Effect of Seleptine on Retrieval of Active Avoidance Task in Rats

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We have examined seleptine, a new derivative of the atypical neuroleptic clozapinum, on the retrieval of the active avoidance task in rats placed in a shuttlebox. Retention of the conditioned response was assessed in the test of repeated training for the same task to the score achieved in the first session. After oral seleptine (100 mg/kg), the retention of the active avoidance task was deteriorated to a greater extent than the ability for a new learning.

Key Words: *seleptine; neuroleptics; avoidance response*

As all conditioned responses (CR) developed by negative reinforcement, two-way active avoidance (AA) in a shuttlebox is controlled by endogenous substances that determine the emotion-motivational status of experimental animals [3]. Logically, chemical agents that decrease motivation level of response (neuroleptics and tranquilizers) impede learning and disturb consolidation of the memory trace [1]. Our aim was to study the effect of the putative tranquilizer seleptine (8-chloro-11-(4-methyl-1-piperazinyl)-5-acetylamino-dibenzo-[*b*,*e*][1,4]-diazepine), a new structural analog of clozapinum (azaleptine, an atypical benzodiazepine neuroleptic), on retention and repeated training for the conditioned active avoidance response (CAAR).

MATERIALS AND METHODS

Male Wistar rats with (body weight 230-260 g) were trained for CAAR in the shuttlebox of a Reflex-6 system (Columbus Instruments Inc.). The rats were trained for AA task by the modified method [4] to 10 successive correct avoidance responses. The conditioned stimulus was a 5-sec tone. The unconditioned stimulus was a footshock with the strength tuned individually for each rat. The period of combined presentation of conditioned and unconditioned stimuli was no longer than 15 sec; the interval between the combined stimuli was 20-40 sec. During a single session the rats were subjected to no more than 40 footshocks. If this criterion was not achieved, the rat was discarded. Only 61% of the tested rats acquired this reflex.

The state of the temporal connection was assessed according to the retrieval of AA task after the second session: 7 days after acquisition of CAAR the rats were trained to the same score of 10 successive correct responses. Retention (R) of CR was calculated from the following formula $R=(A-B)/A\times 100\%$, where A and B are the numbers of combined stimuli presented to develop CR in the first and second session, respectively. Seleptine was synthesized at the Novokuznetsk Chemical-Pharmaceutical Institute. Water solution of seleptine (10, 30, and 100 mg/kg) was administered orally 30 or 60 min prior to the second training session for CAAR. The total volume of liquid was no more than 0.5 ml. During the same period the control rats were treated with 0.5 ml saline. Each rat was tested only once, every group consisted of 7 rats. The results were statistically analyzed using nonparametric one-factor analysis for independent variants (Kruskal-Wallis test).

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RESULTS

Seleptine suppressed the retrieval of CAAR only when it was used in a dose of 100 mg/kg (Table 1). However, its effect did not reach the statistical confidence level (T=11.20 for 17 variants of the same rank).

We used a specific parameter — the number of combined stimuli necessary to meet the requirements of a more slack criterion of CAAR development: 8 correct successive responses instead of 10 responses in the first session. According to this criterion, the effect of seleptine on the retrieval of CAAR was more pronounced: it was statistically significant (p<0.05, T=18.33 for 8 variants of the same rank, Table 2). In contrast to the control group, the disturbances in CAAR retrieval were significant at 30 and 100 mg/kg seleptine.

A comparison of the data on training in the second session controlled by a relatively slack criterion with the data employing the initial criterion leads to the hypothesis that seleptine disturbs the retrieval of CR, while the ability to acquire a new task (repeated training to the level characterized by the slack criterion) is deteriorated to a lesser extent.

As other benzodiazepine preparations, seleptine caused amnesia of the task acquired in normal conditions and impaired training under stress with a negative reinforcement [1,6]. In addition, seleptine provokes marked deficiency of the previously acquired task (declarative memory) in comparison with the retrieval with a hint and additional training (procedural memory) [5]. At the same time, analysis of the seleptine effect on CAAR attests to its possible effect on the cerebral transmitter systems, that provide the emotion-motivation basis of a particular CAAR. It is tempting to suppose that seleptine has adrenolytic properties, because injection of the neurotoxin 6-hydroxydopamine into the *locus coeruleus* or its electrolytic destruction results in amnesia, retardation of training for electrodefensive tasks, and disturbances in the retrieval of memory trace [2], while the development of CAAR is strongly affected [3]. The effect of seleptine on serotoninergic system is also possible: an increase in the cerebral serotonin content impairs the learning and amnesia of developed CR [2,3], and to a greater extent degree it disturbs consolidation of temporal connection [3]. Parallel neurochemical studies showed that in addition to a high affinity for benzodiazepine receptors, seleptine competitively replaces the agonists of serotonin receptors, but not the antagonists of α_1- or agonists of α_2-adrenoreceptors. Therefore, functional insufficiency of the noradrenergic system can result from a concomitant relative enhancement of the efficiency of serotoninergic system due to reciprocity of the relationships between both systems [2]. This hypothesis needs further experimental support.

TABLE 1. Effects of Various Doses of Seleptine on the Retaining of CAAR ($M\pm m$)

Dose, mg/kg	Period between administration of seleptine and test, min	Retaining of CAAR, %
Control	30	46.40±8.04
	60	46.13±6.36
10	30	28.86±8.46
	60	29.47±3.22
30	30	32.55±6.42
	60	22.88±7.19
100	30	16.79±7.43*
	60	18.98±6.03*

Note. Here and in Table 2: *p<0.05 compared with the control.

TABLE 2. Effects of Seleptine on CAAR Retention According to Slack Criterion of Task Retention (M-m)

Dose, mg/kg	Period between administration of seleptine and test, min	Retaining of CAAR, %
Control	30	74.08±3.57
	60	73.66±2.28
10	30	63.30±5.68
	60	57.62±5.23
30	30	51.74±9.32*
	60	51.33±7.90*
100	30	26.78±8.94*
	60	32.60±7.92*

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