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Vigabatrin Has an Anxiolytic Effect in the Elevated Plus-Maze Test of Anxiety

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SAYIN, U., N. PURALI, T. ÖZKAN, T. ALTUG AND S. BÜYÜKDEVRIM. *Vigabatrin has anxiolytic effect in the elevated plus-maze test of anxiety.* PHARMACOL BIOCHEM BEHAV 43(2) 529–535, 1992.—γ-Vinyl GABA (vigabatrin, GVG) is a novel antiepileptic drug that irreversibly inhibits GABA transaminase and elevates GABA levels in all parts of the brain. In the present study, we investigated the anxiolytic and behavioral effects of GVG in the elevated plus-maze and the hole board compared to diazepam. Doses of 500 and 1,000 mg/kg GVG were injected IP to different groups of male Wistar rats and animals were tested either 4 or 24 h after injection. Animals administered diazepam (1.5 mg/kg, IP) and saline (1 ml) were tested 20 min after injection. GVG and diazepam were found to decrease significantly the number of squares visited and rearing; both had a suppressant effect on locomotor activity. Neither drug had an effect on exploration (head dipping). GVG at a dose of 1,000 mg/kg was shown to have a similar anxiolytic activity either after 4 or 24 h as diazepam, while GVG at 500 mg/kg did not show any significant anxiolytic effect.

γ-Vinyl GABA Elevated plus-maze Anxiety Epilepsy Hole board Locomotor activity Exploration

γ-VINYL GABA (vigabatrin; 4-amino-hex-5-enoic acid; GVG) is a novel antiepileptic drug that inhibits GABA transaminase irreversibly and increases GABA levels in all parts of the brain (34,48). It has been used successfully in patients with drug-resistant epilepsy, reducing seizure frequency by about 50–60% (40,47,63,64); its efficacy in complex partial seizures (CPS) has also been demonstrated (14–16,49,53,59). GVG has been found to have a powerful anticonvulsant activity in kindling phenomenon, which is an accepted animal model for temporal lobe epilepsy (TLE) (38,57,60), as well as in audiogenic (48), electroshock (36), pentylenetetrazol (8,52), bicuculline, and picrotoxin seizures (8) in rodents. GVG is still under investigation and its long-term effects are being evaluated in some countries where its application has been approved. The behavioral effects of GVG are likely to be important, as elevated GABA levels and enhanced GABA activity induce changes that can considerably alter behavior (33,41,51).

Depression and anxiety are serious concomitants of TLE and are observed more frequently in TLE than in the normal population (3,45,61). Bear (6) mentioned a syndrome of sensory limbic hyperconnection in patients with TLE, whereby TLE involves limbic system structures more than other forms of epilepsy precipitating behavioral alterations. Robertson et al. (50) also pointed out that epileptics are more anxious and depressed than subjects in the control group and equal or more so than psychiatric outpatients. It has been shown in models of CPS by amygdaloid partial kindling (e.g., in the cat) that animals become very defensive and anxious after being partially kindled, that is, undergoing electrographic seizures (1). With respect to anxiety observed in TLE, a likely candidate for a receptor system that would underlie an emotional disturbance are the benzodiazepine (BDZ)-$GABA_A$ receptor complex (9,11,62) and possibly NMDA receptors to some extent (69). Because GVG increases GABA levels two- or threefold in cerebrospinal fluid (7) during the first 48 h after administration, one might expect the drug to induce some favorable or unfavorable behavioral changes (e.g., anxiolytic effects or drowsiness, etc.).

There are some case reports pointing out that GVG induces mild paranoia, hallucinations, or delusions (13,20), but there are no reports yet available about the effects of GVG in respect to anxiety, one of the predominant psychiatric problems in TLE patients.

Although GVG has been shown in a number of animal models (8,36,38,52,57,60) to reduce or abolish experimental seizure frequency, there are not many reports on its behavioral effects in situations designed specifically to investigate anxiety and depression. Proven to have anxiolytic effects, GVG may become an important double face drug in the treatment of CPS because some TLE patients may benefit from both anti-

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convulsant and anxiolytic properties of this drug. Hence, further investigation is needed in the behavioral aspects of agents that elevate GABA levels.

In the present study we investigated the effects of GVG in the elevated plus maze test of anxiety, which is one of the most validated methods to measure anxiety (22,44). Because the BDZ-$GABA_A$ receptor complex and the GABAergic system in general interact with the regulatory mechanisms of motor activity, we also tested the effects of GVG on motor activity (44) and exploratory behavior (26,27) in the hole board.

METHOD

Animals

Male Wistar rats weighing 200–250 g (inbred at DETAM) were used in the experiment. They lived in individual cages, were allowed access to water and food (pellets containing essential nutrients) ad lib, and were kept in a room at 22 ± 2°C with a 12 L : 12 D cycle. Each rat was handled three times for 1 min during the week of the experiment.

Drugs

Vigabatrin was a generous gift from Merrill Dow Institute (Strasbourg, France). Diazepam was a gift from Deva Holding (Istanbul, Turkey).

Apparatus

The plus-maze consisted of two open arms, 50 × 10 cm, and two closed arms, 50 × 40 × 10 cm, with open roofs at right angles. The maze was elevated to a height of 50 cm from the ground, causing aversive stimuli to animals in the open arms. The color of the maze was cream enamel and the probable reflection of light on the maze was prevented; the light casting on any arm was nearly the same (44).

The hole board was a wooden box, 60 × 60 × 35 cm, with four holes of 4 cm in diameter symmetrically spaced in the floor (26,27,44). The ground was divided into nine squares, thus allowing an observer to count the number of squares visited during a period of time.

The behavior of each rat in the hole board or plus-maze was videotaped by a camera mounted on a tripod above the apparatus for future evaluation by two separate observers.

Procedure

Seventy rats were randomly assigned into 6 groups as follows: The control group received only saline IP (n = 14); GVG 500-4 (n = 10) and GVG 1,000-4 (n = 12) groups were injected with 500 and 1,000 mg/kg GVG IP, respectively, and tested 4 h following injection. GVG 500-24 (n = 10) and GVG 1,000-24 (n = 12) groups were administered 500 and 1,000 mg/kg GVG IP, respectively, and tested 24 h following injection. The BDZ control group (n = 12) was given 1.5 mg/kg diazepam IP and tested 20 min later.

For testing, the animal was taken from the home cage and placed on the hole board for 5 min. The number of head dips (exploration), number of squares visited (NSV) (with all four feet on one square), and number of rearings were counted.

After the hole board test, the animal was placed in the center of the plus-maze with its head facing the open arm for

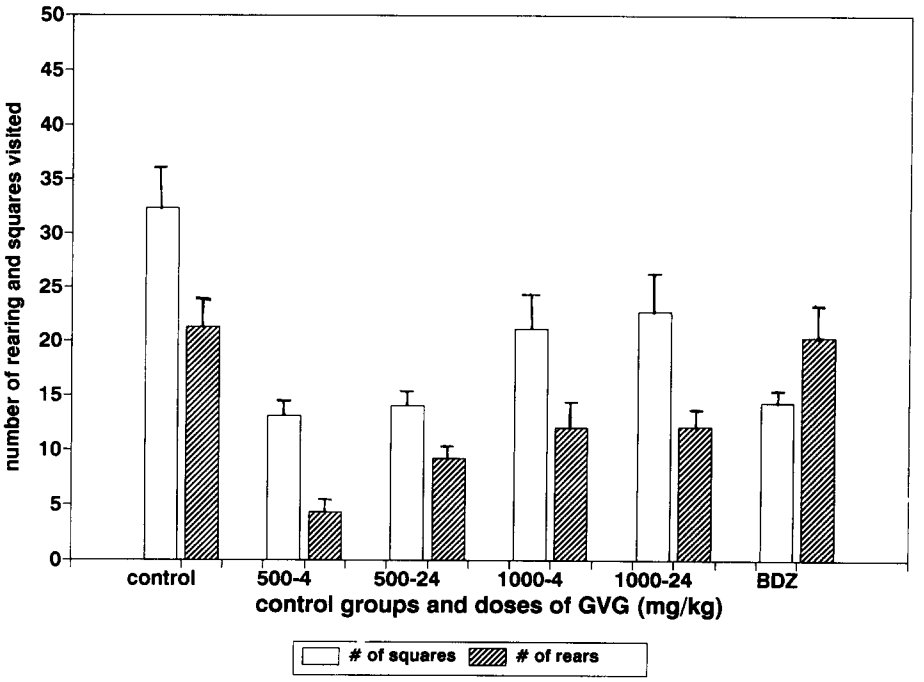

FIG. 1. Effect of GVG and diazepam on locomotor activity. Blank bars represent number of squares visited by the animal during a period of 5 min, hatched bars represent number of rears during the same period. Data are expressed as the mean ± SEM. 500-4 and 1,000-4 are the groups that received 500 and 1,000 mg/kg GVG, respectively, and were tested 4 h later; 500-24 and 1,000-24 are the groups that received 500 and 1,000 mg/kg GVG and were tested 24 h later. BDZ, diazepam (1.5 mg/kg, checked bars).

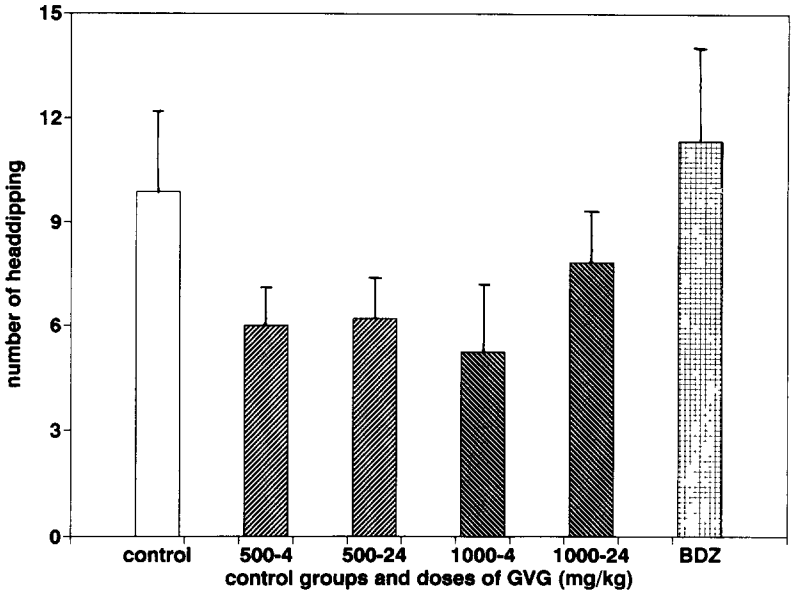

FIG. 2. Effects of GVG and diazepam on exploration measured by head dipping (mean ± SEM). The groups are the same as those in Fig. 1.

a period of 5 min. It was accepted on a certain arm when all four feet were on that arm. Indeed, it has been shown that anxiolytic drugs increase the time spent on open arms while anxiogenic drugs do the contrary (22,35,44).

An anxiety measure (AM) was computed according to the formula.

AM = (total time spent in open arms)/(total time spent in all arms).

Statistics

One-way analysis of variance (ANOVA) was used to evaluate motor activity, rearing, head dipping, and anxiety measures (PC/OXSTAT 1986). Posthoc Dunnett's procedure was used to compare group means with the control and Tukey's procedure was used to compare group means with each other. Data are expressed as the mean and SEM.

RESULTS

The effect of GVG on motor activity in terms of number of squares visited (NSV) and number of rearings during 5 min is given in Fig. 1. ANOVA for number of squares and number of rears yielded $F(5, 64) = 6.08$, $p < 0.01$, and $F(5, 64) = 7.79$, $p < 0.01$, respectively.

Control and experimental groups were compared with Dunnett's procedure. GVG decreased NSV in all groups; t-values (one tailed) for GVG 500-4 (I), GVG 500-24 (II), GVG 1,000-4 (III), GVG 1,000-24 (IV), and BDZ (V) are 4.37, 4.15, 2.62, 2.30, and 4.29, respectively ($p < 0.05$ for all). This shows that at all doses and times tested GVG caused a decrease in activity, as did diazepam. Tukey's test showed no differences between experimental groups.

GVG also decreased rearing in all GVG groups significantly (t-values: I = 5.1, II = 3.64, III = 2.9, IV = 2.92; $p < 0.05$), while diazepam was ineffective (t-value, V = 2.25, $p > 0.05$). Tukey's test showed the only significant difference between BDZ (V) and GVG-500 groups (I and II, $p < 0.05$).

Figure 2 shows the mean values of head dipping. ANOVA for head dipping yielded $F(5, 64) = 2.80$, $p < 0.05$. Neither Dunnett's nor Tukey's test showed any significant difference between experimental groups. GVG or BDZ did not affect exploration.

Figure 3 summarizes the average anxiety measures for each group. ANOVA for anxiety measures yielded $F(5, 64) = 25.57$, $p < 0.01$. Groups I and II were not different from control; however, groups III–V were significantly different from the control (t-values in Dunnett's procedure: III = 8.9, IV = 6.36, V = 8.9; $p < 0.05$). The same-dose GVG groups were not different from each other, but GVG-500 4-h and GVG-500 24-h groups were different from GVG-1,000 4-h and GVG-1,000 24-h groups, respectively ($p < 0.05$), while the BDZ group was also significantly different from GVG-500 groups but not from GVG-1,000 groups. This finding shows that 1,000 mg/kg GVG has anxiolytic activity of the same amplitude as diazepam after either period.

DISCUSSION

There are different reports about the effects of the GABAergic system on locomotor activity (LA) and exploration. Some of these studies focus on certain areas or nuclei treated with GABA agonists or antagonists microinjected locally, while others deal with the effects of systemic injection. In the substantia innominata/lateral preoptic area, which appears to be located between nucleus accumbens and motor areas of the brain—probably receiving GABAergic projection from nucleus accumbens—muscimol (GABA agonist) antagonized increased LA induced by non-NMDA receptor agonists; picrotoxin (GABA antagonist) increased LA (43,58). GABA was found to block the hyperrunning activity originating from ventromedial hypothalamus (70); intrahippocampal (dentate gyrus of dorsal hippocampus) injections of picrotoxin increased LA, while injection of GABA antagonized this reaction (46); picrotoxin and bicuculline microinjection into the ventral pallidum produced a dose-related hyperactivity, inter-

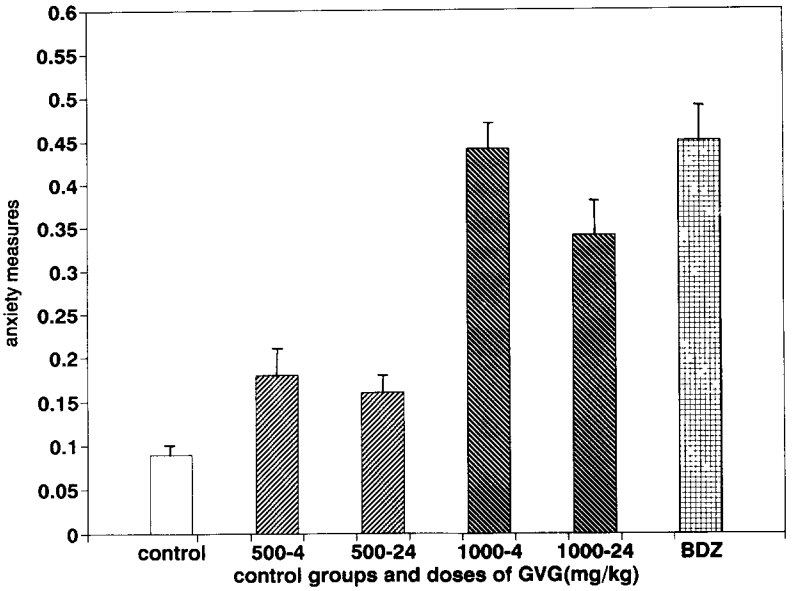

FIG. 3. Effects of GVG and diazepam on anxiety measures in each group in the elevated plus-maze (mean ± SEM). Anxiety measure is the ratio of the time spent on the open arm to the time spent in all arms. Note that the higher the anxiety measure the less anxious animals are.

acting with opioids (5). Microinjection of muscimol to median raphe was reported to increase LA (28); baclofen ($GABA_B$ receptor agonist) reduced locomotion, while THIP ($GABA_A$ receptor agonist) did not have any effect and a GABA-T inhibitor, τ-acetylenic acid (similar to GVG), decreased LA, implicating the more probable role of $GABA_B$ receptor in LA (2). Some researchers have found different results at different doses; File and Pellow mentioned a reducing effect of picrotoxin on head dipping and LA at 2 but not at 4 mg/kg (24); some GABA mimetics increased LA in low doses but decreased it in higher doses (66); systemic administration of muscimol caused inhibition of LA at high doses (higher than 1.5 mg/kg) but stimulated LA at low doses (0.025–1 mg/kg) (55,65), a finding still not explained. Many studies found that systemic administration of GABA mimetics, BDZs, and GABA-elevating agents decrease LA (23,39). This can be attributed to the muscle-relaxing effect of BDZs or striatonigral and striatopallidal GABAergic systems, where GABAergic interneurons play an inhibitory role, regulating the expression of locomotor behavior (54). However, LA is a resultant appearance of the function of many different systems and systemic injection of a certain agent can give only an overall idea about its effects on LA.

Our study, first, shows a correlation between rearing and moving in a novel environment ($r = 0.58$), that is, the more the animal walks the more it will rear. GVG injection at both doses, and also diazepam, decreased LA in terms of rearing and visiting the squares, consistent with previous findings (Fig. 1). However, Alvarez and Banzan (4) reported contrary results to ours; GABA and GVG injected into the hippocampus increased LA, while GABA depressed rearing and GVG increased it. Their findings are inconsistent with the other studies (5,23,28,39,43,46,58,70); the question that arises from their study is how GVG, as a GABA-elevating drug, can increase number of rearings, while GABA does the opposite at the same area of microinjection. Our observation [(52) and the present study] in rodents shows that GVG induces a dose-dependent reduction of activity, resulting in inactivity at higher doses, beginning from the fourth hour of injection and lasting for nearly 24–48 h.

We did not find any effect of the drug tested on head dipping; GVG and BDZ do not seem to affect exploration (Fig. 2). Van der Laan et al. (67) reported that four GABA-T inhibitors—GVG, τ-aminooxyacetic acid, γ-acetylenic acid, and ethanolamine-*O*-sulfate—decreased hole board exploration at higher doses; File et al. (25) found BDZ antagonists and β-carbolines to elevate exploratory head dipping in the hole board and concluded that picrotoxin decreased head dipping at low doses (24); Crawley (19) found contrary results, indicating that BDZs increase head dipping in the hole board. Alvarez and Banzan (4) reported that intrahippocampal GABA and GVG injection did not affect HD, similar to our findings. At the present time, it is not possible to make a clear correlation between exploratory behavior and the GABAergic system; the effect of GABAmimetic drugs may be two sided depending upon primarily possible influence on other targets, the site of application in the brain, and, of course, the probable alterations of the experimental conditions (i.e., temperature, season, humidity, food, etc).

GVG at a dose of 1,000 mg/kg has an anxiolytic effect nearly as marked as diazepam. Halonen et al. (32) reported that after a single dose of 1,000 mg/kg GVG GABA levels increased to 658% at 5 h and 1,349% at 24 h in the cisternal fluid of rats; our results did not show a time-dependent anxiolysis but dose dependency; further analysis may reveal more about the time-dependent effects of GVG, as it did in Gale and Iodorala's study (29). The latter implicated that the anticonvulsant and probably other effects of GABA are associ-

ated with its concentration in the nerve terminals and not that in cerebrospinal fluid or other compartments in that brain area.

The results from different types of animal tests of anxiety have identified anxiolytic and anxiogenic drugs acting on the BDZ-$GABA_A$ receptor complex (21,22). However, is it the GABAergic activity enhanced by BDZ that has this anxiolytic property or does BDZ have other effects different from those correlated with GABA? There are reports about BDZ subunits of the $GABA_A$ receptor that lack affinity for the $GABA_A$ site and may be responsible of BDZ's anxiolytic activity through a non-GABAergic mechanism (41). It has also been shown that BDZs provoke an allosteric modification of the $GABA_A$ recognition site that allows interaction between this site and endogenously released GABA, thus augmenting the individual molecular effects of GABA (31). Although muscimol and THIP (GABA agonists) given systemically do not exhibit anxiolytic activity (51), they are anxiolytic when administered into the ventricles (17,56). Moreover, sodium valproate, which elevates GABA levels like GVG, has a similar anticonflict effect (68) and the anticonflict effect of chlordiazepoxide and oxazepam are antagonized by picrotoxin at doses that do not modify unpunished responding (10). Furthermore, the anticonflict effect of diazepam is blocked by bicuculline ($GABA_A$ receptor antagonist) and thiosemicarbazide (GAD or GABA synthesis inhibitor) (71), and isoniazid, a GABA synthesis inhibitor, potentiates the anxiogenic effects of FG 7142, a β-carboline derivative that directly binds to the $GABA_A$ receptor with high affinity and reduces the functions of GABA-chloride ionophore in the brain (18). In concordance with our findings, treatment with the GABA-T inhibitor aminooxyacetic acid, having similar effects to GVG, potentiated the anticonflict properties of diazepam (42); also, sodium phenobarbital has anxiolytic action in the plus-maze, an effect reversed by pentylenetetrazol (a drug having antagonizing properties to the $GABA_A$ receptor) (37).

Taken together the above data implies that GABA and $GABA_A$ receptors carry one of the major roles in the mechanisms of anxiety, although baclofen (a $GABA_B$ agonist) is also mentioned to eradicate panic attacks in some clinical trials (12). Probably, there may be other indirect mechanisms where the GABAergic system is involved in the origins of anxiety states; for instance, the monoaminergic system has been emphasized because GABAergic neurons terminate on norepinephrine cells in the locus coeruleus and on serotonergic neurons in dorsal raphe, both of which exert strong anxiogenic reactions when stimulated, and inhibition of this system by means of GABAergic transmission has been shown to reduce anxiety (41). To elucidate our results, some questions may arise as to whether GABAergic transmission is enhanced if GABA levels increase at a certain area and whether this increased GABAergic tonus results in anxiolytic activity. From the studies cited above, GABAergic transmission is, at least, correlated with the concentration of GABA at a certain brain area. The agonists of $GABA_A$ receptors or BDZ agonists, binding to the α-subunit, and barbiturates, binding to the β-subunit, either increase the opening frequency of chloride channels or the probability of opening by activating endogenously released GABA (30), so it is questionable whether more GABA released will augment the anxiolytic activity with or without the agonist; with the agonist there are supporting studies that it does (37,42). Our study answers the latter question: The GABA increase elicited alone by GVG at a certain dose has an anxiolytic effect; thus, increased GABAergic transmission seems to result in reduction of anxiety. Therefore, it is worthwhile to conduct further clinical and experimental research about the behavioral effects of GABA-elevating agents, like vigabatrin.

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