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Effects of Fluoxetine on Memory Processes in the Rats with Different Phenotypes of Nervous System and Different Levels of Biogenic Monoamines of the Brain

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Abstract

The present paper explores the effects of the psychopharmacological agent - fluoxetine - on mnestic processes, using a model of passive avoidance on male Wistar rats with different nervous system phenotypes and different activity ratios of the monoaminergic systems of the brains. In the re-test session under administration of fluoxetine, the seizure-tolerant rats compared to the seizure-sensitive rats were characterized by a more pronounced fear response to the "unsafe" compartment and enhanced anxiety facilitating the retention of memory trace. The individual sensitivity of the animals to the action of fluoxetine and the direction of its effects on mnestic processes are supposed to be determined by different primary activity ratios of the monoaminergic systems of the brain.

Keywords: Seizure-tolerant and seizure-sensitive rats • Passive avoidance response • Fluoxetine • Serotonin • Dopamine• Noradrenaline

Introduction

In recent years, increasing attention has been paid to the study of the functional specificity of the central nervous system (CNS), determined by both genetic (different strains of rats) and individual (differences within one strain) peculiarities of behaviour, memory, learning, adaptation and plasticity. It is known, that the individual reactivity of organism to the action of different stress-factors are associated with the innate difference in activities of the monoaminergic (MA) systems of the brain, involved in the neurochemical organization of various types of innate and learned behaviour [1]. In this regard, the most significant neurotransmitter is serotonin (5-HT) being an important biochemical factor forming mixed anxiety-depressive disorders and disturbing cognitive functions [2]. In particular, deficiency of 5-HT leads to a disturbance of synaptic transmission in the CNS and forms depressive states. Therefore, most psychotropic medications applied in medical practice are targeted at enhancing serotonin neurotransmission. Among the medications that affect intra-synaptic serotonin metabolism, the selective serotonin reuptake inhibitors, such as fluoxetine, play a key role [3]. The medication binds to the specific protein – serotonin transporter – selectively blocking serotonin reuptake in the presynaptic ending, which leads to increase in concentration of the neurotransmitter in the synaptic cleft and to enhancing its action on the postsynaptic receptors.

A lot of scientific papers are dedicated to the comparative study of the effects of acute and chronic administration of fluoxetine on behaviour in various models of rats and mice of different strains [4,5]. In addition, they contain the information about the variety of the neuro-psychotropic medications that depends on the animal genotype, nature of the test conditions [6] and the baseline psycho-emotional state of the individuals [7].

Based on the aforementioned, of particular interest is to study the effects of 5-HT excess caused by fluoxetine on the mnestic processes, using a model of passive avoidance (PA) on male Wistar rats with different nervous system phenotypes and different activity ratios of the catecholaminergic and 5-HT-ergic systems of the brain. Passive avoidance test is one of the main techniques of testing neuro-psychotropic medications' effects and, moreover, it is especially popular in studying mnestic process patterns [8].

Materials and Methods

The study was carried out on male Wistar rats (body mass of 180-220 g) under chronic conditions. The rats were preliminarily tested for tolerance to acoustic startle stimulus. For that purpose, each animal was exposed to the sound of an electric bell (90-120 dB) for 2 min in the soundproof box. The indicator of sensitivity was the intensity of seizure in the rats. The difference in the responses to acoustic stimulus allowed dividing the animals into 2 groups: seizure-sensitive (SS – prone to seizures) and seizure-tolerant (ST – without motor excitation) rats.

From the total number (121) of the rats, 29 ST and 27 SS rats were selected. Both types of the animals were divided into the experimental and control animals. 1 h prior to the experiment, the experimental animals (ST (n=15), SS (n=14)) were intraperitoneally injected with fluoxetine (Pharm science, Montreal, Canada) at a dose of 25mg/kg. The control rats (ST (n=14), SS (n=13)) were administered with the diluent - distilled water - in the equal volume. During 2 days prior to the main experiments, the animals were handled for 5 min per day in order to equalize their responses to this stimulus.

PA-elaboration was carried out according to the common technique in the light-dark box. The rats were placed in the light compartment with their tails to the guillotine door between the light and dark compartments. The latency to enter the dark compartment was recorded (unconditioned "mink" reflex). When the animal entered the dark compartment, the guillotine door was closed and a mild electric foot shock (0.5 mA; 2 sec) was delivered through the grid floor. Then the animals were quickly removed. The stability of the formed response was characterized by the degree of its retention in the re-test session on the 2nd day, which allowed identifying the peculiarities of the memory traces retention. The time spent by the animals in the light "safe" compartment was recorded for 300 sec. The behavioural (search movements, rearing, grooming) and vegetative (number of faecal boluses) indices registered in PA re-test session were also analysed.

While processing the experimental material, we have considered the total

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time spent by the rats in the light compartment and the number of rats that retained the formed PA response, as well as analysed the range of behavioural (search movements, rearing, grooming) and vegetative (number of faecal boluses) indices in PA re-test session.

All the experimental procedures were carried out in accordance with the international and national standards for the care and use of laboratory animals and approved by the appropriate commit-tee of the Institute of Physiology, ANAS. The results of the study were processed with application of a nonparametric Mann–Whitney U test and Student's t-test. Mathematical calculations were performed using an analytics software package – STATISTICA.

Results and Discussion

The comparative analysis of learning in the animals with different proneness to seizures identified the peculiarities of PA response retention in the re-test session on the 2nd day after training. It has been found that the control ST rats compared to the SS ones had lower rate of PA response retention (17.8% and 22.4% respectively, $p<0.05$). However, under administration of fluoxetine, the lower rate of response retention was observed in the SS rats compared to the ST ones (12.9% and 53.2% respectively, $p<0.01$) (Table 1). The number of entries to the dark compartment was larger in the SS rats compared to the ST ones. Thus, one part of the SS rats entered and left the dark compartment for several times, while the other part entered immediately the dark compartment and stayed there until the end of the experiment, demonstrating an impairment of retention of the formed response.

The total time spent in the "safe" compartment on the 2nd day after training in the control ST rats made up 189.2 ± 0.6 sec on average, which was significantly lower ($p<0.01$) than the total time spent by the SS rats in the light compartment – 283.6 ± 0.9 sec (Table 2).

However, acute administration of fluoxetine led to the opposite effects on memory traces retrieval in the experimental animals of both types. Under administration of the medication, high rate of retention of the formed PA response in the re-test session on the 2nd day was identified in the ST rats compared to the control ones. That was manifested in increase in the total time spent in the light compartment – 230.5 ± 0.7 sec, while in the SS rats; the-re was significant decrease in the mentioned parameter – 122.2 ± 0.6 sec ($p< 01$).

Under administration of the medication, the differences in PA response retention capacity of the rats of both types were more pronounced in the context of the number of animals that retained the formed response. Thus, on the 2nd day after training, the share of the control SS rats that retained the response made up 83%, while in the ST rats it was 43%. However, under administration of fluoxetine, that parameter made up 40% in the SS rats and 60% in the ST ones.

The analysis of the range of behavioural and vegetative indices accompanying the PA response in the re-test session on the 2nd day showed the behavioural differences between 2 experimental groups of the animals administered with fluoxetine (Fig. 1). There were enhanced search activity and low level of the vegetative indices in the control SS rats, whose time spent in the light compartment was longer in comparison to the ST rats. Under ad-ministration of the medication, high rate of PA response retention was observed in the ST rats, manifested in increase in the total time spent by the animals in the "safe" compartment, enhanced search activity and low level of the vegetative index. In the SS rats compared to the control ones, those parameters were lower. However, under the effects of fluoxetine there was a completely opposite pattern of memory traces retrieval in the experimental group of both animal types. Under administration of the medication, high rate of PA response retention on all days of testing were identified in the ST rats. That was manifested in increase in the total time spent by the animals in the "safe" compartment and the level of search activity. In the SS rats compared to the control, there was decrease in the mentioned parameters (Figure 1).

Thus, under the effects of administration of the medication, the ST rats compared to the SS rats are characterized by a more pronounced fear response to the "unsafe" compartment and enhanced anxiety facilitating the formation of long-term memory traces and showing individual sensitivity of the animals to the action of fluoxetine on mnestic processes. The differences in the processes of memory traces retrieval under the effects of fluoxetine in the animals of different phenotypes are apparently supposed to be due to the impact of the medication on metabolism of monoamines, which changes an innate activity ratio of the noradrenaline (NA)-, dopamine (DA)-, and serotonin (5-HT)-ergic systems of the brain. The manifestation degree of the effects of the medication de-pends on both the individual specificity of the CNS and the specific brain area. Thus, acute administration of fluoxetine identified the response peculiarities of the MA ergic systems of various brain areas to its effects [9]. In particular, after administration of the medication, there was significant decrease in 5-HT level in the hypothalamic of the SS rats, as well as significant increase in NA level, which led to PA response extinction. The aforementioned is substantiated by the data that Wistar rats with different phenotypic peculiarities of the nervous system, whose activity ratio of the MA-ergic systems shifted toward the predominance of the 5-HT-ergic system of the brain, have the best ability to retain PA response [10]. However, under the effects of fluoxetine, in the ST rats, there was significant increase in 5-HT level in the frontal cortex ac-companied by decrease in NA level and significant decrease in DA level, which led to PA response recovery. The obtained data is consistent with the opinion of R.I. Kruglikov on increasing time spent in the "safe" compartment during reducing NA in the brain by disulfiram. In addition, our data is corroborated by the works of many investigators, indicating increase in 5-HT level in the frontal cortex after administration of fluoxetine at a dose of 3-154 mg/kg, as well as an inhibitory effect of increased 5-HT level on the DA-ergic system [11-13].

Table 1. Retention of PA response (%) under administration of fluoxetine in the rats with different levels of proneness to seizures.

Groups	Control	Experimental
ST rats	17.8	53.2*
SS rats	22.4	12.9**

*p < 0.05; **p < 0.01.

Table 2. The total time (sec) spent in the "safe" compartment on the 2nd day after PA response elaboration under administration of fluoxetine in the rats with different levels of proneness to seizures.

Groups	Control	Experimental
ST rats	189.2	230.5
SS rats	283.6	122.2 **

**p < 0.01

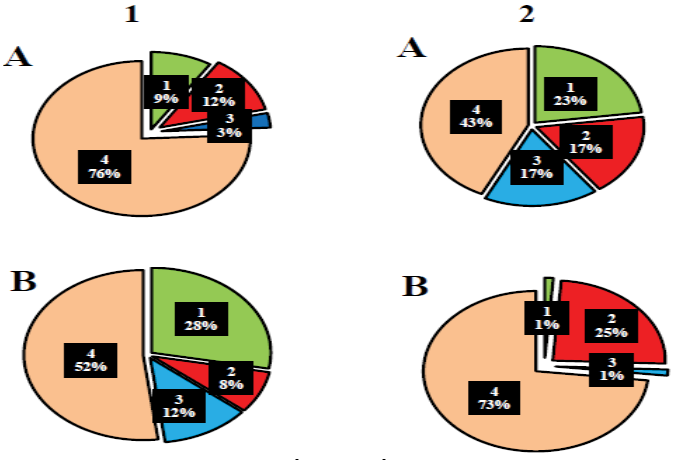

Figure 1. Range of the behavioral and vegetative indices revealed in PA re-test session on the 2nd day after training in the rats with tolerance (1) and sensitivity (2) to acoustic startle under administration of fluoxetine. A – Control group; B – Experimental group. Numbers on the sectors of the circles indicate the manifestation degree (%) of some behavior's components: 1 – Search activity; 2 - Grooming; 3 - Rearing; 4 – Fecal boluses.

Conclusion

Thus, extinction of mnestic processes, observed in our studies, under the effects of the medication in the SS rats is probably associated with weakening genetically determined activity of the 5-HT-ergic system of the hypothalamic while a better retention of memory traces in the ST rats is correlated with increased 5-HT- ergic and decreased NA-ergic systems' activity of the frontal cortex. The individual sensitivity of the animals to the action of the psychopharmacological agent – fluoxetine – and the direction of its effects on mnestic processes are supposed to be determined by different primary activity ratios of the MA-ergic systems of the brain.

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Conflict of Interests

The author claims that there is no conflict of interests.

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