https://doi.org/10.59883/ajp.53 UDC 612.821.6

COMPARISON OF THE EFFECTS OF AMITRIPTYLINE, MELIPRAMINE AND FLUOXETINE ON ACQUISITION AND SPATIAL ALTERATION OF AVOIDANCE RESPONSES IN RATS

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The effects of amitriptyline (10 mg/kg), melipramine (10 mg/kg), and fluoxetine (5 mg/kg) on the acquisition of conditioned active avoidance responses and their spatial alteration in rats were studied. During the acquisition of avoidance, a passage in the partition was open, adjacent to the rear wall of the shuttle chamber. On the 5th experimental day after the end of the training, this distal opening was closed and the proximal one was opened, after which avoidance performance under changed conditions was tested for 20 trials. Melipramine and amitriptyline accelerated the acquisition of avoidance responses. Changing the location of the opening disrupted the learned skill, especially in the control animals. Melipramine and fluoxetine statistically significantly (in contrast to amitriptyline) accelerated the recovery of the level of avoidance. The positive effect of melipramine and fluoxetine is explained by a psychostimulating component in their spectrum. The inability of amitriptyline to produce a significant effect in this model is due to its psychosedative properties. The data obtained allow us to conclude that the acquisition of the active conditioned avoidance responses and their spatial modification can be used to analyze the antidepressant activity of pharmacological agents.

Keywords: rats, amitriptyline, melipramine, fluoxetine, avoidance.

INTRODUCTION

Depression is one of the most common affective disorders, and the development of antidepressants is one of the most rapidly developing areas of psychopharmacology. Success in studying the mechanisms of depression and the development of new antidepressants significantly depend on experimental models that provide the possibility of extrapolation of results obtained on the model to the modulated process, for which it needs to be similar to the original in some respects. In relation to depression, this means, in particular,

that the factors determining the occurrence of clinical depression with the corresponding behavioral disorders should be similar to the factors that cause similar violations of animal behavior in a model experiment. It is the essence of the requirement of validity criteria reflecting the etiology, genesis, and symptoms of depression [7, 9, 25, 26].

The etiology of clinical depression is heterogeneous, but one of the most important causes is stress. There are several tests based on a single exposure to stressors such as forced swimming, learned helplessness, and hanging by the tail that are used to identify the antidepressant activity of pharmacological agents [1]. However, these models and the results achieved with their help have recently been the subject of critical analysis [10, 11, 13, 18]. In particular, the short duration of the action of stressors, not fully meeting the above criteria for validity, and the non-selectivity of models in providing the antidepressant effect of drugs are noted.

Considering the fact that depression occurs as a result of repeated, long-term exposure to stressors, new models have been proposed. In particular, a model was developed based on the alternation of ultrasonic waves, one of which, in rodents, serves as a danger signal while others are associated with food behavior [6]. The conflict between these motivations creates a stressful situation that is the basis for the development of depression.

It should be noted that stressors are of a purely physical nature in all models used. At the same time, stress and subsequent depression in the person for whom antidepressants are eventually developed are caused not only by physical but also by emotional factors. Taking this factor into account, experimental models of reversible functional disorders of learning and memory have been developed based on an emergency change in unambiguous cause-and-effect and spatial relationships in the experimental environment. It has been shown that these disorders cause a dramatic drop in the level of avoidance and an increase in emotional stress. Models have been successfully used to analyze the effects of nootropics and anxiolytics on learning and memory in rats under emotional stress [14].

One of the significant indicators characterizing depression is the impairment of learning and memory [22]. However, it did not become an indicator, the provision of which was pursued when creating models, as was the case, for example, with anhedonia. To study depression-induced impairment in learning and memory following the induction of depression-like behavior, researchers are forced to turn to other models, such as passive or active avoidance conditioning. Works in this area are few and contradictory. Thus, a positive effect of fluoxetine on the development of active avoidance in rats under normal conditions and under conditions of neurotoxic oppression from lead has been shown [4, 5]. The suppression of this reaction in rats by fluoxetine, imipramine, amitriptyline, and other antidepressants has also been described [17, 23, 24]. Inhibition of the passive avoidance-conditioned reflex by tricyclic antidepressants has also been shown [8, 12, 19-21].

The goal of this work is to compare the effects of tricyclic antidepressants (melipramine and amitriptyline) and the selective serotonin reuptake inhibitor fluoxetine on the formation of the avoidance reaction in rats as a model of learning and memory, as well as on its spatial alteration as a model of emotional stress caused by an emergency change in spatial relationships in an experimental environment and associated with the need to learn a modified skill.

MATERIALS AND METHODS

The work was performed on 26 male Wistar rats weighing 180–200 g. In rats, a conditioned active avoidance response was trained for 5 days (20 exposures daily) in a shuttle box equipped with a partition with two openings. During training, the opening at the distal end of the partition was open. The experiment proceeded as follows: in the box in which the animal was at the moment, a conditioned stimulus (sound) was turned on. If the rat moved to the other half of the box within 10 s, the sound was switched off; otherwise, the

electric current was switched on. The animal's transition to the other half of the chamber turned off both stimuli, after which an intersignal period of 30 s set in. On the 5th experimental day after the end of the training, the distal opening was closed and the proximal one was opened, after which the performance of the avoidance response under changed conditions was tested for 20 trials.

Animals were divided into control (n=6) and three experimental groups. Two experimental groups, 7 animals per group, were injected with 3-cyclic antidepressants - melipramine and amitriptyline, at a dose of 10 mg/kg. The third experimental group (n=6) received the selective serotonin reuptake inhibitor – fluoxetine (5 mg/kg). Antidepressants were administered to experimental animals and distilled water to control animals intraperitoneally for 40 minutes before every experiment.

The experiments were carried out in accordance with the provisions of the international convention on the rules for working with experimental animals "European Communities Council Directives, November 24, 1986, 86/609/EEC".

RESULTS AND DISCUSSION

Melipramine and amitriptyline, starting from the 2nd experiment, accelerated the formation of a conditioned reaction of active avoidance, as shown in Fig. 1. Amitriptyline had the greatest effect on acceleration. Thus, in the second experiment, the number of avoidance reactions under its effect was 3.4 times higher than the control value. Data on the effect of these antidepressants are not consistent with the previously described suppression of active avoidance [17]. Fluoxetine did not have a statistically significant effect on the acquisition of avoidance, which is not consistent with either the data on the suppression of the avoidance responses [17] or the data on its positive effect [4, 5].

In the course of the experiment, the difference between the level of avoidance in experimental and control animals decreased. The latter is explained by the fact that the number of avoidance responses in control animals approaches its maximum as learning progresses, just as it does in experimental rats. In particular, in the last 5 trials, both control and experimental animals performed avoidance responses without error (Fig. 2).

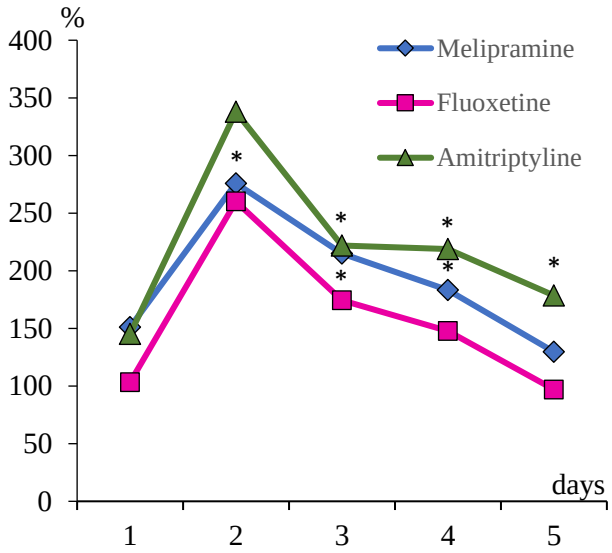

Figure 1. The effects of antidepressants on the avoidance response acquisinion.
The x-axis shows the days of experiments; the y-axis shows the rate of avoidance responses in % compared to the control.
* - p <0.05 compared to the control.

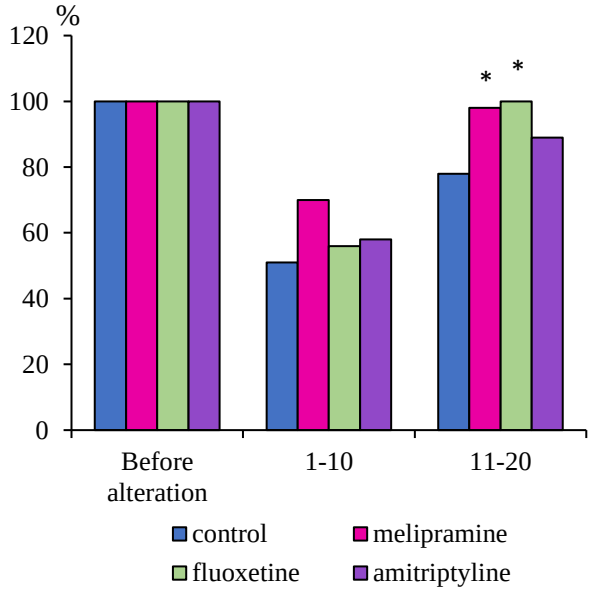

Figure 2. The effects of antidepressants on the spatial alteration of the avoidance response.

The x-axis shows blocks of trials; the y-axis shows the rate of avoidance responses in % compared to the number of trials.

* - $p < 0.05$ compared to the control

A change in the location of the opening, forcing the animal to relearn avoidance of the electric pain effect, caused a decrease in the number of avoidance reactions, which was especially pronounced in control animals, in which it decreased by half after the alteration (Fig. 2). In the course of the experiments, a recovery in the level of avoidance was observed, which occurred faster under the effects of antidepressants. At the same time, the increase in the number of avoidance reactions compared to the control that occurred under the effects of amitriptyline did not reach a statistically significant level, unlike the other two drugs.

The noted difference in the effects of antidepressants was due to the peculiarities of their pharmacological activity and the characteristics of the experimental model used. Earlier [14], it was shown that a change in the location of the opening caused by a sudden change in the experimental environment causes stress and reversible impairments of cognitive and mnestic processes. Nootropics, which have an activating effect on the central nervous system, stimulate the assimilation of a new skill. In contrast, the reduction of the fear caused by the electric current with the help of anxiolytics accelerated the development of the avoidance reaction but did not contribute to the spatial alteration of the skill [3].

The peculiarities of the pharmacological activity of the antidepressants used are that melipramine and fluoxetine, in addition to the antidepressant, have a psychostimulating property, which, in our opinion, stimulates the assimilation of a new skill, just as it happened under the effects of the activating effect of nootropics (see above). Amitriptyline does not have this effect, and its psychosedative effect, which, like anxiolytics, promotes the development of avoidance, does not provide its spatial alteration since, in addition to reducing stress, it is necessary to master a new skill.

So, the obtained results on the effect of antidepressants on the acquisition of the avoidance response are ambiguous. Together with the known data on the suppression of active and passive avoidance [8, 12, 17, 19-21, 23, 24], this casts doubt on the possibility of using this experimental model to assess the effect of antidepressants on learning and memory. Fortunately, however, there are some counterarguments.

Firstly, such ambiguity has been repeatedly described, not only with respect to antidepressants, which did not prevent the use of this model in experimental psychopharmacology. So, nootropics improved learning and memory in some experiments, but in others they had no effect. To identify their positive effect, they resorted to additional influences, such as sleep deprivation according to Jouvet, maximum shock, etc. [2]. The same goal is served by the spatial alteration of the developed habit [14], which established the positive effect of fluoxetine in this work.

Secondly, the conclusion that antidepressants inhibit passive avoidance cannot preclude the use of active avoidance reactions to analyze their effect on learning and memory. This conclusion is based on a decrease in the latent period of entry into the dark compartment after an electric shock there the day before. This conclusion is vulnerable to criticism since this decrease may be the result of not only amnestic effects but also a decrease in fear [15]. Thus, the antioxidant mexidol reduced the latent period but increased the choice of a safe compartment (in a 3-chamber setup), in which the rats were not subjected to electric shock the day before. This indicates the formation of a memory trace about the place of electric shock application under the effects of mexidol [16].

CONCLUSION

Thus, the multidirectional effect of antidepressants on the acquisition of the avoidance response and overcoming its violation after spatial alteration was established. Both tricyclic antidepressants accelerated the formation of avoidance, but only melipramine, which has a psychostimulant effect, was effective in the spatial alteration of the acquired

skill. Fluoxetine did not accelerate the development of the reaction but contributed to its spatial alteration. An analysis of the results obtained allows us to conclude that the acquisition of a conditioned active avoidance response and its spatial alteration can be used to identify the antidepressant activity of pharmacological agents.

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СОПОСТАВЛЕНИЕ ВЛИЯНИЯ АМИТРИПТИЛИНА, МЕЛИПРАМИНА И ФЛУОКСЕТИНА НА ВЫРАБОТКУ И ПРОСТРАНСТВЕННУЮ ПЕРЕДЕЛКУ РЕАКЦИИ ИЗБЕГАНИЯ У КРЫС

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Изучено влияние амитриптилина (10 мг/кг), мелипрамина (10 мг/кг) и флуоксетина (5 мг/кг) на выработку условной реакции активного избегания и её пространственную переделку у крыс. При выработке избегания открытым был проход в перегородке, прилегающий к задней стенке челночной камеры. На 5-й опытный день по окончании обучения закрывали это дистальное отверстие и открывали проксимальное, после чего мелипрамин и амитриптилин ускорили формирование реакции избегания. Перемена местоположения отверстия нарушила выработанный навык, особенно у контрольных животных. Мелипрамин и флуоксетин статистически значимо (в отличие от амитриптилина) ускорили восстановление уровня избегания. Положительный эффект мелипрамина и флуоксетина объясняется наличием психоактивного компонента в их спектре. Неспособность амитриптилина вызвать значимый эффект в условиях этой модели обусловлена его психоседативными свойствами. Полученные данные позволяют заключить, что выработка условной реакции активного избегания и её пространственная переделка могут использоваться для анализа антидепрессивной активности фармакологических агентов.

Ключевые слова: крысы, амитриптилин, мелипрамин, флуоксетин, избегание

AMİTRİPTİLİN, MELİPRAMİN VƏ FLUOKSETİNİN SİÇOVULLARDA QAÇINMA REAKSİYASININ YARANMASINA VƏ MƏKAN DƏYİŞİKLİYİNƏ TƏSİRİNİN MÜQAYİSƏSİ

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Amitriptilin (10 mq/kq), melipramin (10 mq/kq) və fluoksetinin (5 mq/kq) siçovullarda şərti aktiv qaçınma reaksiyasının yaranmasına və onun məkan dəyişikliyinə təsiri öyrənilmişdir. Qaçışın öyrənilməsi zamanı arakəsmədə məkik kamerasının arxa divarına bitişik bir keçid açıq idi. Təlim olduqdan sonra 5-ci təcrübə gündə bu distal keçid bağlanırdı və proksimal açıldı, bundan sonra, 20 təqdimat zamanı dəyişdirilmiş şəraitdə qaçınma reproduksiyası sınaqdan keçirildi. Melipramin və amitriptilin qaçınma reaksiyasını sürətləndirdi. Keçidin yerini dəyişdirmək, xüsusən nəzarət heyvanlarında öyrənilən bacarıqları pozdu. Melipramin və fluoksetin statistik əhəmiyyətli dərəcədə (amitriptilindən fərqli olaraq) qaçınma səviyyəsinin bərpasını sürətləndirdi. Melipramin və fluoksetinin müsbət təsiri onların spektrində psixoaktiv komponentin olması ilə izah olunur. Amitriptilinin bu modeldə əhəmiyyətli təsir göstərə bilməməsi onun psixosedativ xüsusiyyətləri ilə bağlıdır.

Əldə edilən məlumatlar, aktiv qaçınma şərti reaksiyasının yaradılması və onun məkan modifikasiyasının farmakoloji agentlərin antidepressant fəallığını təhlil etmək üçün istifadə edilə biləcəyi qənaətinə gəlməyə imkan verir.

Açar sözlər: siçovullar, amitriptilin, melipramin, fluoksetin, qaçınma

Çapa təqdim etmişdir: Nəzakət Naib qızı Əliyeva, b.ü.f.d., dosent
Redaksiyaya daxil olma tarixi: 10.01.2023.
Təkrar işlənməyə göndərilmə tarixi: 21.01.2023.
Çapa qəbul edilmə tarixi: 14.06.2023. https://ajp.az