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CHANGES OF ANIMAL BEHAVIOR IN TERMS OF INFLUENCE ON MEMORY PROCESSES

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Abstract

In experiments on white rats, changes of behavioral indexes were determined in the open field test, in terms of both impairment and improvement of mnestic reactions, established under influence of electroshock or nootropic medicinal products. Piracetam, arginine-vasopressin (AVP) and sydnocarb (S) (psychomotor stimulant similar in biological effects) were used as investigated medications.

It was found that electroshock amnesia of conditioned passive defensive skills (CPAR) was accompanied by a significant inhibition of mobility and duration of grooming in rats. At the same time, animals with lost and retained CPAR were observed to reduce number of researched burrows, reflecting the state of unconditioned reflex activity. Nootropic effect of piracetam was combined with decrease of research activity and AVP effect was combined with inhibition of all forms of behavior determined by methodology used. Improvement of mnestic reactions in terms of a two-week administration of S was accompanied by stable increased mobility of rats, while shifts of other behavioral indexes had a phase character. The deterioration of conditioned reflex memory performance due to S neurotoxic effects 30 minutes after administration on the 3rd and 14th day of course administration, was combined with a steady decrease of research activity and anxiety, 2 weeks after S administration inhibition of mobility and research activity of animals were added.

INTRODUCTION

At present, among noninfectious diseases, nervous system diseases and mental disorders have occupied a leading position in growth of proportion of life years after loss of ability to work to total lifetime (disease-adjusted life years, DALY) (1, 2), if in 1990 according to DALY about 10.0% of total losses were accounted for these pathology forms, in 2000 - 12.3%, then by 2020 it could reach 15.0%.

Study of this index for ten leading psychiatric diseases (including, in particular, dementia and depression) led to conclusion (3, 4) that "... they became a number of the main reasons of public health deterioration in all countries".

Particular attention (5) was attracted to the fact that around 157 millions of people on the globe suffered from vascular dementia. In 2010, in Ukraine more than 3 million of patients suffered from various cerebrovascular diseases and brain vascular disorders which required use of nootropic drugs (6). The reason of this disability of this category of patients were both motor and cognitive (including mnestic) disorders (7,8).

In accordance with this, one of the urgent problems of neuropharmacology is to find effective nootropic medicinal products (MP), both among drugs with dominant mnestic effect, and neuroprotective drugs with mixed type of action ("neuroprotectors").

It should be noted that now the study of neuropharmacological properties of nootropic medications is performed against the background of intensive development of "cognitive neuroscience" concepts. (9) This direction of clinical studies were caused by intense formation of concept of cognitive functions (CF) in the second half of the last century, which included the most sophisticated nervous processes of cerebrum (C), that resulted in rational perception of the world (10-13). Decrease of cognitive deficits (CD) manifests as impairments of different types of memory (M), count, speech, attention, space-time orientation, abstract thinking, slowing of thinking flow (14, 15), thus memory disorders become the part of series of interrelated essential elements of CD.

Such a close relationships of memory indexes with other CD in humans predetermine necessity of parallel definition of shifts of mnestic reactions and behavioral processes in experimental practice. This approach allows under conditions of both M disorders, and at its pharmacological improvement not only to determine behavioral changes which accompany them, but also evaluate their possible role in detected mnestic changes.

According to it, the aim of this work is to identify behavioral indexes of white rats recorded in such a widely used test as open field test (OpF) (16), in terms of electroshock amnesia of a conditioned passive avoidance reaction (CPAR) and administration of piracetam, arginine-vasopressin (AVP) and sydnocarb (S), which have a significant impact on M processes. Impacts of piracetam (pyrrolidine derivative), AVP (neurohypophyseal hormone) and sydnocarb (psychomotor stimulant, similar to amphetamine in biological effects) on mnestic reactions were identified in preceding studies (17-21).

MATERIALS AND METHODS

The study was conducted on 222 adult white non-linear rats, weighing 200,0-230,0 grams.

The experiments were performed according to existing international requirements and standards of humane treatment of animals (Convention of the Council of Europe dd 18.03.1986.; Law of Ukraine No 3447-IV dd 21.02.2006).

Changes of rat behavioral indexes against the background of action of substances with nootropic activity were determined in open field unit 100x100 cm in size with 10 cm distance between false burrows. A horizontal motor activity (HMA) was measured by the number of squares fully crossed for 3 minutes, research vertical motor activity (VMA) was measured by the number of rises on hind legs, emotional reactivity was measured by numbers of defecation boluses (NDB), unconditioned reflex activity - by numbers of examined false burrows (NEB). Along with these indexes, duration of washing movements was recorded (grooming; Gr) in seconds for the test time (16).

Before determination of behavioral shifts under the influence of nootropic MP, animals along with formed CPAR were exposed by electroshock and 3 days after they were sorted into subgroups with retained (non-amnesic, NAm) and lost (amnesic, Am) conditioned reaction (21), which were set OpF parameters. Both subgroups were administered investigated medications, piracetam (500 mg/kg) and vasopressin (1 mg/kg) were administered once intraperitoneally, sydnokarb (5mg/kg) was administered intragastrically for 2 weeks.

40 minutes after administration of piracetam and vasopressin, rats with recovered CPAR were isolated in Am group, and, on the contrary, rats with lost CPAR were isolated in NAm group, which were defined to change behavior parameters.

Stimulation of memory engrams reproduction (MER) under impact of S was accompanied by such significant manifestations of stereotyping (20) that a question about the possibility of false positive performance of CPAR was raised. In this connection and taking into account (14-daily) administration of this psychostimulant daily for 14 days, conditioned active avoidance reaction (CAAR) tested in Y-shaped labyrinth (20) was used for determination of M

status. It allowed to reveal a constant CRAA improvement after the first injection of S and deterioration of conditioned reflex M immediately after administration on the 3rd and 14th days .

Statistical processing of the results of quantitative indexes was carried out taking into account Student´s t-Test (22), of qualitative indexes - by comparing radians of indexes (23).

RESULTS

Observations showed (Table 1) that training procedure of amnesic rats significantly decreased a number of defecation boluses and number of examined false burrows by 24.1% and 56.6% respectively compared to baseline. Electroshock effect caused loss of CPAR and resulted in a significant reduction of horizontal motor activity by 24.8%, VMA – by 35.7% and duration of Gr by 79.3% compared to animals´ training.
After exposure of electric current, rats with remained CPAR were noted to decrease only NEB compared to the initial background by 63.8% ($p < 0.05$) after training, and by 56.9% ($p < 0.05$) after amnesic exposure.

Table 1 : Effect of individually acquired memory on rat behavior

Study series (quantity of animals)		Stat. indexes	Behavioral indexes				
			HMA	VMA	Gr (sec.)	NEB	NDB
Amnesic animals	Initial background (59)	M ± m	54,3 4,0	5,6 0,5	21,3 2,4	4,6 0,3	2,9 0,2
	Training(30)	M ± m	54,4 3,6	7,0 0,5	16,1 2,2	2,0* 0,4	2,2* 0,2
	Electroshock (59)	M ± m	40,9* ** 2,1	4,5** 0,3	4,4* ** 0,7	2,4* 0,3	2,3* 0,2
Non - amnesic animals	Initial background (21)	M ± m	43,1 6,4	6,7 1,2	17,9 4,3	5,8 0,9	3,3 0,2
	Training (10)	M ± m	57,5 9,3	6,8 1,3	16,5 5,1	2,1* 0,8	2,3 0,4
	Electroshock (21)	M ± m	50,2 3,3	7,1 1,0	9,8 3,0	2,5* 0,3	2,6 0,3

Notes: * - $p < 0.05$ compared to the initial background;
** - $P < 0.05$ compared to training procedure.

Thus, training process of CPAR and simulation of amnesia of conditioned skills led to a decrease of unconditioned reflex behavior in all animals. In addition, in terms of amnesia of passive defensive skills, significant decrease in mobility, anxiety and duration of grooming in rats was noted.

As it was mentioned earlier, the study of neurotrophic effects of piracetam and AVP was performed in animals with formed CPAR, which were separated into Am and NAm after electroshock exposure. After administration of specified medicines, animals with recovered CPAR were isolated in the group of amnesic rats and, on the contrary, rats with lost CPAR were isolated in NAm group, which were defined to change behavior parameters. Observations showed (Table 2) that against the background of administration of piracetam in dose of 500 mg/kg in both examined subgroups only HMA was changed significantly compared to the initial background with average decrease in 2 times. Other significant differences in behavior parameters were not determined.

Table 2: The impact of nootropics on behavior of white rats in open field test.

Study Series (quantity of animals)	Stat. indexes	Behavioral indexes				
		HMA	VMA	Gr (sec.)	NEB	NDB
1. Piracetam (38)	M	22,1	4,2	13,3	3,9	1,5

Initial background	± m	1,9	0,5	2,9	0,9	0,4
Amnesic animals	M ± m	17,0 4,1	2,0* 0,4	11,3 8,0	5,6 1,6	1,0 0,3
Non- amnesic animals	M ± m	16,1 3,1	1,5* 0,5	9,7 4,2	5,9 1,3	1,0 0,4
2. AVP (24) Initial background	M ± m	40,2 2,6	3,1 0,3	11,0 2,0	2,0 0,2	2,9 0,2
Amnesic animals	M ± m	3,5* 1,2	1,1* 0,6	2,0* 0,1	0,2* 0,1	0,1* 0,1
Non- amnesic animals	M ± m	7,6* ** 1,4	1,4* 0,1	3,0* 0,5	0,6* 0,4	0,1* 0,1

Note: * - p <0.05 compared to the initial background;

** - P <0.05 compared to Amnesic animals.

Electroshock-induced amnesic rats with recovered reproduction of CPAR under influence of AVP, showed sharp decline of studied behavioral indexes. For research activity, decline was 64.5% (p <0.05) compared to the initial background, and it exceeded 90% for other parameters. Non-amnesic rats with lost CPAR on the background of AVP had slightly less manifested decline of behavioral activity, although in comparison with initial indexes it exceeded the threshold of statistical significance. The essential difference between animals with recovered and lost reproduction of M engrams was that the latter had significantly higher mobility (117.1%).

The essential difference of the impact of psychomotor stimulant sydnocarb on integrative functions of C (in particular, behavior and memory) is its dependence on period of use of this pharmaceutical product (20).

The peculiarity of the effect of this MP on memory processes is that up to the 3rd day of a two-week administration, training of CAAR reaches 90.3%, that is significantly higher than indexes of the control group (18.0%). However, direct administration of this pharmaceutical product during this period results in deterioration of conditioned reaction performance (up to 28.3%).The similar picture is observed on the 14th day of administration of this medicinal product, when training in control group, before and after administration of sydnocarb, were 59.4%, 92.0% and 55.0% respectively. Improvement of memory indexes against the background of sydnocarb was accompanied by stable increase of rat´s mobility (Table 3). Observations on the 3rd day showed also a significant increase of VMA by 66.7%, number of examined false burrows in 2 times and grooming in 2.9 times compared to the initial background. Om the contrary, on the 14th day the increase of mobility was combined with a decrease of VMA by 56.8%, HMA, NEB– by 70.8% and absence of defecation boluses.

The deterioration of conditioned reflex memory, observed 30 minutes after sydnocarb administration, on the 3rd day was accompanied by inhibition of research activity and anxiety in rats and reduced duration of Gr by 71-73% compared to the values established before MP administration. On the 14th day, negative M shifts were combined with mobility inhibition (by 32.5%), reduction of anxiety, termination of research activity and examination of false burrows in animals. The observed changes of two last indexes considerably differ from behavioral parameters of established at deterioration of M on the 3rd day of sydnocarb administration.

Table 3: Behavioral changes of rats in open field test during a two-week sydnocarb administration

Study Series (quantity of animals)	Stat. indexes	Behavioral indexes				
		HMA	VMA	Gr (sec.)	NEB	NDB

1. Initial background (80)		M ± m	35,5 1,9	8,1 0,6	10,1 1,3	2,4 0,3	3,0 0,3
2. 3rd day (18)	Before sydnocarb administration	M ± m	54,3* 5,2	13,5* 2,9	29,3* 2,4	5,0* 1,2	2,5 0,2
	After sydnocarb administration	M ± m	59,0* 10,9	3,9* ** 1,1	8,6** 2,7	4,3 0,9	0,8* ** 0,3
3. 14th day (10)	Before sydnocarb administration	M ± m	53,3* 6,8	3,5* 0,3	12,0 2,3	0,7* 0,1	0* –
	After sydnocarb administration	M ± m	36,0** 2,6	0* ** • –	9,0 2,3	0* ** • –	0,3* 0,2

Notes: * - p <0.05 compared to the initial background;
** - p <0.05 compared to the indexes before sydnocarb administration on the respective day of the experiment;
● - p <0.05 compared to the indexes after sydnocarb administration on the respective day of the experiment.

Analysis of behavioral changes of rats in conditions of improved and deteriorated M, including pharmacological effects, allowed to reveal significant differences in animals with various MER changes. At the same time, despite large number of differences of Am-NAm pairs as per concrete impact factors on mnestic reactions (electroshock, piracetam, AVP, sydnocarb), stable shifts of behavioral changes combined with manifestations of nootropic activity were failed to establish. It can be concluded that changes of memory and behavior in rats, are concrete parallel manifestations of neurotropic action of studied factors. Character of revealed shifts depends on mechanisms of influence of electric current and studied MP on C.
It is must not be excluded that it is also due to thinner relationship between integrative functions of C (memory, behavior, emotions, cognitive functions, and others), in particular, in relation of individually acquired and specific, genetically deterministic forms of M, that requires further study.

CONCLUSION

1. Electroshock amnesia of CPAR in rats was accompanied by significant behavioral changes (decrease in mobility and duration of grooming). After exposure of electric current animals with lost and retained conditioned skill almost equally had reduced unconditioned reflex behavior, manifested in the number of false burrows.

2. Compared to others MP used, nootropic effect of piracetam was the least at combination with behavioral changes in open field test, when only research activity of white rats was decreased.

3. Use of arginine - vasopressin in a dose of 1 mg/kg resulted, along with memory improvement, in inhibition of all behavioral indexes registered according to the methodology used.

4. Improvement of mnestic processes at two-week administration of psychostimulant sydnocarb similar in biological activity to amphetamine, was accompanied by significant changes in behavioral reactions that were closely connected with time period of MP use. On the 3rd day MER stimulation was combined with increase of mobility, duration of grooming, research and unconditioned reflex activity. On the 14th day of observation, along with memory improvements, only motor form of activity remained increased, while research and unconditioned reflex forms of activity, on the contrary, were decreased.

5. The deterioration of performance of conditioned reflex memory, defined immediately 30 minutes after sydnocarb administration, was combined with behavioral shifts, in particular, with the reduction of research activity and anxiety in rats. By the end of 2 weeks observations of MER impairment caused by sydnocarb neurotoxic manifestations, were accompanied by decrease of mobility and unconditioned reflex activity.

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