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BRIEF COMMUNICATION

The Effect of Subchronic Administration of Vigabatrin on Learning and Memory in Nonepileptic Rats

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SIRVIÖ, J., A. YLINEN, H. LAHTINEN, A. RONKAINEN, P. RIEKKINEN, JR., T. HALONEN AND P. J. RIEKKINEN. *The effect of subchronic administration of vigabatrin on learning and memory in nonepileptic rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 205–210, 1991.—The present experiments investigated whether subchronic administration of vigabatrin, a GABA-mimetic drug, affects the performance of normal rats in the behavioural tasks assessing learning and memory. The effects of vigabatrin [50–200 mg/kg (IP)/day] administration on the acquisition and retention of water maze and passive avoidance task were studied. According to the results of three experiments, vigabatrin treatment did not markedly impair the acquisition or retention of water maze task. Furthermore, vigabatrin-treated rats were not inferior to saline-treated rats in reversal learning of water maze task. On the other hand, vigabatrin treatment slightly increased the speed of swimming in rats. The administration of vigabatrin did not affect the performance (training latency, number of training trials, testing latency) of rats in the passive avoidance task. According to these results, the effects of vigabatrin, a new antiepileptic drug, on the performance of nonepileptic rats were modest in behavioural tasks used to assess learning and memory.

Amino acids Antiepileptic drugs Gamma-aminobutyric acid Learning Memory Rat brain Vigabatrin

COGNITIVE dysfunctions are associated with epilepsy, especially with the seizures of the temporal lobe origin (17). This is due to focal morphological pathologies of brain tissue and epileptiform electrophysiolocal activity. On the other hand, some antiepileptic drugs affect cognitive functions, including attention and memory (34). Vigabatrin is a new antiepileptic drug which elevates the brain levels of gamma-aminobutyric acid (GABA) due to inhibition of GABA-transaminase, an enzyme responsible for the breakdown of GABA (11, 18, 30). The side effects (drowsiness, dizziness, nausea) found in some patients are mild and transient (15,24).

The GABAergic system plays a role in the mechanisms underlying memory. GABA agonists and antagonists affect memory storage in the aversively motivated tasks (21). Furthermore, the administration of vigabatrin and subsequently elevated levels of GABA may inhibit the activity of cortical cholinergic and noradrenergic afferents originating from the nucleus basalis and locus coeruleus, respectively (29,35). Both cholinergic and noradrenergic systems play a role in cortical activation and cognitive functions (5, 9, 19, 28). Subchronic administration of vigabatrin increased slightly the amount of slow-wave activity in the immobility-related cortical electroencephalogram of rats (12). The increased amount of slow-wave activity has been related to decreased cholinergic activity and cognitive capacity in nucleus basalis-lesioned rats (5,26) and the patients with Alzheimer's disease (27).

Thus the present experiments were undertaken to study whether administration of vigabatrin induces deficits in the performance of nonepileptic rats in tasks used to assess learning and memory. Therefore, we investigated the effects of different doses of vigabatrin administered subchronically on the acquisition and retention of passive avoidance and water maze tasks.

METHOD

Animals

Adult male Kuo:Wistar rats (350–400 grams) were used in

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these studies. Rats were housed in cages (2 or 3 rats/cage) under temperature- and humidity-controlled environment. Lights were turned on from 0700–2100. Water and food pellets were given ad lib.

Drugs

Vigabatrin (Merrell Dow Research Institute, Winnersh Research Centre, UK) was dissolved in saline. It was injected intraperitoneally (IP, 4 ml/kg) once a day. Vigabatrin treatment (50, 100, 200 mg/kg) was started three days before the water maze task training. During training period of the water maze task, vigabatrin was injected after daily training (1500–1700 h). In passive avoidance experiments, vigabatrin treatment (50, 200 mg/kg) was started four days before training. The rats received the last injection of vigabatrin or saline 24 hours before the retention test of passive avoidance task. The rats treated with 50 mg/kg and 200 mg/kg vigabatrin were tested in separate experiments in the passive avoidance task.

For the confirmation of the biochemical effects of vigabatrin treatment during the beginning of training, one group of rats was treated with saline (n = 6), other two groups were treated with 50 mg/kg (n = 6) or 200 mg/kg (n = 4) vigabatrin for four days. One day after the last injection, the rats were decapitated, and the cerebellum was quickly dissected and frozen using liquid nitrogen. The cerebellum was used as a reference brain area, because the variation of results has been found to be least in this brain area. The GABA levels are, however, affected in other areas of brain, also (13). The samples were stored for 10 days at −70°C before the analysis of GABA and some other amino acids.

Behavioral Equipment and Testing

For the testing of spatial navigation ability, we used a modified version of Morris water maze task (22) which has been described in detail previously (25). In our system, the pool which is black is filled with clear water. We have also tested the visibility of the platform in water pool. For this purpose, two groups of rats were trained to find the submerged platform either in clear water or in water with wooden chips on the surface of water. During the first day, the rats were trained 16 times. On the second day, the position of the platform was reversed, and the rats were tested 10 times. Escape latency did not differ between the two groups of rats tested (data not shown). This further suggests that the rats do not see the platform.

In the vigabatrin experiments, testing consisted of 2–5 days of training (5–10 trials a day, maximum duration of 60 seconds, 10 seconds on the platfrom, 20–60 seconds recovery period between daily training trials). The details of three different experiments are given in Table 1. Rats which failed to find the hidden platform within 60 seconds were placed on it. In Experiment 1 and 2, the platform was in the same position. In Experiment 3, the position of the platform was reversed for the second day of training. In Experiment 1, the retention of water maze task was assessed using a probe trial 24 hours after the last training trial. In Experiment 2, the retention of the task (3 days after training) was assessed using single trial to a submerged platform (which was in a previous position) because of possible floor effect if assessed using a probe trial. In the probe trial, the rats were allowed to swim for 60 seconds in the pool without the platform. The computerized system calculated the total swimming time and path length as well as the swimming path length in all quadrants and annuli separately. The number of platform crossings were counted from the printed swim path of the rat.

TABLE 1

THE EXPERIMENTS ASSESSING THE ACQUISITION AND RETENTION OF WATER MAZE TASK IN SALINE- AND VIGABATRIN- (GVG, 50–200 mg/kg) TREATED RATS

	Experiments		
	1	2	3
Subjects:	saline (8)* GVG 50 (8) GVG 100 (8) GVG 200 (8)	saline (8) GVG 50 (6) GVG 200 (7)	saline (9) GVG 50 (7) GVG 200 (7)
Training:	4 days (5 trials/day)	5 days (4 trials/day)	2 days (10 trials/day)
Recovery:	20 seconds	20 seconds	60 seconds
Platform:	normal	normal	1 day:normal 2 day:reversed
Retention:	probe trial 24 hours	a single platform trial 3 days	—

*The number of rats is in parentheses.

The passive avoidance apparatus consisted of a rectangular Plexiglas box, divided into dark and lighted compartment by a sliding guillotine door. The dark compartment had a metal grid floor which was connected to shock generator (26). The rat was placed in the lighted side. After 60 seconds a door was opened into the dark side. After the entry to the dark side, a 0.9 mA shock was delivered to the rat's feet. The shock remained on until the rat returned to the lighted side. Training continued until the rat remained on the lighted side for 60 seconds. Latency to the first entering of the dark chamber (training latency) and number of entries were recorded by the experimenter (number of training trials). Those rats which did not enter the dark chamber within 60 seconds during the first trial were dropped out from further testing. Testing occurred 48 hours after training. The rat was kept on the lighted side, and the door was opened. The session continued until the rat entered the dark side (maximum 300 seconds). The latency to enter into the dark chamber (testing latency) was recorded.

Biochemical Analysis

Frozen brain tissue was weighed and then immediately sonicated for 30 seconds in 19 volumes of 70% methanol containing 250 μmol norvaline/l as the internal standard. The homogenate was allowed to precipitate on ice for 10 minutes, after which it was centrifuged for 5 minutes at 10,000 × g. The supernatant was divided into aliquots and frozen immediately and stored at −80°C until assayed.

The concentrations of the amino acids in the supernatant were measured by high performance liquid chromatography as their precolumn o-phthalaldehyde derivatives as described previously (13).

Statistical Analysis of Data

Water maze data (escape latency and distance as well as the speed of swimming) was evaluated using analysis of variance (ANOVA) training day (Experiments 1 and 2) or training trial (Experiment 3) as a covariate. Passive avoidance data was evaluated using Mann-Whitney U-test. Biochemical data was evaluated using ANOVA and post hoc Mann-Whitney U-test.

TABLE 2

THE LEVELS OF THE NEUROTRANSMISSION-RELATED AMINO ACIDS AFTER 4 DAYS TREATMENT WITH VIGABATRIN (50 and 200 mg/kg)

	Saline (n=6)	Vigabatrin 50 (n=6)	Vigabatrin 200 (n=4)
Aspartate	2.32 ± 0.12	1.97 ± 0.08*[a]	1.92 ± 0.06*[a]
Glutamate	10.39 ± 0.50	9.90 ± 0.75	11.21 ± 0.32
Asparagine	0.17 ± 0.01	0.18 ± 0.02	0.18 ± 0.02
Glutamine	5.89 ± 0.20	6.13 ± 0.16	6.02 ± 0.56
Glycine	0.68 ± 0.02	0.67 ± 0.04	0.62 ± 0.03
Taurine	4.88 ± 0.16	4.78 ± 0.11	4.57 ± 0.14
GABA	1.65 ± 0.06	2.04 ± 0.20†[a]	3.85 ± 0.24†[a]

Values (μmol/g tissue) are expressed as mean ± SEM.
n = number of rats used.
*$p<0.01$, using ANOVA, $F(2,13)=7.339$; †$p<0.001$, using ANOVA, $F(2,13)=66.944$. [a]$p<0.05$, compared to saline-treated rats using Mann-Whitney test.

RESULTS

Biochemical Data

The rats treated with vigabatrin had higher levels of GABA in the cerebellum than saline-treated rats (Table 2). Vigabatrin-treated rats also had lower levels of aspartate than saline-treated rats.

Water Maze Task

Because vigabatrin-treated rats had slightly increased speed of swimming (Fig. 1), the escape distance is used as a parameter to express the acquisition data.

Experiment 1. The analysis of variance revealed a group difference in the escape distance, $F(3,635)=3.336$, $p=0.019$, between saline- and vigabatrin-treated rats (Fig. 2). The rats treated with 50 mg/kg vigabatrin had slightly increased escape distance, $F(1,317)=6.237$, $p=0.013$, as compared to saline-treated rats. The rats treated with 100 mg/kg vigabatrin had also slightly increased escape distance, $F(1,317)=3.804$, $p=0.052$. The escape distance did not differ between saline and 200 mg/kg vigabatrin-treated rats, $F(1,317)=0.017$, $p=0.897$.

In the probe trial (24 hours after training), the relative amount (% of total distance) of swimming in the previous training quad-

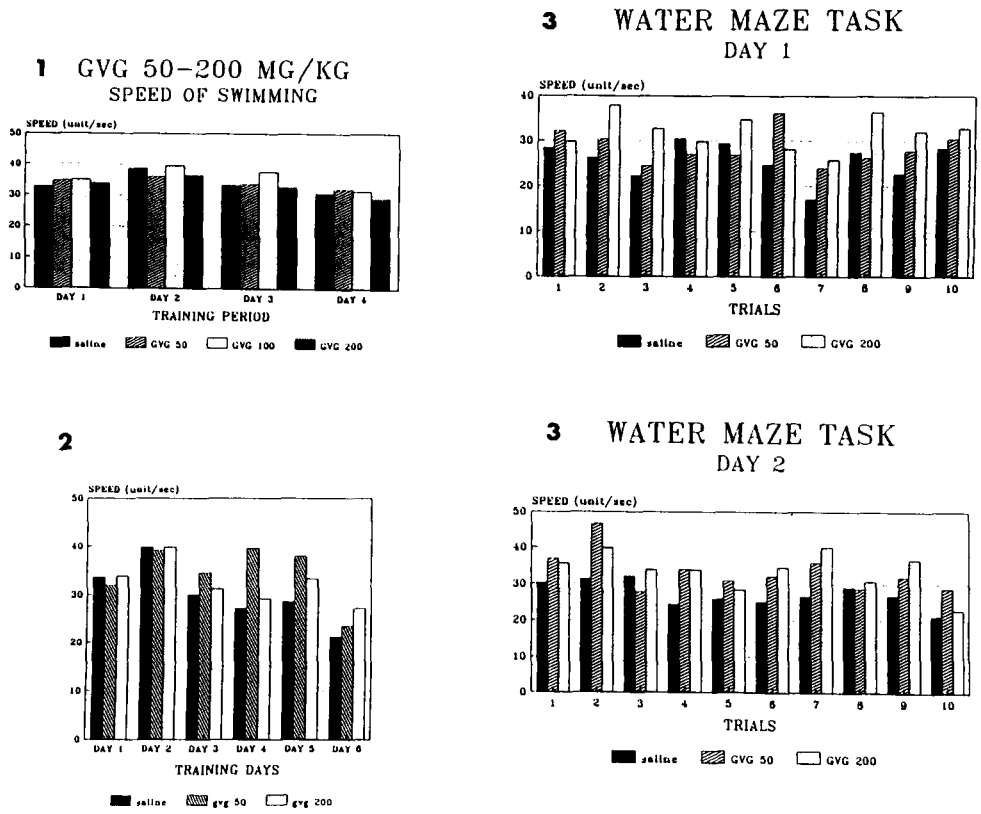

FIG. 1. The swimming speed (arbitrary units/second) of saline- and vigabatrin-treated rats during the water maze training period. The results are expressed as a group mean of daily trials (Experiments 1 and 2) or as a group mean of different trials in a day (Experiment 3). Statistical analysis using ANOVA: Experiment 1: $F(3,667)=3.148$, $p<0.05$ (using training day as a covariate). Experiment 2: $F(2,317)=11.433$, $p<0.01$ (using training day as a covariate). Experiment 3: Day 1, $F(2,226)=12.934$, $p<0.001$ (using trial as a covariate). Day 2, $F(2,226)=6.673$, $p<0.01$ (using trial as a covariate). Post hoc analysis revealed significant ($p<0.05$) difference between saline and GVG 50 as well as saline and GVG 200 groups, except in Experiment 1.

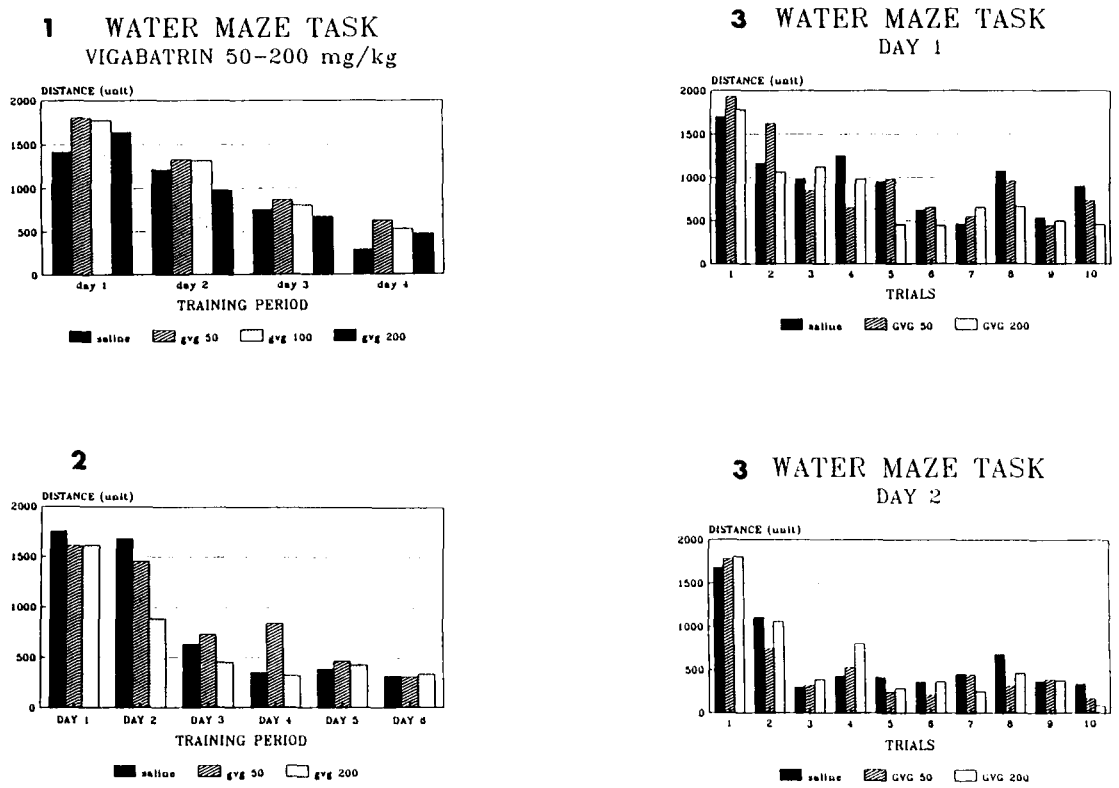

FIG. 2. The escape distance (arbitrary units) of saline- and vigabatrin- (50, 100 and 200 mg/kg) treated rats during the water maze training period. The results are expressed as a group mean of daily trials (Experiments 1 and 2) or as group mean of different trials in a day (Experiment 3).

rant (mean ± SD) did not differ between saline, (31 ± 11), 50 mg/kg (32 ± 16), 100 mg/kg (32 ± 10) and 200 mg/kg (38 ± 10) vigabatrin-treated rats, $F(3,28) = 0.672$, $p = 0.577$). Furthermore, the number of the platform crossings did not differ between saline- and vigabatrin-treated rats (data not shown).

Experiment 2. ANOVA (training day 1–5 as a covariate) revealed a nonsignificant group effect in the escape distance between saline- and vigabatrin- (50 and 200 mg/kg) treated rats, $F(2,317) = 0.026$, $p > 0.1$.

After three days, (day 6) the escape distance (a single trial to a submerged platform which was in a previous position) did not differ between saline- and vigabatrin- (50 and 200 mg/kg) treated rats, $F(2,18) = 0.018$, $p > 0.1$.

Experiment 3. During the first day, the escape distance to the submerged platform did not differ between saline- and vigabatrin- (50 and 200 mg/kg) treated rats [$F(2,226) = 1.199$, $p > 0.1$, ANOVA training trial as a covariate]. On the second day, escape distance to the submerged platform which was in the opposite quadrant did not differ between the groups of rats, $F(2,226) = 0.430$, $p > 0.1$.

Passive Avoidance Task

In passive avoidance task, the training latency, number of training trials and testing latency did not differ between saline and 50 mg/kg or 200 mg/kg vigabatrin treated rats (Table 3).

DISCUSSION

In the present experiments, we investigated whether a subchronic administration of vigabatrin affected learning and memory in aversively motivated task (passive avoidance test) and spatial navigation task (water maze test) in nonepileptic rats. Administration of vigabatrin not only increased the GABA levels in the cerebellum, but also affected the levels of aspartate as found previously (13). According to our previous studies, GABA levels are also increased in the cerebral cortex and hippocampus (13) which have been shown to be important in spatial functions (2,16).

TABLE 3

THE EFFECT OF VIGABATRIN (GVG) ON THE LEARNING AND MEMORY OF RATS IN PASSIVE AVOIDANCE TASK

	Training Latency (s)	Number of Trials	Testing Latency (s)
saline	34.4 ± 5.7 (n = 16)	1.1 ± 0.1 (n = 12)	263 ± 24 (n = 12)
GVG 50 mg/kg	41.5 ± 4.7 (n = 17)	1.1 ± 0.1 (n = 11)	273 ± 23 (n = 11)
saline	23.9 ± 9.3 (n = 10)	1.3 ± 0.5 (n = 8)	194 ± 55 (n = 8)
GVG 200 mg/kg	32.1 ± 10.5 (n = 9)	1.2 ± 0.4 (n = 6)	235 ± 110 (n = 6)

Results are expressed as mean ± SEM.
n = number of rats used.
Training latency, number of trials and testing latency do not differ between saline- and GVG- (50 mg/kg or 200 mg/kg) treated rats ($p > 0.050$, Mann Whitney U-test).

In Experiment 1, a low dose of vigabatrin induced a mild deficit in the acquisition of water maze task. In further experiments, the difference between saline- and 50 mg/kg vigabatrin-treated rats was not significant. Moreover, the rats treated with 200 mg/kg vigabatrin were not inferior to controls in the acquisition of this spatial navigation task. Furthermore, the retention of water maze task assessed 24 hours or 3 days after training was not impaired by vigabatrin treatment.

In Experiment 3, we assessed whether vigabatrin-treated rats are able to locate the new position of the platform in water pool, because it is reasonable to believe that increased perseveration (frontal lobe dysfunction) or impaired working memory (hippocampal dysfunction) would retard this kind of learning (16). However, vigabatrin-treated rats were not inferior to saline treated rats in the performance of this task.

Vigabatrin treatment slightly increased the speed of swimming of rats possibly reflecting increased forced motor activity. These results exclude the possibility that vigabatrin treatment decrease motivation of rats in water maze task. Previously, increased locomotor activity (assessed using hole board task) was found in rats which were intrahippocampally administered with vigabatrin (1). On the other hand, large doses of systematically administered vigabatrin reduce spontaneous locomotor activity (30).

The present results showing that vigabatrin treatment did not affect learning and memory in passive avoidance task are not in agreement with the previous findings which showed that post-training administration of GABA-A (muscimol) or GABA-B agonist (baclofen) impair, whereas GABA antagonist (picrotoxin) improve memory consolidation in aversive conditioning or Y-maze tasks [(4, 6–8, 33); see also (20)]. This apparent discrepancy may be due to the differences in the effects of subchronic elevation of GABA levels as compared to an acute administration of GABA agonist. However, it has also been reported that GABA-antagonist (bicuculline) impaired memory in aversive conditioning task (23). Furthermore, it is important to note that the paradigm of drug administration used in the present study does not exclude the effect of state-dependency (20).

One reason for negative results of the present study could be that the doses used were not appropriate. Using subchronic administration, we studied the dose range from 50–200 mg/kg, because 300–1500 mg/kg of vigabatrin as a single dose has been effective in some experimental models of epilepsy (10, 14, 31). The antiepileptic dose in humans is 3 g/day (35–50 mg/kg) (30,32). In rats, a subchronic administration of vigabatrin (100 mg/kg lasting for 4–12 days) increased the amount of GABA in the cerebrospinal fluid (13) as found previously (3) and the power of slow wave activity in the electroencephalogram (13). It is possible that the synaptic pool of GABA is not affected as markedly as the total levels of GABA in brain (10).

Administration of GABAmimetics might be associated with antinociception (21). This nuisance factor would be expected to increase the number of training trials due to vigabatrin treatment. This was not the case in the present study. Another nuisance factor of passive avoidance task is locomotor activity. Although there was a trend that fewer vigabatrin-treated than saline-treated rats enter the dark chamber in the training period, vigabatrin treatment did not, however, increase training latency significantly. Thus it is not evident that changes in locomotor activity have affected the present results of passive avoidance task.

In conclusion, the effects of vigabatrin on the performance of nonepileptic rats were modest in behavioural tasks used to assess learning and memory. It is, therefore, interesting to note that vigabatrin treatment does not impair cognitive functions in epileptic patients (15).

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