Palestrica of the third millennium – Civilization and Sport
Vol. 15, no. 3, July-September 2014, 183–188

ORIGINAL STUDIES
ARTICOLE ORIGINALE

Motor and emotional behaviour in experimentally induced schizophrenia

Comportamentul motor şi emoţional în schizofrenia indusă experimental

Mihnea C. Manea[1], Maria G. Puiu[1], Mirela Manea[1], Simona Tache[2]
[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest
[2] "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca

Abstract

Background. Schizophrenia is a serious psychiatric disorder with 0.5-1% prevalence worldwide. Administration of MK-801 and exposure to intermittent hypobaric hypoxia were experimentally used to establish schizophrenia models in rats.

Aims. We aimed to study experimentally in male and female rats the following: the postnatal induced schizophrenia model by MK-801 administration and intermittent hypobaric hypoxia exposure during postnatal days 7-21; the changes in motor and emotional behaviour in rats with schizophrenia, and the gender differences between male and female rats.

Methods. The research was performed in 6 groups of rats (n=10 animals/group) as follows: group I - male, control; group II - female, control; group III - male with schizophrenia induced by MK-801 administration; group IV - male with schizophrenia induced through intermittent hypobaric hypoxia exposure; group I - female with schizophrenia induced by MK-801 administration; group IV - female with schizophrenia induced through intermittent hypobaric hypoxia exposure. Involuntary motility and emotional behaviour were tested using the Open Field test. The examination moments were postnatal days 22 (T_0) and 49 (T_{28}).

Results. The Open Field test values - emotional score, evidenced very statistically significant differences between all groups (III-VI) with schizophrenia, compared to controls (I-II) at moment T_{28}. The Open Field test values - motility score, evidenced very statistically significant differences between all groups (III-VI) with schizophrenia, compared to controls (I-II) at moment T_{28}. The emotional score and the motility score showed statistically significant differences between the male and female group (III, V) in rats with schizophrenia induced by MK-801 administration, compared to initial values.

Conclusions. Emotional behaviour increases in male and female rats with schizophrenia, compared to controls. Involuntary motor behaviour decreases in male and female rats with schizophrenia, compared to controls. We did not observe a significant gender difference.

Keywords: schizophrenia, MK-801, hypobaric hypoxia, Open Field test.

Rezumat

Premize. Schizofrenia este o tulburare psihică gravă, cu o prevalenţă de 0,5-1% la nivel mondial. Administrarea de MK-801 şi expunerea la hipoxie hipobară intermitentă au fost utilizate pentru a induce modele experimentale de schizofrenie la şobolani.

Obiective. Ne-am propus să studiem experimental la şobolani masculi şi femele următoarele: modelul de schizofrenie indusă postnatal prin administrarea MK-801 şi expunerea intermitentă la hipoxie hipobară în zilele postnatale 7-21, schimbările comportamentului motor involuntar şi emoţional la şobolani cu schizofrenie şi diferenţele de gen între şobolanii masculi şi femele.

Metode. Studiul a fost efectuat pe 6 loturi de şobolani (n=10 animale/lot), după cum urmează: lotul I - masculi, control; lotul II - femele, control; lotul III - masculi, cu schizofrenie indusă prin administrarea MK-801; lotul IV - masculi, cu schizofrenie indusă prin expunerea intermitentă la hipoxie hipobară; lotul V - femele, cu schizofrenie indusă prin administrarea MK-801; lotul VI - femele, cu schizofrenie indusă prin expunerea intermitentă la hipoxie hipobară. Motilitatea involuntară şi comportamentul emoţional au fost testate cu ajutorul testului Open Field. Momentele pentru examinare au fost zilele postnatale 22 (T_0) şi 49 (T_{28}).

Rezultate. Valorile testului Open Field pentru scorul emoţional arată diferenţe înalt semnificative statistic între toate loturile (III-VI) cu schizofrenie, comparativ cu martorii (I-II), la momentul T_{28}. Valorile testului Open Field pentru scorul de motilitate arată diferenţe înalt semnificative statistic între toate loturile (III-VI) cu schizofrenie, comparativ cu martorii (I-II), la momentul T_{28}. Privind scorul emoţional şi scorul de motilitate, au fost observate diferenţe înalt semnificative statistic între loturile de masculi şi femele (III, V) la şobolanii cu schizofrenie indusă prin administrarea MK-801, comparativ cu valorile iniţiale.

Concluzii. Comportamentul emoţional creşte la şobolanii masculi şi femele cu schizofrenie, comparativ cu martorii. Comportament motor involuntar scade la şobolanii masculi şi femele cu schizofrenie, comparativ cu martorii. Nu am observat o diferenţă semnificativă între masculi şi femele.

Cuvinte cheie: schizofrenie, MK-801, hipoxie hipobară, testul Open Field.

Received: 2014, August 16; *Accepted for publication:* 2014, September 16;
Address for correspondence: "Carol Davila" University of Medicine and Pharmacy Bucharest, No.8 Eroilor Sanitari Street
E-mail: mihnea.manea@live.com

Introduction

Schizophrenia is a serious psychiatric disorder with 0.5-1% prevalence worldwide (Jablenski, 2000; McGrath et al., 2008). A large number of different animal models for the study of schizophrenia have been described. The administration of MK-801 and the exposure to intermittent hypobaric hypoxia have been experimentally used as schizophrenia models in experimental animals.

MK-801 (dizolcipine) induced in rat a pharmacological model of schizophrenia aspects, based on the N-methyl-D-aspartic acid (NMDA) receptor antagonist, which is known to produce many positive and negative cognitive symptoms of schizophrenia (Kesby et al., 2006; Ozyurt et al., 2007; Gururajan et al., 2011; Wedzony et al., 2008).

Hypoxia represents a factor of obstetric complications in the pathophysiology of schizophrenia. Hypobaric hypoxia is an environmental factor that requires a complex neuroendocrine response with adaptive specific changes involving the circulatory, respiratory, metabolic, enzymatic systems (Cârmaciu, 1996, Tache, Artino, 1996; Guyton, Hall, 1996). The exposure to chronic and intermittent pre-, peri- and postnatal short-term hypobaric hypoxia induced several effects in the neurodevelopmental mechanisms of schizophrenia. Hypobaric hypoxia represents a biophysical model of schizophrenia aspects in rats (Boksa et al., 2006; Schmidt-Kastner et al., 2006; Tiul'kova et al., 2010; Graf et al., 2005).

According to the neurodegenerative pathogenesis theory of schizophrenia, this occurs as a result of a process of chronic progressive degeneration of the brain neurons (dopaminergic and glutamatergic neurons), which could be prevented by treatment with neuroleptics (Stahl, 2002).

In schizophrenia, there are clear differences in gender, in the incidence of complications at birth, age of onset and the presence or extension of brain abnormalities (Leung, Chue, 2000).

Objectives

We aimed to experimentally study in male and female rats the following: a) the postnatally induced schizophrenia model by MK-801 administration and intermittent hypobaric hypoxia exposure during postnatal days 7-21, b) the changes in motor and emotional behaviour in rats with schizophrenia, and c) the gender differences between male and female rats.

Hypothesis

Changes of locomotor and emotional behaviour have been studied particularly in animals with schizophrenia models induced by postnatal MK-801 administration or through exposure to hypobaric hypoxia (Vázquez-Roque et al., 2012; Hains et al., 2009; Pietraszek et al., 2009).

Materials and methods

Research protocol

a) *Period and place of the research*

Male and female albino Wistar rats, weighing 130-150 g, obtained from the Biobase of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca were used in this study. The study was carried out in the Experimental Research Laboratory of the Department of Physiology, with the approval of the Bioethics Board.

Before any experiment, all animals were kept for 1 week in the experimental laboratory of the Physiology department, under the same laboratory conditions of temperature (22±2ºC), relative humidity (70±4%), in a 12 h light/dark cycle. They received a nutritionally standard diet (combined grain feed, Cantacuzino Institute, Bucharest); water *ad libitum*.

All procedures were carried out with the approval of the local animal use committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy and were in accordance with Directive 86/609/EEC of 24 November 1986 regarding the protection of animals used for experimental and scientific purposes.

b) *Subjects and groups*

The selected animals were postnatally exposed, between days 7-21, to MK-801 and hypobaric hypoxic stress, according to the animal model of schizophrenia in rats.

The animals were randomly divided into 6 groups of 10 rats/group: I – male control group; II – female control group; III – male schizophrenic group (MK-801 administration); IV – male schizophrenic group (exposure to hypobaric hypoxia); V – female schizophrenic group (MK-801 administration); VI – female schizophrenic group (exposure to hypobaric hypoxia).

MK-801 (dizocilpine) was given intraperitoneally at a dose of 0.3 mg/kg, 4 doses, on days 7, 12, 16, 21, during 14 days (days 7-21).

Exposure to hypobaric hypoxia – 349 mmHg, air pO_2 = 75 mm Hg, arterial blood pO_2 = 71% O_2 (corresponding to 6000 m altitude) was performed in a barometric chamber at the experimental laboratory of the Physiology Department, for 14 days (days 7-21), 2 h/day.

c) *Tests applied*

Involuntary motility was tested using the open field test (OFT), according to Denenberg & Whimby (1963). The monitored indicators were emotivity and motility. Emotivity was calculated based on the emotional score (ES): the sum of micturitions and defecations expressed in absolute values. The increase of their number is considered an indicator of anxiety. Spontaneous motility was calculated based on the motility score (MS): the sum of crossings and rearings. The increase of motility is and indicator of the absence of anxiety.

The examination moments were postnatal days 22 (T_0) and 49 (T_{28}).

At the end of the experiment, the animals were euthanized with ketamine in a dose of 0.2 ml/100 g animal.

d) *Statistical analysis*

Statistical processing was performed using the Excel application (Microsoft Office 2007) and the StatsDirect v.2.7.2. program. Statistical comparisons between the groups were done by the Student t test. Significance was accepted at the level of $p<0.05$.

Results

a) *Analysis by moments*

The statistical analysis of the open field test values - emotional score (Table I) - showed the following:

Table I

Comparative analysis for open field test values and statistical significance.

Group	OPEN FIELD Test		Mean	SE	Median	SD	Min.	Max.
I	Emotional score	T_0	5.6	0.4761	5.5	1.5055	3	8
		T_{28}						
	Motility score	T_0	24.5	0.5821	24	1.8409	21	27
		T_{28}						
II	Emotional score	T_0	6	0.3944	5.5	1.2472	5	8
		T_{28}						
	Motility score	T_0	28.7	0.9315	28	2.9458	25	34
		T_{28}						
III	Emotional score	T_0	11.6	0.4	12	1.2649	10	13
		T_{28}	10.9	0.3480	11	1.1005	9	12
	Motility score	T_0	8.1	0.2769	8	0.8756	6	9
		T_{28}	9.8	0.4422	9.5	1.3984	8	12
IV	Emotional score	T_0	9	0.4216	9	1.3333	7	11
		T_{28}	9.6	0.4	9.5	1.2649	8	12
	Motility score	T_0	11.9	0.5044	11.5	1.5951	9	14
		T_{28}	12.3	0.3667	12.5	1.1595	10	14
V	Emotional score	T_0	11.4	0.5416	11	1.7127	9	15
		T_{28}	7.6	0.5416	7.5	1.7127	5	10
	Motility score	T_0	11.2	0.1333	11	0.4216	11	12
		T_{28}	13.8	0.5538	14	1.7512	11	16
VI	Emotional score	T_0	8.8	0.3266	9	1.0328	7	10
		T_{28}	7.4	0.3055	7	0.9661	6	9
	Motility score	T_0	12.6	0.3712	13	1.1738	10	14
		T_{28}	13	0.6146	13.5	1.9437	10	16

Statistical significance (p) – unpaired samples

Group	Emotional score T_0	Emotional score T_{28}
I-II		0.6354
I-III	< 0.0001	< 0.0001
I-IV	0.0001	< 0.0001
III-IV	0.001	0.03
II-V	< 0.0001	0.034
II-VI	0.0002	0.0217
V-VI	0.0005	0.8236
III-V	0.6044	0.0002
IV-VI	> 0.9999	0.0006

Group	Motility score T_0	Motility score T_{28}
I-II		0.0008
I-III	< 0.0001	< 0.0001
I-IV	< 0.0001	< 0.0001
III-IV	< 0.0001	0.0007
II-V	< 0.0001	< 0.0001
II-VI	< 0.0001	< 0.0001
V-VI	0.007	0.3603
III-V	< 0.0001	0.0001
IV-VI	0.3688	0.3581

Statistical significance (p) – Paired samples

Emotional score		Motility score	
I: –	IV: 0.3125	I: –	IV: 0.7344
II: –	V: 0.002	II: –	V: 0.0039
III: 0.2031	VI: 0.0234	III: 0.0078	VI: 0.7422

• taking into account the 6 studied groups of rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - highly statistically significant differences between at least two groups ($p<0.0001$)

• taking into account the 3 studied groups of male rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - highly statistically significant differences between at least two groups ($p<0.0001$)

• taking into account the 3 studied groups of female rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - statistically significant differences between at least two groups ($p=0.035$).

The statistical analysis of the open field test values - motility score - evidenced the following:

• taking into account the 6 studied groups of rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - highly statistically significant differences between at least two groups ($p<0.0001$)

• taking into account the 3 studied groups of male rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - highly statistically significant differences between at least two groups ($p<0.0001$)

• taking into account the 3 studied groups of female rats

- at moment T_0 - highly statistically significant differences between at least two groups ($p<0.0001$)

- at moment T_{28} - highly statistically significant differences between at least two groups ($p<0.0001$).

b) *Analysis by groups*

The statistical analysis of the open field test values for unpaired samples showed the following:

• emotional score

- at moment T_0 - highly statistically significant differences between groups I-III, I-IV, II-V, II-VI and V-VI ($p<0.001$) and highly statistically significant differences between groups III and IV ($p<0.01$)

- at moment T_{28} - highly statistically significant differences between groups I-III and I-IV ($p<0.001$) and statistically significant differences between groups III-IV, II-V and II-VI ($p<0.05$)

• motility score

- at moment T_0 - highly statistically significant differences between groups I-II, I-III, I-IV, III-IV, II-V and II-VI ($p<0.001$) and highly statistically significant differences between groups V-VI ($p<0.01$)

- at moment T_{28} - highly statistically significant differences between groups I-III, I-IV, III-IV, II-V and II-VI ($p<0.001$).

The statistical analysis of the open field test values for paired samples (T_0-T_{28}) evidenced the following:

• emotional score - highly statistically significant differences for group V ($p<0.01$) and statistically significant differences for group VI ($p<0.05$)

• motility score - highly statistically significant differences for groups III and V ($p<0.01$).

c) *Correlation analysis of scores by groups and moments*

For group I, the statistical correlation analysis between the values of the studied indicators showed (Table II):

- at moment T_0 - a weak/null correlation between the emotional score and the motility score.

For group II, the statistical correlation analysis between the values of the studied indicators showed:

- at moment T_0 - a good positive correlation between the emotional score and the motility score.

For group III, the statistical correlation analysis between the values of the studied indicators showed:

- at moment T_0 - a weak/null correlation between the emotional score and the motility score

- at moment T_{28} - a weak/null correlation between the emotional score and the motility score.

For group IV, the statistical correlation analysis between the values of the studied indicators showed:

- at moment T_0 - *an acceptable negative correlation* between the emotional score and the motility score

- at moment T_{28} - a good positive correlation between the emotional score and the motility score.

For group V, the statistical correlation analysis between the values of the studied indicators showed:

- at moment T_0 - a weak/null correlation between the emotional score and the motility score

- at moment T_{28} - a weak/null correlation between the emotional score and the motility score.

For group VI, the statistical correlation analysis between the values of the studied indicators showed:

- at moment T_0 - a weak/null correlation between the emotional score and the motility score

- at moment T_{28} - an acceptable positive correlation between the emotional score and the motility score.

Table II

Statistical correlation analysis between the open field test scores in the six groups.

Group	**Moment**	Emotional score – motility score	
I	T_0	-0.0064	*
II	T_0	0.5024	***
III	T_0	0.0072	*
	T_{28}	-0.0880	*
IV	T_0	-0.4304	**
	T_{28}	0.5343	***
V	T_0	-0.0887	*
	T_{28}	-0.1615	*
VI	T_0	0.0000	*
	T_{28}	0.4838	**

Discussions

The emotional score

Our results show significant increases of the emotional score at 28 days in the groups of males (group III) and females (group V) with schizophrenia induced by MK-801 and hypobaric hypoxia (groups IV, VI), compared to control animals (groups I and II).

At 28 days, in male animals in which schizophrenia was induced by hypoxia (group IV), there were significant decreases of the emotional score compared to male animals in which schizophrenia was induced by the administration of MK-801 (group III).

Compared to initial values, in female animals with induced schizophrenia (groups V and VI), there were significant decreases of the emotional score at 28 days.

At 28 days, in male animals with induced schizophrenia (groups III, IV), there were significant increases of the emotional score compared to female animals with schizophrenia induced by the same method (groups V and VI).

The induction of schizophrenia by MK-801 administration in male animals (group III) caused significant increases of the emotional score compared to female animals (group V) in which schizophrenia was induced by the same methods.

The motility score

In female control animals (group II), there were significant increases in the motility score at 28 days compared to male control animals (group I).

The motility score at 28 days presented significant decreases in male and female animals with schizophrenia induced by MK-801 administration (groups III, V) and hypobaric hypoxia (groups IV, VI) compared to the control animals (groups I-II).

At 28 days, in male animals in which schizophrenia was induced by hypoxia (group IV), there were significant increases in the motility score compared to male animals in which schizophrenia was induced by MK-801 administration (group III).

The correlation analysis between the emotional score and the motility score at 28 days showed a good positive correlation for the group of female control animals and the group of males with schizophrenia induced by hypobaric hypoxia.

Compared to initial values, in female animals with schizophrenia induced by MK-801 administration (group V) and in male animals in which schizophrenia was induced by the same procedure (group III), significant increases in the motility score occurred.

At 28 days, in male animals in which schizophrenia was induced by MK-801 administration (group III), there were significant decreases in the motility score compared to female animals with schizophrenia induced by the same method (group V).

Our results regarding the model of schizophrenia induced by subchronic postnatal MK-801 administration are consistent with data from other authors regarding the effects of MK-801 administration to increase anxiety and emotional reactions, to decrease motility and exploratory behaviour and to influence memory and the learning ability (Akillioglu et al., 2012; Kubík et al., 2014; Lobellova et al., 2013; Vales et al., 2006; Li et al, 2011).

The experiments showed that MK801 was more effective in stimulating ataxia and locomotion and inhibiting stationary behaviour in female animals, while in male animals it stimulated stereotyping and thigmotaxis and inhibited rearing and grooming movements (Feinstein, Kritzer, 2013).

The effects of MK-801 on behaviour are dependent on the temporal profile, the administered dose, the number of daily injections (acute, subacute, and chronic), the age and sex of experimental animals. Female rats expressed 4-10 times more behavioural changes induced by MK-801 and presented about 25 times higher concentrations of MK-801 in the serum and brain than male rats (Andiné et al., 1999). Other studies suggest that MK-801-induced effects are more reproducible in female animals (Farber, 2003; Dickerson, Sharp, 2006; Nakki et al., 1996). Low doses result in increased concentrations of MK-801 in the frontal and parietal cortex, hypothalamus, striatum and hippocampus of male and female animals (Feinstein, Kritzer, 2013).

Hypobaric hypoxia is classified as histotoxic hypoxia (Cârmaciu, 1996, Tache, Artino, 1996; Guyton, Hall, 1996). Our data regarding the use of intermittent hypobaric hypoxia for the induction of schizophrenia in rats show similar changes in anxiety, emotivity, motility to those induced in the model of schizophrenia by the administration of MK-801, compared to controls.

Postnatal exposure to intermittent hypobaric hypoxia to induce schizophrenia in rats has been relatively little used experimentally (Samoilov et al., 2014; Rybnikova et al., 2008, 2009, 2012; Langmeier, Maresová, 2005; Lima-Ojeda et al., 2014; Schaeffer et al., 2013).

Our experimental results show that the models we used are valid neurobiological models for inducing postnatal schizophrenia in rats and for observing its manifestations on postnatal day 49, at the postpubertal age of 8 weeks (adolescents) (1).

The postnatal induction of schizophrenia on days 7-21 was followed by significant behavioural changes compared to controls, which occurred from day 22 (moment T_0). On day 49 (moment T_{28}), the changes were significant compared to values at 22 days.

Conclusions

1. Anxiety and emotivity increased significantly in male and female animals with induced schizophrenia compared to controls; spontaneous motility decreased significantly in male and female animals with induced schizophrenia compared to controls.

2. Locomotor activity decreased significantly in animals with induced schizophrenia, the most significant decreases being found in male animals with schizophrenia induced by hypoxia.

3. The models of schizophrenia experimentally induced by subchronic MK-801 administration and exposure to moderate intermittent hypobaric hypoxia are valid and original models.

Conflicts of interests

There are no conflicts of interest.

Acknowledgments

This paper is based on research data for the first author's doctoral thesis.

References

Akillioglu K, Babar Melik E, Melik E, Kocahan S. The investigation of neonatal MK-801 administration and physical environmental enrichment on emotional and cognitive functions in adult Balb/c mice. Pharmacol Biochem Behav, 2012; 102(3):407-414.

Andiné P, Widermark N, Axelsson R, Nyberg G, Olofsson U, Mårtensson E, Sandberg M. Characterization of MK-801-induced behaviour as a putative rat model of psychosis. J Pharmacol Exp Ther, 1999; 290(3):1393-1408.

Boksa P, Zhang Y, Amritraj A, Kar S. Birth insults involving hypoxia produce long-term increases in hippocampal [125I] insulin-like growth factor-I and -II receptor binding in the rat. Neuroscience. 2006; 139(2):451-462.

Cârmaciu R (sub red.). Guyton. Fiziologie. Ed. a 5-a, Editura Medicală Amalteea, WB Saunders, Bucureşti, 1996; VIII/30:290-294, XIV/57:577-583.

Denenberg VH, Whimby AE. Behaviour of adult rats is modified by the experiences their mothers had as infants. Science. 1963; 142:1192-1193.

Dickerson J, Sharp FR. Atypical antipsychotics and a Src kinase inhibitor (PP1) prevent cortical injury produced by the psychomimetic, noncompetitive NMDA receptor antagonist MK-801. Neuropsychopharmacol. 2006; 31:1420–1430.

Farber NB. The NMDA receptor hypofunction model of psychosis. Annals NY Acad Sci, 2003; 1003: 119–130.

Feinstein I, Kritzer MF. Acute N-methyl-D-aspartate receptor hypofunction induced by MK801 evokes sex-specific changes in behaviours observed in open-field testing in adult male and proestrus female rats. Neuroscience, 2013; 228:200-214.

Graf AV, Maslova MV, Maklakova AS, Sokolova NA, Goncharenko EN, Baĭzhumanov AA, Krushinskaia IaV. Acute antenatal hypoxia on different stages of embryogenesis changes the offspring behaviour patterns and biogenic amine levels. Ross Fiziol Zh Im I M Sechenova, 2005; 91(2):152-157.

Gururajan A, Taylor DA, Malone DT. Effect of cannabidiol in a MK-801-rodent model of aspects of schizophrenia. Behav Brain Res, 2011; 222(2):299-308.

Guyton AC, Hall JE. Textbook of Medical Physiology. 9th ed., Saunders & Comp., Philadelphia, 1996; VII/4:52, VIII/43:549-552

Hains AB, Vu MA, Maciejewski PK, van Dyck CH, Gottron M, Arnsten AF. Inhibition of protein kinase C signaling protects prefrontal cortex dendritic spines and cognition from the effects of chronic stress. Proc Natl Acad Sci USA, 2009; 106(42):17957-17962.

Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. Eur Arch Psychiatry Clin Neurosci, 2000; 250(6):274-285.

Kesby JP, Burne TH, McGrath JJ, Eyles DW. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: An animal model of schizophrenia. Biol Psychiatry, 2006; 60(6):591-596.

Kubík S, Buchtová H, Valeš K, Stuchlík A. MK-801 Impairs Cognitive Coordination on a Rotating Arena (Carousel) and Contextual Specificity of Hippocampal Immediate-Early Gene Expression in a Rat Model of Psychosis. Front Behav Neurosci, 2014; 8:75.

Langmeier M, Maresová D. Intermittent hypobaric hypoxia during development - morphological and functional changes in the neocortex. Prague Med Rep. 2005; 106(3):275-282.

Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl. 2000; 401:3–38.

Li JT, Su YA, Guo CM, Feng Y, Yang Y, Huang RH, Si TM. Persisting cognitive deficits induced by low-dose, subchronic treatment with MK-801 in adolescent rats. Eur J Pharmacol, 2011; 652(1-3):65-72.

Lima-Ojeda JM, Vogt MA, Richter SH, Dormann C, Schneider M, Gass P, Inta D. Lack of protracted behavioural abnormalities following intermittent or continuous chronic mild hypoxia in perinatal C57BL/6 mice. Neurosci Lett, 2014; 577C:77-82.

Lobellova V, Entlerova M, Svojanovska B, Hatalova H, Prokopova I, Petrasek T, Vales K, Kubik S, Fajnerova I, Stuchlik A. Two learning tasks provide evidence for disrupted behavioural flexibility in an animal model of schizophrenia-like behaviour induced by acute MK-801: a dose-response study. Behav Brain Res, 2013; 246:55-62.

McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 2008; 30, 67–76.

Nakki R, Sharp FR, Sagar SM, Honkaniemi J. Effects of phencyclidine on immediate early gene expression in the brain. J Neurosci Res. 1996; 45:13–27.

Ozyurt B, Sarsilmaz M, Akpolat N, Ozyurt H, Akyol O, Herken H, Kus I. The protective effects of omega-3 fatty acids against MK-801-induced neurotoxicity in prefrontal cortex of rat. Neurochem Int. 2007c; 50(1):196-202.

Pietraszek M, Michaluk J, Romańska I, Wasik A, Gołembiowska K, Antkiewicz-Michaluk L. 1-Methyl-1,2,3,4-tetrahydroiso-

quinoline antagonizes a rise in brain dopamine metabolism, glutamate release in frontal cortex and locomotor hyperactivity produced by MK-801 but not the disruptions of prepulse inhibition, and impairment of working memory in rat. Neurotox Res, 2009; 16(4):390-407

Rybnikova E, Gluschenko T, Tulkova E, Churilova A, Jaroshevich O, Baranova K, Samoilov M. Preconditioning induces prolonged expression of transcription factors pCREB and NF-kappa B in the neocortex of rats before and following severe hypobaric hypoxia. J Neurochem, 2008; 106(3):1450-1458.

Rybnikova E, Glushchenko T, Tyulkova E, Baranova K, Samoilov M. Mild hypobaric hypoxia preconditioning up-regulates expression of transcription factors c-Fos and NGFI-A in rat neocortex and hippocampus. Neurosci Res, 2009; 65(4):360-366.

Rybnikova E, Vorobyev M, Pivina S, Samoilov M. Postconditioning by mild hypoxic exposures reduces rat brain injury caused by severe hypoxia. Neurosci Lett, 2012; 513(1):100-105.

Samoilov M, Churilova A, Gluschenko T, Rybnikova E. Neocortical pCREB and BDNF expression under different modes of hypobaric hypoxia: Role in brain hypoxic tolerance in rats. Acta Histochem. 2014 Apr 17. pii: S0065-1281(14)00056-7.

Schaeffer EL, Kühn F, Schmitt A, Gattaz WF, Gruber O, Schneider-Axmann T, Falkai P, Schmitt A. Increased cell proliferation in the rat anterior cingulate cortex following neonatal hypoxia: relevance to schizophrenia. J Neural Transm, 2013; 120(1):187-195.

Schmidt-Kastner R, van Os J, W M Steinbusch H, Schmitz C. Gene regulation by hypoxia and the neurodevelopmental origin of schizophrenia. Schizophr Res. 2006; 84(2-3):253-271.

Stahl MS. Psychopharmacologie essentielle. Trad. Thierry Faivre et Patrick Leoine, Med. Sci, Paris, 2002; 368-370

Tache S, Artino MG. Fiziologia aparatului respirator. Ed. Dacia, Cluj-Napoca, 1996; XIV:243-255, XVIB:268-279.

Tiul'kova EI, Vataeva LA, Samoĭlov MO. Effect of prenatal hypobaric hypoxia on activity of the rat brain phosphoinositide system. Zh Evol Biokhim Fiziol. 2010; 46(5):406-410.

Vales K, Bubenikova-Valesova V, Klement D, Stuchlik A. Analysis of sensitivity to MK-801 treatment in a novel active allothetic place avoidance task and in the working memory version of the Morris water maze reveals differences between Long-Evans and Wistar rats. Neurosci Res, 2006; 55(4):383-388.

Vázquez-Roque RA, Ramos B, Tecuatl C, Juárez I, Adame A, de la Cruz F, Zamudio S, Mena R, Rockenstein E, Masliah E, Flores G. Chronic administration of the neurotrophic agent cerebrolysin ameliorates the behavioural and morphological changes induced by neonatal ventral hippocampus lesion in a rat model of schizophrenia. J Neurosci Res, 2012; 90(1):288-306.

Wedzony K, Fijal K, Mackowiak M, Chocyk A, Zajaczkowski W. Impact of postnatal blockade of N-methyl-D-aspartate receptors on rat behaviour: a search for a new developmental model of schizophrenia. Neuroscience, 2008; 153(4):1370-1379.

Web sites

(1) www.ratbehaviour.org, accessed on August 2014