decrease in labeling of glutamate and GABA from [1-^{13}C]glucose in the FCR (Kondziella et al., 2005).

Interestingly, localization of the changes in the metabolic results is different than that of histologic results. Several authors reported reversible vacuolization and other histologic abnormalities confined to retrosplenial cortex (RSC), which is part of the FCR, with low doses, involving the temporal lobe only when high doses were given (Olney et al., 1989; Wozniak et al., 1996, 1998). Although the mismatch between metabolic and histologically results seems surprising at first glance, it should be noted that the histological alterations were fully reversible (Wozniak et al., 1996) and that altered cell structure is not always identical with altered cell function.

4.3. Complex polysynaptic network impairments and the kindling effect

Why do different doses of MK801 lead to impairment of different brain areas? While a single high dose and repeated low doses of MK801 lead to biochemical alterations in temporal lobe, repeated high doses spared the temporal lobe largely, but evoked significant disturbances in the FCR. It is highly interesting in this context, that MK801 directly injected into the RSC, which is part of the FCR, does not produce the same neurotoxic reactions as that seen with equivalent systemic doses (Farber et al., 2002). This signifies that NMDA receptor blockade is required at one or more sites outside the RSC to trigger these neurotoxic effects. Thus, polysynaptic network impairments have to be considered. Possibly, different doses of MK801 may have the same local effects in the FCR, but different outcome in other non-FCR areas, whereby low doses of MK801 may change polysynaptic chains in such a way that metabolic disturbances are most pronounced in the temporal lobe. In contrast, high doses of MK801 affect other polysynaptic chains, leading to alterations in FCR. Since only repeated doses, but not a single dose, of 0.5 mg/kg MK801 lead to alterations in the FCR, one might postulate that the relevant polysynaptic changes have to be sensitized, or in other terms, ‘‘kindled’’.

In conclusion; do repeated MK801 injections serve as a model of schizophrenia? The answer is yes, if the chosen dose is high enough. Repeated low doses (0.1 mg/kg) of MK801 mimic the behavioral changes such as a slight hyperlocomotion and increased pre-pulse inhibition (Schulz et al., 2001), but not the neurochemical alterations seen in schizophrenia. Repeated high doses (0.5 mg/kg) mimic both. In conclusion, repeated injection of MK801 at 0.1 mg/kg appears to model the toxic effects of NMDA hypofunction, whereas repeated administration of high doses (0.5 mg/kg) mimics the results observed in first-episode schizophrenia patients.

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