VERSITA

Central European Journal of Medicine
DOI: 10.2478/s11536-007-0033-3
Research article
CEJMed 2(3) 2007 280–293

Effects of $GABA_B$ receptor antagonists CGP63360, CGP76290A and CGP76291A on learning and memory processes in rodents

Damianka P. Getova*, Darinka D. Dimitrova

Department of Pharmacology, Clinical Pharmacology and Drug Toxicology, Medical University, V. Aprilov str. 15A, Plovdiv 4002, Bulgaria

Received 06 March 2007; accepted 24 May 2007

Abstract: Data in literature that use methods for studying the learning and memory processes suggest that GABA and especially $GABA_B$ receptor antagonists may be active against amnesia. The aim of our study was to examine the effects of three new $GABA_B$-antagonists on learning and memory processes. Active and passive avoidance tests with negative reinforcement in rats were used. The rats treated with different $GABA_B$ receptor antagonists showed improving effects in both tests (active and passive avoidances) on learning as well as on memory retention. There are some differences in their activities, probably due to its chemical structures. The phosphinic analogue CGP63360A is potent to the point that the benzoic one CGP76290A and the left isomer of the benzoic analogue CGP76291A has no effect. It may be concluded that the obtained results on the $GABA_B$ receptor antagonists could contribute to their pharmacological characteristics and might be of interest for potential clinical implication.

Keywords: $GABA_B$ receptor antagonists, learning, memory

1 Introduction

In recent years, an increasing interest has been focused on the role of GABA in the neurochemical mechanisms of cognition and especially in learning and memory processes. This focus has been prompted by the revealing of differences in the functions of two GABA receptor subtypes - $GABA_A$ and $GABA_B$, which allows for the better understanding of the diversity of GABA neurotransmission functions. In spite of the intensive studies of the problem, many questions still remain unclear and others are contradicting.

* E-mail: dgetova@yahoo.com

It is already known that $GABA_B$ antagonists can suppress late inhibitory postsynaptic potentials and amplify the acetylcholine and quisqualate signals [1, 2]. Amplification of neurotransmission might improve the signal-to-noise ratio, and thus also enhance memory processing. There are data in the literature showing that learning and retention capacity of experimental animals in cognitive tests can be improved by blockade of the $GABA_B$ receptors [3]. Some [4] pointed out, that after applying of $GABA_B$ receptor antagonist CGP36742, mice performed better in an inhibitory avoidance test, rats did likewise in a partner recognition test and rhesus monkey also in a conditional spatial color task. Other [5] suggest that activation of $GABA_B$ receptors modulates intracranial self-stimulation behavior.

Many effects observed in different spices and using methods for diverse manifestations of learning and memory give the reason to hope that $GABA_B$ receptor antagonists may be a useful against amnesia [6–8].

We have already published data for single dose administration of CGP36742, CGP56433 and CGP61334 [9] and for CGP71982, CGP62349 and CGP55845A over a dose of $0.01-1$ mg/kg [10].

The aim of the present study was to examine the effects of three $GABA_B$-antagonists CGP63360, CGP76290A and CGP7691A on learning and memory processes using an active and a passive avoidance paradigm in rats.

2 Statistical methods and Experimental Procedures

2.1 Animals

Male Wistar rats weighing $200-250$ g were used. They were fed ad libitum and maintained on a 12-h light-dark cycle. Animals were housed in groups of eight each and habituated for 5 min a day before each avoidance test.

2.2 Active avoidance test

Learning session:

Two-way active avoidance test was performed in a shuttle box (Ugo Basile). The learning session consisted of a 5-day training test using the standard programme with 30 trainings per day. Every training session was 6 seconds light and buzzer (670 Hz, 70 dB), followed by 0.4 mA foot stimulation with 4 sec. duration and 12 sec. pause between shocks.

The automatically counted parameters were: (1) number of aversive stimuli, i.e. avoidances; (2) number of unconditioned stimuli, i.e. escapes; (3) number of intertrial crossings; and, (4) latency of reaction in seconds.

Memory retention:

On the 5th week of the experiment a memory retention session was performed (7 days after last training) using the same parameters, but without foot stimulation.

2.3 Passive avoidance test

Step-through passive avoidance was also performed on the same groups of rats.

Learning session:

Rats were trained in a single session of 3 trials. Every trial consisted of 6 seconds delay (closed door between light and dark chambers), before the door was opened for 12 s and the light stimuli was turned on. If the rat crossed the door and went into the dark chamber, then the door closed automatically and the rat received 0.4 mA foot shock for 9 sec. If the rat did not go into the dark chamber in 12 sec., then the counter started to count the seconds until it went to the dark chamber. When the counter stopped automatically, the rat received foot-shock. The maximum time spent in the light chamber was 180 ± 2 s (3 min).

Memory retrieval:

24 hours and 7 days after the learning sessions a memory retention session of 3 trials per session was performed. Every trial consisted of the same parameters without foot shocks.

2.4 Drugs

The chemical structure of the compounds was:

CGP63360A: Cyclohexylmethyl-2-(S)-hydroxy-3-[(6-oxo-1,6-dihydro-pyridin-3-ylmethyl)-amino]-propyl-phosphinic acid, hydrochloride.

CGP76290A: 3-[(3R,6R)-6-(Cyclohexylmethyl-hydroxy-phosphinoylmethyl)-morpholin-3-yl]benzoic acid, di-sodium salt.

CGP76291A: 3-[(3-S, 6S) -6-(Cyclohexylmethyl-hydroxy-phosphinoylnethyl)-morpholin-3-yl]benzoic acid, di-sodium salt.

The rats were divided into the groups ($n = 8$), injected with different doses of CGP compounds or saline. All substances were applied for 15 days before starting the tests and during them. The purpose was to establish their effects on formation and consolidation of memory traces.

2.5 Statistical evaluation

A two way ANOVA for repeated measurements was used to compare the results from the active avoidance test and a one way ANOVA was used to compare the results from the passive avoidance test.

3 Results

3.1 Effects of the $GABA_B$ receptor antagonist CGP63360A on learning and memory processes in active avoidance test.

Control rats showed statistically significant increased number of conditioned stimuli (avoidances) on 2^{nd} ($P < 0.05$), 3^{rd}, 4^{th} and 5^{th} days ($P < 0.01$) compared with 1^{st} day training (Fig. 1).

Learning session rats injected with the $GABA_B$ receptor antagonist CGP63360A at a dose of 0.1 mg/kg showed statistically increased number of avoidances on 3^{rd}, 4^{th} ($P < 0.05$), and 5^{th} day ($P < 0.01$) compared with the respective controls as well as with the 1^{st} day training. Rats treated with 0.01 mg/kg CGP63360 also showed increased number of avoidances on 4^{th} and 5^{th} days ($P < 0.05$) compared with the respective controls. Rats injected with 0.001 mg/kg did not significantly change the number of avoidances during learning session compared to the control (Fig. 1).

On memory retention test (12^{th} day) control group also showed increased number of avoidances ($P < 0.01$) compared with 1^{st} day learning. On memory retention test the number of avoidances was increased as well ($P < 0.05$) in rats treated with 0.1 mg/kg CGP63360A and did not change in the groups treated with 0.01 and 0.001 mg/kg CGP63360A compared with the controls (Fig. 1).

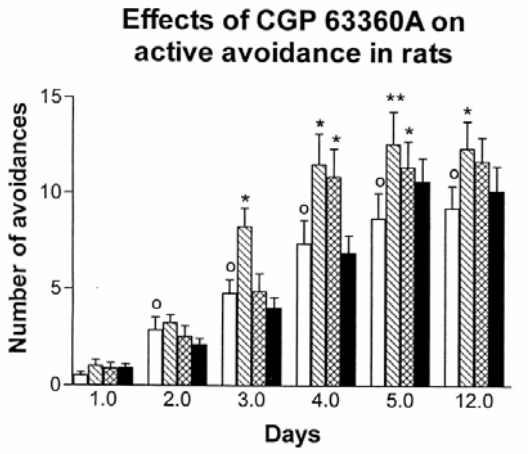

Fig. 1 Effects of the GABAB receptor antagonist CGP63360A on learning and memory processes in active avoidance test. Abscissa - days of testing; Ordinate - number of conditioned stimuli (avoidances). $^{o}P < 0.05$ and $^{oo}P < 0.01$ compared to the 1^{st} day control. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared to the respective controls.

Control rats (saline) did not change significantly the number of unconditioned stimuli (escapes) on learning and memory retention test (Table 1). Rats injected with different doses of CGP63360A also did not change the number of escapes during learning and memory retention sessions compared with controls (Table 1).

Table 1 Effects of CGP 63360 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG	0.001 MG/KG
1	15.37 ± 1.97	12.62 ± 1.79	12.00 ± 1.22	10.00 ± 1.44
2	14.00 ± 1.52	17.75 ± 2.29	15.00 ± 1.98	12.50 ± 1.79
3	12.50 ± 1.47	16.37 ± 1.01	14.62 ± 1.83	12.87 ± 1.77
4	13.37 ± 1.49	14.87 ± 1.98	15.37 ± 2.46	11.25 ± 1.05
5	12.00 ± 1.32	14.12 ± 1.66	19.50 ± 2.84	13.00 ± 1.78
12	12.50 ± 1.28	11.00 ± 1.46	14.50 ± 2.50	11.25 ± 1.81

Number of unconditioned stimuli (escapes) - mean ± SEM.

Control rats (saline) did not change significantly the number of intertrial crossings on learning and memory retention test (Table 2). Rats injected with different doses of CGP63360A also did not change the number of intertrial crossings during learning and memory retention sessions compared with controls (Table 2).

Table 2 Effects of CGP 63360 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG	0.001 MG/KG
1	16.25 ± 2.68	17.25 ± 2.27	20.37 ± 3.02	14.50 ± 1.78
2	15.12 ± 2.57	20.50 ± 2.96	18.87 ± 2.16	12.12 ± 1.04
3	13.50 ± 1.05	17.00 ± 2.70	19.37 ± 3.29	14.62 ± 1.99
4	18.50 ± 2.79	19.12 ± 2.94	17.87 ± 2.28	20.25 ± 2.76
5	16.12 ± 2.87	19.06 ± 2.68	18.25 ± 2.25	15.37 ± 1.39
12	24.00 ± 3.29	24.25 ± 3.10	19.37 ± 3.84	14.87 ± 1.35

Number of intertrial crossings - mean ± SEM.

3.2 Effects of the $GABA_B$ receptor antagonist CGP76291 on learning and memory processes in active avoidance test.

The same control group was used because of its randomized place between the three selective $GABA_B$ receptor antagonists in this series of experiments. This gave the possibility to compare the CGP compounds between themselves during learning and memory retrieval and different tests - active and passive avoidances.

Control rats showed statistically significant increasing number of conditioned stimuli (avoidances) on 2^{nd} ($P < 0.05$), 3^{rd}, 4^{th} and 5^{th} days ($P < 0.01$) compared with 1^{st} day training (Fig. 2).

On learning session rats, injected with different doses of the $GABA_B$ receptor antagonist CGP76291 did not significantly change the number of avoidances during learning session compared to the control (Fig. 2).

On memory retention test (12^{th} day) control group also showed increased number of avoidances ($P < 0.01$) compared with 1^{st} day learning. On memory retention test the

number of avoidances did not change in rats treated with different doses of CGP76291 compared with the controls (Fig. 2).

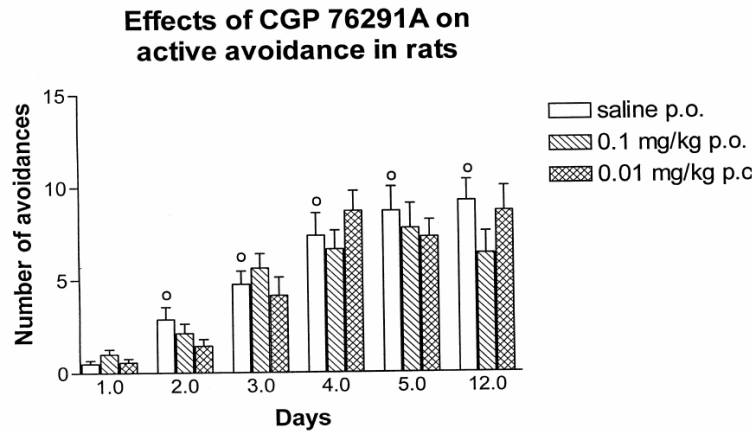

Fig. 2 Effects of the $GABA_B$ receptor antagonist CGP76291 on learning and memory processes in active avoidance test. Abscissa - days of testing; Ordinate - number of conditioned stimuli (avoidances). ${}^{o}P < 0.05$ and ${}^{oo}P < 0.01$ compared to the 1^{st} day control. ${}^{o}P < 0.05$ and ${}^{oo}P < 0.01$ compared to the 1^{st} day control.

As it was already shown control rats (saline) did not significantly change the number of unconditioned stimuli (escapes) on learning and memory retention test (Table 3). Rats injected with both doses of CGP76291 also did not change the number of escapes during learning and memory retention sessions compared with controls (Table 3).

Table 3 Effects of CGP76291 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG
1	15.37 ± 1.97	7.37 ± 0.67	13.71 ± 1.67
2	14.00 ± 1.52	13.75 ± 1.08	15.57 ± 1.76
3	12.50 ± 1.47	10.87 ± 1.17	13.86 ± 1.77
4	13.37 ± 1.49	11.25 ± 1.12	13.43 ± 1.14
5	12.00 ± 1.32	10.50 ± 1.25	13.00 ± 1.82
12	12.50 ± 1.28	13.38 ± 1.25	13.57 ± 1.84

Number of unconditioned stimuli (escapes) - mean ± SEM.

Control rats (saline) did not change significantly the number of intertrial crossings on learning and memory retention test (Table 4). Rats injected with both doses of CGP76291 also did not change the number of intertrial crossings during learning and memory retention sessions compared with controls (Table 4).

Table 4 Effects of CGP76291 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG
1	16.25 ± 2.68	7.75 ± 0.92	14.71 ± 1.29
2	15.12 ± 2.57	8.50 ± 0.89	8.43 ± 0.70
3	13.50 ± 1.05	18.88 ± 1.25	18.28 ± 1.78
4	18.50 ± 2.79	15.25 ± 0.51	16.71 ± 1.80
5	16.12 ± 2.87	11.00 ± 0.78	12.28 ± 1.13
12	24.00 ± 3.29	18.75 ± 1.53	23.00 ± 2.75

Number of intertrial crossings - mean ± SEM.

3.3 Effects of the $GABA_B$ receptor antagonist CGP76290 on learning and memory processes in active avoidance test.

The same control group was used for the purposes already mentioned. The experimental procedures were the same as for CGP63360 and CGP76291. Thus, this gives us the possibility to compare the effects of the CGP compounds studied.

Learning session rats injected with the $GABA_B$ receptor antagonist CGP76290 at a dose of 0.1 mg/kg showed statistically increased number of avoidances on 3^{rd}, 4^{th} ($P < 0.05$), and 5^{th} day ($P < 0.01$) compared with the respective controls as well as with the 1^{st} day training. Rats treated with 0.01 mg/kg CGP76290 did not significantly change the number of avoidances during learning session compared to the control (Fig. 3).

On memory retention test (12^{th} day) control group also showed increased number of avoidances ($P < 0.01$) compared with 1^{st} day learning. On memory retention test the number of avoidances was increased as well ($P < 0.05$) in rats treated with 0.1 mg/kg CGP76290 and did not change in the groups treated with 0.01 mg/kg CGP76290 compared with the controls (Fig. 3).

As it was already mentioned, the control rats did not showed significant changes in the number of unconditioned stimuli (escapes) as during the learning session, as well as on 12^{th} day (test for memory retrieval) (Table 5). Rats injected with both doses of CGP76290 also did not change the number of escapes during learning and memory retention sessions compared with controls (Table 5). Rats injected with both doses of CGP76290 also did not change the number of escapes during learning and memory retention sessions compared with controls (Table 5).

Control rats (saline) did not change significantly the number of intertrial crossings on learning and memory retention test (Table 6). Rats injected with both doses of CGP76290 also did not change the number of intertrial crossings during learning and memory retention sessions compared with controls (Table 6).

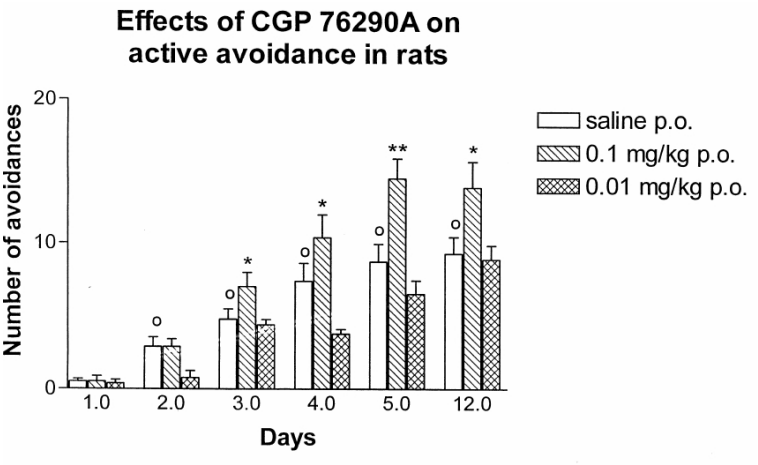

Fig. 3 Effects of the $GABA_B$ receptor antagonist CGP76290 on learning and memory processes in active avoidance test. Abscissa - days of testing; Ordinate - number of conditioned stimuli (avoidances). ${}^{o}P < 0.05$ and ${}^{oo}P < 0.01$ compared to the 1^{st} day control. ${}^{*}P < 0.05$ and ${}^{**}P < 0.01$ compared to the respective controls.

Table 5 Effects of CGP76290 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG
1	15.37 ± 1.97	11.38 ± 0.75	8.00 ± 0.63
2	14.00 ± 1.52	15.75 ± 1.91	14.50 ± 1.82
3	12.50 ± 1.47	12.75 ± 1.31	12.50 ± 1.11
4	13.37 ± 1.49	13.00 ± 1.98	12.70 ± 0.80
5	12.00 ± 1.32	9.05 ± 1.20	13.12 ± 1.06
12	12.50 ± 1.28	11.50 ± 1.17	11.50 ± 1.87

Number of unconditioned stimuli (escapes) - mean ± SEM.

Table 6 Effects of CGP76291 on active avoidance test.

DAY	SALINE	0.1 MG/KG	0.01 MG/KG
1	16.25 ± 2.68	11.50 ± 1.69	8.12 ± 1.82
2	15.12 ± 2.57	18.88 ± 1.31	15.50 ± 2.28
3	13.50 ± 2.05	19.62 ± 2.22	20.50 ± 2.59
4	18.50 ± 2.79	20.88 ± 2.80	18.12 ± 0.86
5	16.12 ± 2.87	18.50 ± 1.42	12.75 ± 1.50
12	24.00 ± 2.29	22.12 ± 2.44	18.00 ± 2.01

Number of intertrial crossings - mean ± SEM.

3.4 Effects of the $GABA_B$ receptor antagonists CGP63360A, CGP76291 and CGP76290 on learning and memory processes in passive avoidance test.

In passive avoidance test with negative reinforcement, step-through controls significantly prolonged the time of staying in light compartment ($P < 0.05$) on 2^{nd} day compared with learning session (1^{st} day), as well as in testing for long memory retention on 7^{th} day (Fig. 4). Rats with the $GABA_B$ receptor antagonist CGP63360A in both smaller doses showed statistically significant prolongation of staying in the light compartment ($P < 0.05$ and $P < 0.01$ respectively) during 1 day learning session compared with controls. The time of staying is prolonged significantly also in short memory retention tests in rats injected with smaller doses of CGP63360 ($P < 0.05$) compared to the control. In long memory retention test all rats injected with CGP63360 fulfill the latency criterion with maximum staying in the light compartment as controls (Fig. 4).

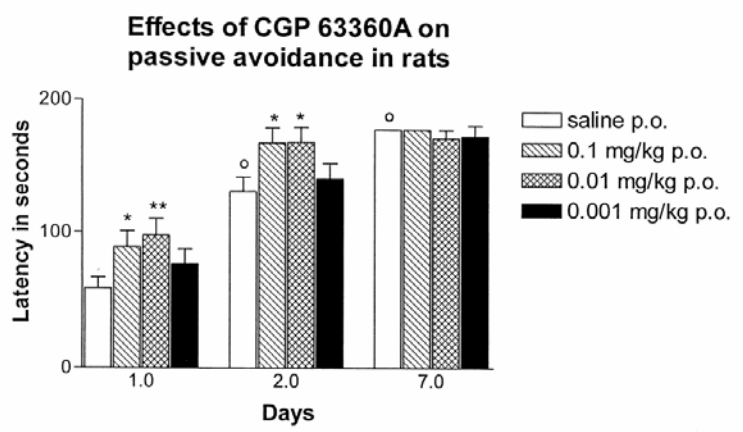

Fig. 4 Effects of $GABA_B$ receptor antagonist CGP63360A on learning and memory retention in rats on passive avoidance test. Abscissa - days of testing; Ordinate - latency(s). $^oP < 0.05$ compared to the 1^{st} day control. $^*P < 0.05$ and $^{**}P < 0.01$ compared to the respective controls.

The experimental procedures were the same for CGP63360, CGP76291 and CGP76290. Thus, this gives us the possibility to compared the effects of the CGP compounds studied. It was used the same control group for the purposes already mentioned.

In learning session rats treated with a larger dose of CGP76291A (0.1 mg/kg), showed statistically significant ($P < 0.05$) prolongation of latency in light compartment compared with the controls. In the short memory retention test, the same group also showed statistically significant ($P < 0.05$) prolonged the latency in light compartment compared with the controls for the respective day. In the long memory retrieval test, rats injected with CGP76291A, as well as the controls, did not differ significantly (Fig. 5).

In learning session rats treated with both doses of CGP76290A, showed statistically significant ($P < 0.05$) prolongation of latency in light compartment compared with the

controls. In the short memory retention test, the same groups also showed statistically significant ($P < 0.05$) prolonged the latency in light compartment compared with the controls for the respective day. In long memory retrieval test rats injected with CGP76290A as well as the controls did not differ significantly, but fulfill the criterion for latency (Fig. 6).

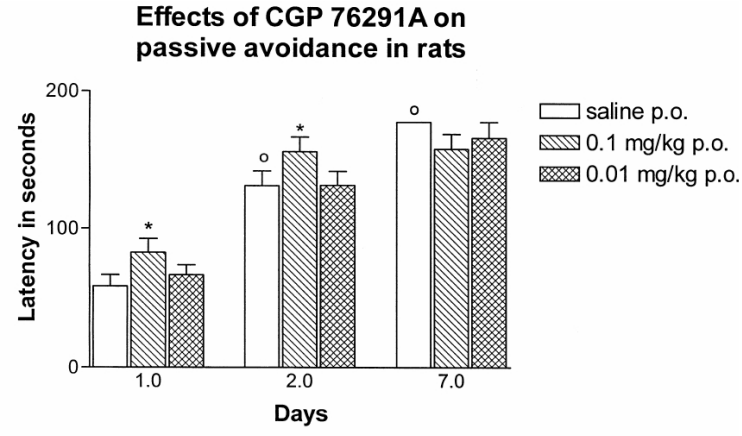

Fig. 5 Effects of $GABA_B$ receptor antagonist CGP76291A on learning and memory retention in rats on passive avoidance test. Abscissa - days of testing; Ordinate - latency(s). $^oP < 0.05$ compared to the 1^{st} day control. $^*P < 0.05$ and $^{**}P < 0.01$ compared to the respective controls.

4 Discussion

The obtained results permitted us to summarize that control rats learned the tasks in both active and passive avoidance tests. The rats treated with different $GABA_B$ receptor antagonists showed improving effects in both tasks. There are some differences in their activities, probably due to differences in its chemical structures. The most pronounced effect showed CGP63360 on learning and memory processes probably because it is phosphinic analogue. The other two CGP76290A and CGP76291A are benzoic acid derivatives and isomers. Evidently the right isomer CGP76290A is more potent than the left isomer CGP76291A.

Favorable effect on diverse manifestation of learning and memory of CGP36742 (the first orally active $GABA_B$ receptor antagonist) was demonstrated in different species [4, 11–13]. Some data with models of retrograde amnesia and shuttle box and step-down avoidance situation show, that this procedure impaired conditioning [14]. However, it is remarkable that cognitive factors are not usually assessed.

The control rat had acquired the active avoidance under saline during learning session and they displayed good memory on retrieval test. When the CGP compounds were given before the test, the acquisition was significantly improved. These results were also interesting, because it means that once acquired, the active avoidance behavior is possible

to be improved by $GABA_B$ receptor antagonists.

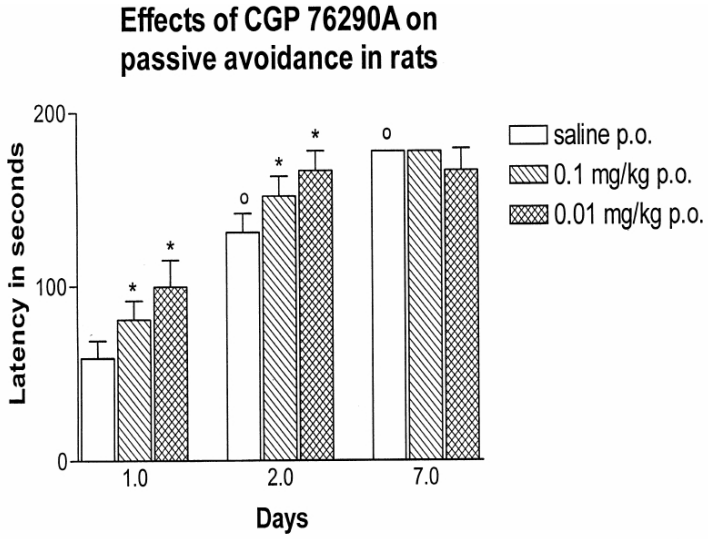

Fig. 6 Effects of $GABA_B$ receptor antagonist CGP76290A on learning and memory retention in rats on passive avoidance test. Abscissa - days of testing; Ordinate - latency(s). $^oP < 0.05$ compared to the 1^{st} day control. $^*P < 0.05$ and $^{**}P < 0.01$ compared to the respective controls.

There are data that, punishment or conflict models clearly involve learning and memory [15]. Indeed, active avoidance, especially shuttle box, is widely used task for studying memory mechanisms [16]. CGP36742, which exhibits a wide range of memory enhancing suggested facilitation the formation of long memory trace [17], because its improvement in performance could be measured after period of 24h or longer.

In the active avoidance test, $GABA_B$ antagonist-treated groups showed improvement in cognitive performance over the 5-day training period, which is well expressed in bigger doses used for CGP63360A and CGP76290A. They produced a linear dose-response curve on learning behavior. By contrast, CGP76291A did not influence it in all doses applied, it had no improving effect on learning and memory retention. The compounds CGP63360A and CGP76290A, at the doses of 0.1 mg/kg, improve memory storage on the 12^{th} day of testing.

Some experimental data suggests that memory storage can be altered by number of treatments that affect different hormones and neurotransmitters [3]. Especially in rats, GABA-ergic agonists impair memory and GABA-ergic antagonists improve it. Thus, this could support the view that GABA-ergic system modulates memory through an interaction with other transmitters. There are some contradictory data, showing that GABA-ergic antagonists may cause amnesia and improvement of performance [18]. These contradictory effects could be explained by the different procedure adapted for the training sessions.

The rat had acquired the passive avoidance under saline and they displayed good memory on short and long retrieval tests. When the CGP compounds were given before

the test, the acquisition was significantly improved. These results were also interesting, because it means that, once acquired the inhibitory avoidance behavior is possible to be improved by GABAB receptor antagonists. There are data, that the GABAB receptor antagonist CGP36742 facilitated the formation of long memory trace [17], because the exact determination of the time-course of the drug effect is passive avoidance was detectable at least 20h after the learning test and treatment.

Nevertheless, because CGP63360A and CGP76290A at doses 0.1 and 0.01 mg/kg affected acquisition, the improvement of inhibitory avoidance in the test session was not enough to be demonstrated in long memory retrieval during training. These results also suggest that CGP63360A and CGP76290A affecting acquisition facilitate also the short-memory traces. The lack of inhibitory avoidance retention presently observed after treatment with CGP63360A and CGP76290A is due probably of the failed effect on long memory trace retrieval. Indeed, the two doses (0.1 mg/kg and 0.01 mg/kg) of CGP63360A and CGP76290A improved inhibitory avoidance in the learning session, but did not significantly affect long memory trace retrieval on the 7^{th} test day.

Therefore, the differences between CGP76290A and CGP76291A could only be quantitative. To test this hypothesis we used 2 doses of both CGP76291A and CGP76290A. The passive avoidance latency observed with CGP76290A compared to that of CGP76291A was longer, and the dose of 0.01 mg/kg for CGP76291A was ineffective.

Some authors pointed out, that the inhibitory avoidance is different in the apparently similar punishment, like passive avoidance or anxiety tests [15]. Similarly, one-way or two-way escapes from foot shocks were not affected by the same doses of CGP76291A in all tested doses.

One of the brain sites more directly related with learning and memory processes is the hippocampus. In conscious mice it was observed the activity-dependent changes which take place at the hippocampal CA3-CA1 synapse during the acquisition, extinction and recall of an associative tasks [19].

It is well established that amygdala lesions attenuate the expression of emotional behavior and memory, whereas its integrity does not seem to be required for other type of memory [20]. Thus, one could argue that memory for active avoidance conditioning is mediated with the participation of $GABA_B$ receptors sensitive brain areas, whereas memory for passive escapes behavior is modulated by other brain regions, not quite sensitive to $GABA_B$ influence.

Macey *et al.*, [5] try to determine the role of $GABA_B$ receptor function on brain stimulation reward using discrete-trial current-intensity threshold procedure and the effects of $GABA_B$ receptor antagonists CGP56433A and CGP51176. They found that $GABA_B$ receptor antagonists induced a reward decrement when administered alone. In addition, co-administration of either of the two $GABA_B$ receptor antagonists with GABA agonist CGP44532 induced an additive effect on thresholds. They concluded that the activation of $GABA_B$ receptor modulates intracranial self-stimulation behavior in a complex fashion possibly through pre- and post-synaptic $GABA_B$ receptors.

There are evidence that improve or impair learning can facilitate or block ethanol tol-

erance, respectively. Since $GABA_B$ receptors have been shown to be involved in processes related to learning, it is possible that this system could play a role in the rapid tolerance to ethanol. Zalesky *et al.*, [21] found that mice pretreated with $GABA_B$ receptor antagonists CGP36742 or CGP56433 facilitate rapid tolerance in a dose-dependent way. The blockade of rapid tolerance by baclofen was antagonized by previous administration of $GABA_B$ antagonists. They concluded that rapid tolerance to ethanol is subject to inhibition by GABA-ergic $GABA_B$ receptor-mediated system in the mouse.

In conclusion, the present comparative study of the effects on active and passive avoidance situations of three new $GABA_B$ receptor antagonists shows that this class of antagonists, especially phosphinic analogue may provide effective cognitive enhancing agents. The exact brain structures involved still remain unclear.

Ackonwledgements

We thank Dr. W. Froestl for the $GABA_B$ antagonists and the National Scientific Fund Project U-L-05/2003 for financial support.

References

[1] U. Karlsson and H.R. Olpe: "Late inhibitory postsynaptic potentials in rat prefrontal cortex may be mediated by GABA-B receptors", *Experientia*, Vol. 45, (1989), pp. 157–158.

[2] P. Andre, T. Ferrat, M. Steinmann and H.R. Olpe: "Increased acetylcholine and quisqualate responsiveness following blockade of GABA(B) receptors", *Eur. J. Pharmscol.*, Vol. 218, (1992), pp. 137–143.

[3] C. Castellano, J.D. Brioni and J.L. McGuaugh: "GABA-ergic modulation of memory", In: L. Squire, E. Lindenlaub (Eds.), *The Biology of Memory , Symposia Medica Hoechst,* Schattauer, Stuttgart/New York., 1990, pp. 361–378.

[4] C. Mondadori, J. Jaekel and U. Preiswerk: "CGP 36742: the first orrally active GABA B blocker improves the cognitive performance of mice, rats and Rhesus monkeys", *Behav. Neural. Biol.*, Vol. 60, (1993), pp. 62–68.

[5] D.J. Macey, W. Froestl, G.F. Koch and A. Markou: "Both GABA-B receptor agonists and antagonists decreased brain stimulation reward in the rat", *Neuropharmacology*, Vol. 40, (2001), pp. 676–685.

[6] K.Chen, H-Z. Li, N. Ye, J. Zhang and J-J. Wang: "Role of GABA(B) receptors in GABA and baclofen-induced inhibition of adult rat cerebellar interpoditus nucleus neurons *in vitro*", *Brain Res. Bull.*, Vol. 67, (2005), pp. 310–318.

[7] O. Deschaux, W. Froestl and C. Gottesmann: "Influence of GABA(B) and GABA(C) receptor antagonist on sleep-waiking cycle in the rat", *Eur. J. Pharmacol.*, Vol. 535, (2006), pp. 177-181.

[8] A. Handforth, M. DeLorey, G.E. Homanics and R.W. Olsen: "Pharmacologic evidence for abnormal thalamocortical functioning in GABA(A) receptor ß3 subunit-deficient mice, a model of Angelman syndrome", *Epilepsia*, Vol. 46, (2005), pp. 1860–1870.

[9] D. Getova, N.G. Bowery and V. Spassov: "Effects of GABA-B receptor antagonists on learning and memory retention in a rat model of absence epilepsy", *Eur. J. Pharmacol.*, Vol. 320, (1997), pp. 9–13.

[10] D. Getova and N.G. Bowery: "The modulatory effects of high affinity GABAB receptor antagonists in an active avoidance learning paradigm in rats", Psychopharmacology (Berlin), Vol. 137, (1998), pp. 369–373.

[11] Y. Nakagawa and T. Takashima: "The GABA (B) receptor antagonist CGP 36742 attenuates the baclofen- and scopolamine-induced deficit in Morris water maze task in rats", *Brain Res.*, Vol. 766, (1970), pp. 101–106.

[12] C. Mondadori, H.J. Moebius and M. Zingg: "CGP 36742, an orally active GABA B receptor antagonist facilitates memory in a social recognition test in rats", *Behav. Brain Res.*, Vol. 77, (1996), pp. 227–229.

[13] C. Mondadori, H.J. Mobius and J. Borkowski: "The GABA B receptor antagonist CGP 36742 and the nootropic oxiracetam facilitate the formation of long-term memory", *Behav. Brian Res.*, Vol. 77, (1996), pp. 323–325.

[14] C.A. Boast and D.C. McIntyre: "Bilateral kindled amygdala foci and inhibitory avoidance behavior in rats: A functional lesion effect", *Physiol. Behav.*, Vol. 8, (1977), pp. 25–28.

[15] M. Viana, C. Tomaz and F. Graeff: "The elevated T-maze: a new animal model of anxiety and memory", *Pharmacol. Biochem. Be.*, Vol. 49, (1994), pp. 549–554.

[16] J. Bures and O. Buresova: "Learning and memory", In: J. Bures, O. Buresova, J. Huston (Eds), *Techniques and basic experiments for the study of brain and behavior*, Elsevier Science Publishers B.V., New York, 1983, pp. 135–208.

[17] C. Mondadori , G. Preiswerk and J. Jaekel: "Treatment with a GABAB receptor blocker improves the cognitive performance of mice, rats and rhesus monkeys", *Pharmacol. Comm.*, Vol. 2, (1992), pp. 93–97.

[18] S.E. Cruz-Morales, G.L. Quirarte, M.A. Diaz del Guante and R.A. Prado-Alcala: "Effects of GABA antagonists on inhibitory avoidance", *Life Sci.*, Vol. 53, (1993), pp. 1325–1330.

[19] A. Gruart, M.D. Munoz and J.M. Delgado-Garcia: "Involvement of the CA3-CA1 synapse in the acquisition of associative learning in behaving mice", *J. Neurosci.*, Vol. 26, (2006), pp. 1077–1087.

[20] S. Zola-Morgan, L. Squire, P. Alvarez-Royo and R. Clower: "Independence of memory functions and emotional behavior: Separate contributions of the hippocampal formation and the amygdale", Hippocampus, Vol. 1, (1991), pp. 207–220.

[21] M.J. Zaleski, J.R. Nunes Filho, T. Lemos and G.S. Morato: "GABA-B receptors play a role in the development of tolerance to ethanol in mice", *Psychopharmacology* (Berl), Vol. 153, (2001), pp. 415–424.