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Learning And Memory Alterations in Rats Following Postnatal Hypoxia and Effects of Haloperidol; Implications For Schizophrenia

KEYWORDS: learning, memory, hypoxia, Haloperidol, schizophrenia

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ABSTRACT *Background. Postnatal hypoxia may create conditions for complex changes in neurodevelopmental origin of schizophrenia. Exposure to hypobaric hypoxia affect the brain structural and functional integrity.*

Aims. We study the effects and the gender differences of intermittent hypobaric hypoxia in male and female rats and the effects of Haloperidol administration.

Methods. Rats were exposed during postnatal days 7-21 to intermittent hypobaric hypoxia and tested using Morris water maze (MWM) test in day 22 and day 49.

Results. In male and female rats with schizophrenia MWM test evidenced decreases of motor learning and memory, compared to controls and increases of motor learning and memory after Haloperidol treatment, compared to the initial values. The Haloperidol treatment determined significant memory increases in male rats, compared to female rats.

Conclusions. Haloperidol would be effective in treating cognitive dysfunction in schizophrenia.

Introduction

Neurodevelopment in schizophrenia

Neurodevelopmental hypothesis proposes that the schizophrenia's etiopathogenesis is linked to genetic and environmental factors that lead to abnormal brain development during pre- or postnatal period (Schmitt et al., 2014; Rapoport et al., 2012; Dean & Murray, 2005).

Disturbances of brain development during fetal or perinatal period, affecting neurogenesis, myelination, synaptogenesis and Wnt gene family, cause changes manifest at puberty or adolescence (Weinberger, 1987; Verdoux, 2004; Nadri et al.,2003). In biochemical terms, hypo-frontalization involves important changes of mediators in subcortical floors, with increased dopamine and glutamate, responsible for the appearance of psychotic symptoms (Fatemi & Folsom, 2009).

Gender differences in schizophrenia are clear differences in male / female, the incidence of complications at birth, age of onset and presence or expansion degree of brain abnormalities (Leung & Chue, 2000). There is clear evidence that men are more vulnerable to negative and cognitive symptoms of schizophrenia, while women are more often affected by positive symptoms (Feinstein & Kritzer, 2013; Cotton et al., 2009; Ochoa et al., 2012).

Hypobaric hypoxia

The influence of advanced hypobaric hypoxia on the development of normal brain has repercussions in adolescence, the occurrence of schizophrenia.

Exposure to hypobaric hypoxia has effects on the structure (Gribanov et al., 2004; Schaeffer et al., 2013) and functions of brain tissue (Jandova et al., 2012; Maiti et al., 2007; Baitharu et al., 2013; Sharma et al., 2013; Langmeier & Maresová, 2005) and affect the neurotransmitters (Ray et al., 2011) cholinergic type (Muthuraju et al., 2011a, 2011b), the cerebral biogenic amines (Ray et al., 2011; Laplante et al., 2012), glutamate (Ikonomidou et al., 1989a, 1989b); impaire the nerve activity, the cerebral metabolism in frontal cortical areas (Bogdanova et al., 2014), enzymes and oxidant / antioxidant balance in the neocortex, subcortical structures, cerebellum, medulla (Maiti et al., 2010; Kislin et al., 2011; Barhwal et al., 2009a, 2009b; Sharma et al., 2011; Maiti et al., 2006). Experimental can be produced an increasing tolerance of brain neurons to severe hypoxia by preconditioning by repeated moderate hypobaric hypoxia (Samoilov et al., 2014).

Aims

In the present work, in animals with schizophrenia induced experimentally by exposure to intermittent hypobaric hypoxia, we aimed to study:

- ability to motor learning and memory in rats;
- behavioral effects caused by administration of Haloperidol, a typical antipsychotic;
- gender differences in male and female rats.

Material and methods

The research was conducted in the experimental laboratory of the Department of Physiology at the University of Medicine and Pharmacy "Iuliu Haţieganu" Cluj-Napoca, with the approval of the Ethics Commission.

Groups

The groups (I-VI) were composed of n = 10 Wistar rats / group, male and female, 150-200 g weight:

- witnesses, saline injected intramuscular: group I - males, group II - females;
- animals with schizophrenia induced by intermittent exposure to hypobaric hypoxia: group III - males, group IV - females;

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- animals with schizophrenia induced by intermittent exposure to hypobaric hypoxia and treated with Haloperidol, 28 days: group V - males, group VI - females.

Methods
Rats were exposed during postnatal days 7-21 to intermittent hypobaric hypoxia, 2 hours per day, inside the hypobaric chamber, simulating altitude of 6,000 m. Rats' behavior was tested using Morris water maze (MWM) test.

Intermittent hypobaric hypoxia exposure (on-off method of exposure)
The simulated exposure in hypobaric chamber was made with vacuum pump 0016 KB D.

The exposure was made during postnatal period, by a blinking daily pattern, for 14 days, from day 7 to day 21:

- hypobaric hypoxia - 2 hours/day, at a pressure equivalent to an altitude of 6000 m, with a O_2 concentration in inspired air of 10% and pO_2 = 75 mmHg;
- normobaric normoxia - 22 hours/day, at a corresponding pressure of a low altitude 363 m, with an O_2 concentration of the air inspired by 20%, and pO_2 = 156 mmHg.

The Haloperidol administration (SC Rompharma Company SRL®) was done by oropharyngeal gavage; the dose was 0,075 mg / kg (0.015 mg / animal);

Methods of behavior's study
The determination of motor learning and memory capacity was based on the Morris water maze (MWM) test. The postnatal examination moments were: day 22 (T_0 moment) and day 49 (T_{28} moment).

The MWM test (Morris et al., 1982) considers as indicators: learning / acquisition information during training days and learning ability and memory or learning control, in the test day.

Statistical analysis
Statistical processing was performed with Excel (Microsoft Office 2007), with SPSS v.17 or online applications OpenEpi V.2.3.1 and SISA.

Results
The results showed in female control animals (group II) a motor learning capacity and memory significantly decreased, compared to male controls (group I).

The male animals with schizophrenia (group III) showed significant decreases in spatial motility and in learning ability at 28 days, compared with control animals (group I). The learning control (memorizing) shows significant decreases in spatial motility and increasing memorizing capacity, compared to control animals.

In female animals with schizophrenia (group IV) were found changes similar to those in males with induced schizophrenia (group III), both in the learning ability and memory capacity, after 28 days.

Learning ability **(Table I)**
At 28 days, as compared to the corresponding control groups with schizophrenia, we found (Table I):
- significant decreases in spatial motility of male animals group with schizophrenia induced by exposure to hypobaric hypoxia (group V) and treated with Haloperidol, versus the control group (group III);
- significant decreases in spatial motility of animals with schizophrenia induced by exposure to hypobaric hypoxia, male treated with Haloperidol (group V) and females treated with Haloperidol (group VI);
- significant increases in learning ability in males animal groups with schizophrenia treated with Haloperidol (group V) compared to the control group (group III);
- significant increases in learning ability in all groups (V, VI) from initial values at the time T_0.

Memorizing capacity **(Table II)**
At 28 days, compared to the corresponding control groups with schizophrenia, there were increases in memorizing capacity in all groups, the most significant increases were in group V.

The increases in memory capacity at 28 days were significant, in male animals with schizophrenia and treated (group V), compared with females animals with schizophrenia and treated (group VI).

Table I. Comparative analysis for Morris test values (learning) in the studied groups and statistical significance.

Test / Moment			Average	SE	Median	SD	Min.	Max.	Statistical significance (p) – unpaired samples		
									Group	T0	T28
Group I	Diagonals	T0	1,6	0,058	1,54	0,1834	1,4167	2	Diagonals		
		T28							I-II	0,3006	
	Rotations	T0	2,93	0,0562	2,92	0,1776	2,67	3,33	I-III	0,012	0,8488
		T28							II-IV	0,0142	0,0495
	Time in D quadrant	T0	3,58	0,1369	3,63	0,4329	2,83	4,17	III-IV	0,2116	0,6948
		T28							I-V	< 0,0001	0,0055
	Latency time	T0	32,28	0,6745	32,67	2,133	26,92	34,75	III-V	7,67 x 10−5	0,0045
		T28							II-VI	3,59 x 10−7	0,0002
Group II	Diagonals	T0	1,51	0,0636	1,50	0,2013	1,2067	1,9	IV-VI	1,75 x 10−5	2,15 x 10−6
		T28							V-VI	0,0049	0,0049
	Rotations	T0	2,34	0,0345	2,33	0,1091	2,18	2,55	Rotations		
		T28							I-II	2,2 x 10−7	
	Time in D quadrant	T0	2,02	0,0693	2,03	0,219	1,67	2,33	I-III	0,0018	0,0009
		T28							II-IV	6,76 x 10−5	0,7798
	Latency time	T0	23,49	0,5916	23,04	1,8708	21,5	26,82	III-IV	0,0001	0,076
		T28							I-V	6,15 x 10−15	< 0,0001

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Group III	Diagonals	T0	1,38	0,0485	1,38	0,1534	1,17	1,58	III-V	1,1 x 10−8	< 0,0001
		T28	1,66	0,0809	1,67	0,2559	1,33	2	II-VI	1,73 x 10−15	4,02 x 10−9
	Rotations	T0	2,49	0,0974	2,54	0,3079	1,92	2,83	IV-VI	2,98 x 10−8	< 0,0001
		T28	2,53	0,0778	2,5	0,246	2,17	2,83	V-VI	0,7555	0,3201
	Time in D quadrant	T0	10,37	0,2247	10,5	0,7106	9,17	11,5	Time in D quadrant		
		T28	11,21	0,0768	11,17	0,243	10,92	11,58	I-II	1,53 x 10−7	
	Latency time	T0	55,98	0,7686	55,92	2,4305	51	60,33	I-III	7,62 x 10−14	5,14 x 10−17
		T28	48,11	0,5514	47,71	1,7436	45,83	50,75	II-IV	2,6 x 10−11	2,51 x 10−15
Group IV	Diagonals	T0	1,28	0,0515	1,25	0,1629	1,08	1,5	III-IV	6,92 x 10−9	1,42 x 10−10
		T28	1,7	0,066	1,67	0,2086	1,42	2	I-V	1,14 x 10−10	6,33 x 10−9
	Rotations	T0	1,9	0,0678	1,92	0,2144	1,5	2,25	III-V	2,63 x 10−10	1,43 x 10−20
		T28	2,34	0,0519	2,29	0,1641	2,17	2,58	II-VI	3,57 x 10−19	2,38 x 10−17
	Time in D quadrant	T0	7,28	0,1864	7,54	0,5895	6,17	8	IV-VI	0,0005	0,0067
		T28	8,59	0,1386	8,67	0,4382	7,83	9,33	V-VI	0,0597	1,9 x 10−12
	Latency time	T0	47,19	0,5426	46,83	1,716	44,92	50,92	Latency time		
		T28	36,11	0,7386	35,88	2,3337	33,67	41	I-II	< 0,0001	
Group V	Diagonals	T0	1,06	0,0374	1,04	0,1182	0,92	1,25	I-III	< 0,0001	< 0,0001
		T28	1,34	0,0472	1,29	0,1493	1,17	1,58	II-IV	< 0,0001	< 0,0001
	Rotations	T0	1,07	0,0369	1,04	0,1165	0,92	1,25	III-IV	6,99 x 10−8	2,84 x 10−10
		T28	1,46	0,0435	1,42	0,1375	1,33	1,67	I-V	< 0,0001	0,0021
	Time in D quadrant	T0	6,04	0,1147	6,08	0,3627	5,25	6,50	III-V	3,58 x 10−11	9,77 x 10−13
		T28	5,40	0,0911	5,38	0,2881	4,83	5,92	II-VI	< 0,0001	< 0,0001
	Latency time	T0	41,68	0,5795	41,79	1,8327	38,83	44,83	IV-VI	6,72 x 10−5	8,51 x 10−5
		T28	34,66	0,3866	34,75	1,2225	32,67	36,67	V-VI	6,42 x 10−10	3,41 x 10−9
Group VI	Diagonals	T0	0,83	0,0602	0,83	0,1902	0,58	1,17	Statistical significance (p) – paired samples (T0-T28)		
		T28	1,1	0,058	1,13	0,1834	0,75	1,42	Group	Diagonals	Rotations
	Rotations	T0	1,05	0,0377	1,04	0,1192	0,92	1,25	I	–	–
		T28	1,38	0,066	1,33	0,2086	1,00	1,67	II	–	–
	Time in D quadrant	T0	6,33	0,08	6,33	0,2529	5,92	6,75	III	0,007	0,7336
		T28	8,03	0,116	8,00	0,3668	7,50	8,67	IV	0,0012	0,002
	Latency time	T0	50,88	0,4685	51,04	1,4815	48,83	53,42	V	0,0002	0,002
		T28	40,74	0,4212	40,5	1,3319	38,83	43,5	VI	0,0098	0,0065

									Time in D quadrant	Latency time
									0,0044	5,82 x 10−7
									0,0001	7,44 x 10−9
									0,0019	1,1 x 10−7
									4,41 x 10−7	1,23 x 10−7

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Table II. Comparative analysis for Morris test values (control) in the studied groups and statistical significance.

Test / Moment			Average	SE	Median	SD	Min.	Max.	Statistical significance (p) – unpaired samples		
									Group	Group	Group
Group I	Diagonals	T0	4,9	0,3145	5	0,9944	4	7	Diagonals		
		T28							I-II	0,5525	
	Rotations	T0	10,5	0,654	10	2,0683	8	14	I-III	< 0,0001	< 0,0001
		T28							II-IV	< 0,0001	0,0002
	Time in D quadrant	T0	32,2	2,5465	33,5	8,0526	18	42	III-IV	0,5631	0,0287
		T28							I-V	0,0004	0,0355
	Latency time	T0	60	–	60	–	60	60	III-V	4 x 10–5	0,0002
		T28							II-VI	< 0,0001	0,0032
Group II	Diagonals	T0	5,2	0,3266	5	1,0328	4	7	IV-VI	0,2659	0,2281
		T28							V-VI	0,0339	0,6177
	Rotations	T0	10,9	0,6403	10	2,0248	8	14	Rotations		
		T28							I-II	0,6678	
	Time in D quadrant	T0	32,7	2,2806	34	7,2119	21	42	I-III	< 0,0001	< 0,0001
		T28							II-IV	1,46 x 10–7	< 0,0001
	Latency time	T0	60	–	60	–	60	60	III-IV	0,3913	0,2422
		T28							I-V	< 0,0001	< 0,0001
Group III	Diagonals	T0	1,6	0,2211	1,5	0,6992	1	3	III-V	0,0013	0,0053
		T28	2	0,2582	2	0,8165	1	3	II-VI	4,99 x 10–8	< 0,0001
	Rotations	T0	3,3	0,2134	3	0,6749	2	4	IV-VI	0,0134	0,3623
		T28	4,8	0,2494	5	0,7888	4	6	V-VI	0,0685	0,2169
	Time in D quadrant	T0	20	0,7746	19,5	2,4495	17	24	Time in D quadrant		
		T28	21,1	0,6046	21	1,912	18	24	I-II	0,8853	
	Latency time	T0	60	–	60	–	60	60	I-III	0,0008	0,0017
		T28	60	–	60	–	60	60	II-IV	0,0004	0,0008
Group IV	Diagonals	T0	1,9	0,2769	2	0,8756	1	3	III-IV	0,6206	0,5542
		T28	3	0,2582	3	0,8165	2	4	I-V	0,0052	0,4519
	Rotations	T0	3,7	0,3	4	0,9487	2	5	III-V	0,0089	2,66 x 10–7
		T28	4,3	0,2134	4	0,6749	3	5	II-VI	0,0003	0,007
	Time in D quadrant	T0	20,5	0,6191	21	1,9579	17	23	IV-VI	0,6673	0,0049
		T28	21,7	0,7895	21,5	2,4967	18	26	V-VI	0,0063	0,0001
	Latency time	T0	60	–	60	–	60	60	Latency time		
		T28	60	–	60	–	60	60	I-II	–	

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Group V	Diagonals	T0	3,2	0,2	3	0,6325	2	4	I-III	–	–
		T28	3,9	0,2333	4	0,7379	3	5	II-IV	–	–
	Rotations	T0	1,8	0,2494	2	0,7888	1	3	III-IV	–	–
		T28	3,3	0,3667	3,5	1,1595	1	5	I-V	–	–
	Time in D quadrant	T0	22,9	0,6046	23	1,912	20	26	III-V	–	–
		T28	30,1	0,875	30	2,7669	26	35	II-VI	–	–
	Latency time	T0	60	–	60	–	60	60	IV-VI	–	–
		T28	60	–	60	–	60	60	V-VI	–	–
Group VI	Diagonals	T0	2,4	0,2211	2,5	0,6992	1	3	Statistical significance (p) – paired samples (T0-T28)		
		T28	3,6	0,3399	4	1,075	2	5	Group	Diagonals	Rotations	Time in D quadrant	Latency time
	Rotations	T0	2,6	0,2667	3	0,8433	1	4	I	–	–	–	–
		T28	3,9	0,2769	4	0,8756	2	5	II	–	–	–	–
	Time in D quadrant	T0	20,1	0,6741	19,5	2,1318	18	24	III	0,4316	0,0078	0,2919	–
		T28	24,8	0,5121	25	1,6193	22	27	IV	0,0156	0,2188	0,2055	–
	Latency time	T0	60	–	60	–	60	60	V	0,0625	0,0156	0,0002	–
		T28	60	–	60	–	60	60	VI	0,0234	0,0195	0,0002	–

Discussions

Haloperidol is indicated for schizophrenia and relapse prevention.

Numerous studies have evaluated the effects of Haloperidol administration in animals with induced schizophrenia, for example: Andiné et al., 1999; Sawada et al., 2005; Pillai et al., 2007; Enomoto et al., 2008; Paine et al., 2009; Teixeira et al., 2011; McNamara et al., 2011; Feinstein & Kritzer, 2013; Genius et al., 2013; English et al., 2013.

Our results show favorable effects of Haloperidol in animals, with improved cognitive activity, regarding the acquisition of information and its control, in animals with experimentally induced schizophrenia. The effects of decreasing in sensibility and increasing in learning ability and memory capacity are significantly higher in male animals with schizophrenia treated with Haloperidol.

Relatively recent studies showed the ineffectiveness of Haloperidol in the treatment of schizophrenic cognitive deficits in rodents (Meltzer et al., 2013).

Conclusions

1. The learning and memory capacity significantly lower in animals with induced schizophrenia, compared with controls.
2. The learning ability is significantly decreased in male animals with induced schizophrenia, versus females and control animals.
3. The memory capacity is significantly decreased in male animals with induced schizophrenia, versus control animals.
4. The learning ability increases significantly in all groups of animals with schizophrenia treated with Haloperidol, versus initial values. The increases are significant in the treated male animals groups, compared with controls.
5. The memory capacity increases significantly in all groups of animals with schizophrenia treated with Haloperidol versus initial values. The increases are significant in male animals, compared with females.

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