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Some anticonvulsant drugs alter monoamine-mediated behaviour in mice in ways similar to electroconvulsive shock; implications for antidepressant therapy

A. Richard Green[1], Pauline Johnson, Judith A. Mountford & Vishwajit L. Nimgaonkar

MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE

1 The effects in mice of administration of the anticonvulsants, progabide, sodium valproate, diazepam, carbamazepine and phenytoin on 5-hydroxytryptophan (5-HTP)-induced head-twitch, apomorphine-induced locomotion, clonidine-induced sedation, and β-adrenoceptor and 5-HT_2 receptor number have been examined.

2 Repeated progabide administration (400 mg kg^{-1}, i.p. twice daily for 14 days) enhanced the head-twitch response the effect lasting for over 8 days after the last dose, and also increased 5-HT_2 receptor number in frontal cortex.

3 Progabide (400 mg kg^{-1}, i.p.) enhanced the head-twitch response when given once daily for 10 days and when given intermittently (5 times over 10 days) but not after 1 day of administration.

4 Repeated Na valproate (400 mg kg^{-1}, i.p.) also increased the 5-HTP-induced head-twitch response and 5-HT_2 receptor number in the frontal cortex when given twice daily for 14 days, but no behavioural enhancement was seen after 10 days' treatment.

5 Diazepam (1.25 mg kg^{-1}, i.p.) twice daily for 14 days increased the head-twitch response and 5-HT_2 receptor number.

6 Repeated progabide and valproate (but not diazepam) administration attenuated the sedation response to the α_2-adrenoceptor agonist, clonidine (0.15 mg kg^{-1}) but neither drug altered β-adrenoceptor number in the cerebral cortex.

7 No changes in apomorphine-induced locomotor behaviour were seen after progabide, valproate or diazepam.

8 Repeated carbamazepine (20 mg kg^{-1}) or phenytoin (40 mg kg^{-1}) administration failed to alter any of the biochemical or behavioural parameters listed above.

9 Like repeated electroconvulsive shock (ECS), progabide altered the head-twitch response, clonidine-induced sedation response and 5-HT_2 receptor number. Unlike repeated ECS, it did not alter β-adrenoceptor number or the apormorphine-induced locomotor response. These data suggest that ECS may produce some changes in monoamine function by altering GABA metabolism as has previously been postulated.

Introduction

Repeated administration of electroconvulsive shock (ECS) to rodents results in their displaying altered behavioural responses to monoamine agonists. Rats show an enhanced hyper-activity response to 5-hydroxytryptamine (5-HT) agonists whilst mice show an increased head-twitch response (Evans *et al.*, 1976; Green *et al.*, 1977; Lebrecht & Nowak 1980; Green *et al.*, 1983b).

There is an increase in 5-HT_2 receptor number after repeated ECS (Kellar *et al.*, 1981; Vetulani *et al.*, 1981) which appears to be responsible for the enhanced behavioural response (Green *et al.*, 1983a).

Mice and rats also show an enhanced locomotor response to dopamine agonists (Modigh, 1975; Evans *et al.*, 1976; Deakin *et al.*, 1981) although there does not appear to be any change in dopamine receptor number or dopamine-sensitive adenylate cyclase activity (Green *et al.*, 1977; Bergstrom & Kellar, 1979; Deakin *et al.*, 1981).

[1]Correspondence

With regard to noradrenaline function two major changes have recently been observed. Firstly, in common with many other antidepressant treatments, repeated ECS administration decreases β-adrenoceptor number (Bergstrom & Kellar, 1979; Deakin *et al.*, 1981) and noradrenaline-sensitive adenylate cyclase activity (Vetulani *et al.*, 1976). Secondly, it attenuates both the sedation response of rodents to the α_2-adrenoceptor agonist clonidine and the decrease in brain 3-methoxy-4-hydroxyphenylglycol sulphate (MOPEG-SO_4) concentration produced by this drug (Heal *et al.*, 1981), suggesting a decrease in the function of the, possibly, presynaptic α_2-adrenoceptors in the brain. Again, similar findings have been reported after administration of various other antidepressant treatments (Sugrue, 1982; Heal *et al.*, 1983; Green & Nutt, 1983; 1985).

Following a seizure there is a marked rise in seizure threshold and pharmacological analysis suggests that the mechanism of this change involves an increase in γ-aminobutyric acid (GABA) function (Nutt *et al.*, 1981). There is also an increase in GABA concentration and decrease in GABA synthesis in specific brain regions following repeated ECS (Green *et al.*, 1978; Bowdler *et al.*, 1983) and drug treatments given with the ECS which prevented this rise in GABA concentration prevented the enhancement of 5-HT- and dopamine-mediated behaviour (Green *et al.*, 1982). These findings raised the possibility that administration of drugs which raised seizure threshold by increasing GABA function might produce the changes in monoamine-mediated behaviour associated with repeated ECS. Since the alterations of monoamine function produced by repeated ECS might be involved in the therapeutic response to electroconvulsive therapy, such an approach raises the possibility of a pharmacological treatment of depression having the high degree of efficacy of ECT but with, it is to be hoped, fewer side effects and greater ease of administration.

The current investigation describes an attempt at using various anticonvulsant drugs, some of which are thought to be GABA-mimetic, to produce some of the biochemical and behavioural changes seen after repeated ECS.

Methods

Animals and drug administration

Male C57/B1/6 mice (Olac, Bicester) were used in all studies. They were housed in groups in conditions of constant temperature (21°C) and controlled lighting (light period 07 h 00 min–19 h 00 min) and fed an *ad libitum* diet of modified 41B pellets and tap water.

The drugs were all given intraperitoneally as follows: progabide (400 mg kg^{-1}, twice daily, except where stated otherwise) suspended in 0.9% w/v saline with 2 drops of tween 40; sodium valproate (400 mg kg^{-1}, twice daily) dissolved in saline; phenytoin (40 mg kg^{-1}, once daily, as the commercial preparation 'Epanutin', Parke Davis); diazepam (1.25 mg kg^{-1}, twice daily, as the commercial preparation 'Valium', Roche Products); carbamazepine (20 mg kg^{-1}, once daily) suspended in 0.9% w/v saline containing 1% w/v carboxymethylcellulose. The doses chosen were those previously shown to be anticonvulsant to chemically or electrically induced seizures (see Nutt *et al.*, 1981) and drugs were given twice daily when there were good indications for rapid metabolism of the drug and no problems with toxicity. Control animals were given the appropriate vehicle in each case.

Monoamine-mediated behavioural studies

These were performed exactly as described in our earlier studies. Briefly, 5-HT-mediated responses were examined by administration of carbidopa (25 mg kg^{-1}, i.p.) followed 30 min later by L-5-hydroxytryptophan (5-HTP; 100 mg kg^{-1}, i.p.). The resultant head-twitches were counted over a 2 min period 30 min after the 5-HTP (see Green *et al.*, 1983b). Dopamine-mediated behaviour was examined by measuring the locomotor response on LKB Animex meters of pairs of mice following administration of apomorphine (1 mg kg^{-1}, i.p.) (see Green *et al.*, 1983b). The clonidine-induced sedation response was determined by measuring a group of behavioural changes at 10 min intervals in the 60 min following injection of clonidine (0.15 mg kg^{-1}, i.p.) as described in Heal *et al.* (1981; 1983). In all cases, where practical, the observer and rater was unaware of the previous drug treatment of the animals. Studies on a particular treatment were always performed concurrently with the appropriate control as behavioural scores do change slightly from experiment to experiment.

Radioligand-receptor binding

5-HT_2 receptor binding studies were performed essentially by the method of Rosenfeld & Makman (1981) using [^{3}H]-spiperone (NEN; specific binding activity 26.3 μCi $mmol^{-1}$) as the radioligand and lysergic acid diethylamide (LSD) (1 μM, Sandoz Pharmaceuticals, Felham) as the displacing agent for the measurement of non-specific binding. Frontal cortex tissue from four mice isolated by the method of Bacopoulos (1981) was homogenized in Tris buffer (pH 7.2) using a motor-driven Teflon homogenizer. Both total and non-specific binding was measured in triplicate. Saturation binding curves used radioligand concentrations ranging from 0.3 nm to 5.0 nm. Scatchard

analysis of the data was performed using linear regression analysis on 6 observation points by the method of least squares. Results given are for at least three separate experiments.

For analysis of β-adrenoceptor number, the cerebral cortices minus the frontal cortex from three mice were dissected out on ice and homogenized in Tris Isosaline (Tris HCl 20 mM, sodium chloride 0.9%, pH 7.5), at a concentration of 20 mg wet weight ml^{-1}, using ten strokes of a motor-driven Teflon pestle. The suspension was centrifuged at 18000 *g* for 10 min, and the supernatant discarded. Membranes were resuspended in the buffer at a concentration of 13 mg (wet weight) ml^{-1} and 350 μl of this suspension incubated in triplicate with 50 μl [^{3}H]-dihydroalprenolol (NEN; specific activity 104.8 Ci $mmol^{-1}$) (concentration 0.5 nM–5nM), 50 μl 5′-guanylylimidodiphosphate (final concentration 300 nM) and 50 μl sodium metabisulphite (final concentration 0.2 mM) or 50 μl L-isoprenaline hydrochloride (final concentration 10 μM, dissolved in 0.2 mM sodium metabisulphite). The membranes were incubated for 30 min at 37°C and the incubation then terminated by rapid filtration using Whatman GF/B filters, followed by three 5 ml washes of the filters. Scatchard analysis was performed as described above. Because of the variation in B_{max} and K_D which can occur as the result of differences in batches of radioligand and other variations in the methodology, control animals were always treated and analysed at exactly the same times as the experimental groups.

Drug sources

Drugs were obtained from the following sources (in parentheses): progabide (Synthélabo, Paris), sodium valproate (Sanofi, Stockport, Cheshire), carbamazepine (Geigy, Macclesfield, Cheshire), diazepam ('Valium', Roche Products, Welwyn, Hertfordshire), phenytoin ('Epanutin', Parke-Davies, Hounslow, Middlesex), apomorphine (MacFarlan Smith, Edinburgh), 5-HTP (Sigma, Poole, Dorset), carbidopa (Merck, Sharp & Dohme, Hoddesdon, Hertfordshire), clonidine (Boehringer-Ingelheim,

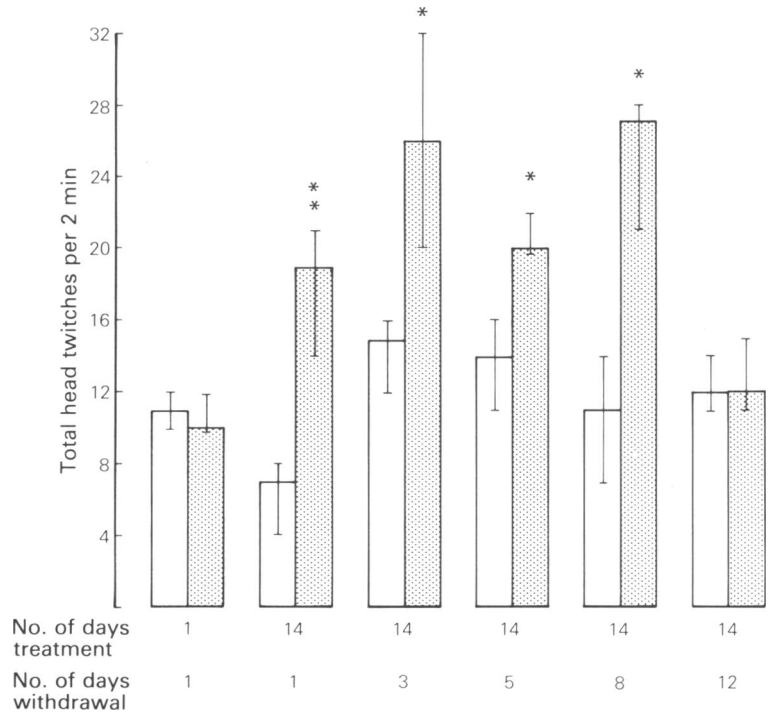

Figure 1 The effect of progabide on 5-hydroxytryptophan (5-HTP)-induced head-twitch behaviour in mice. Mice were administered progabide (400 mg kg^{-1}, i.p.) twice daily for either 1 or 14 days. Twenty-four hours or longer after the last dose they were injected with carbidopa (25 mg kg^{-1}, i.p.) and 5-hydroxytryptophan (100 mg kg^{-1}, i.p.) and the number of head-twitches counted in a 2 min period 30 min after 5-HTP. Results show the median number of head-twitches and bars the interquartile ranges in control (vehicle-injected: open columns) and experimental groups (stippled columns) ($n = 5$ or greater) after 1 day of administration and at various times after the last of 14 days' treatment. Different from appropriate control: $^*P < 0.05$; $^{**}P < 0.01$.

Bracknell, Berkshire), lysergic acid diethylamide (Sandoz, Feltham).

Statistics

Head-twitch and sedation scores were analysed by use of Mann Whitney rank order tests for non-parametric data. Locomotor activity results and biochemical data were analysed by use of Student's *t* test (unpaired).

Results

Effect of progabide on 5-hydroxytryptophan-induced head-twitch

Mice were injected with progabide (400 mg kg^{-1}) twice daily (09 h 00 min and 16 h 00 min) for 14 days. Twenty-four hours after the last dose the 5-HTP-induced head-twitch response was greatly enhanced (Figure 1). No enhancement was seen 24 h after one day's treatment (Figure 1). When mice were treated for 14 days and tested at various times after the last dose, enhancement of the head-twitch response was seen 3, 5 and 8 days later, but not 12 days after the last dose of progabide (Figure 1).

Enhanced 5-HT-mediated behaviour can be seen after ECS has been given either daily for 10 days or 5 times spread out over 10 days (Costain *et al.*, 1979). We therefore next examined the effects of progabide given over 10 days. An enhanced 5-HTP-induced head-twitch response was also seen 24 h after progabide had been given twice daily for 10 days, once daily for 10 days, and when given 5 times over 10 days (Mon, Wed, Fri, Mon, Wed) (Figure 2).

Table 1 Activity response of mice to apomorphine (1 mg kg^{-1}) following repeated administration of three anticonvulsant drugs

Injected	*Total activity counts per 40 min*
Control	798 ± 254 (4)
Progabide	469 ± 105 (4)
Control	1018 ± 313 (4)
Na valproate	1053 ± 354 (4)
Control	523 ± 82 (4)
Diazepam	500 ± 79 (4)

Mice were given progabide (400 mg kg^{-1}), Na valproate (400 mg kg^{-1}) or diazepam (1.25 mg kg^{-1}) twice daily for 14 days or appropriate vehicle. On day 15 they were given apomorphine (1 mg kg^{-1}, i.p.) and the locomotor response of pairs of mice measured during the next 40 min. Results expressed as mean ± s.e. mean with number of experiments in parentheses. No significant changes were observed between experimental and control groups.

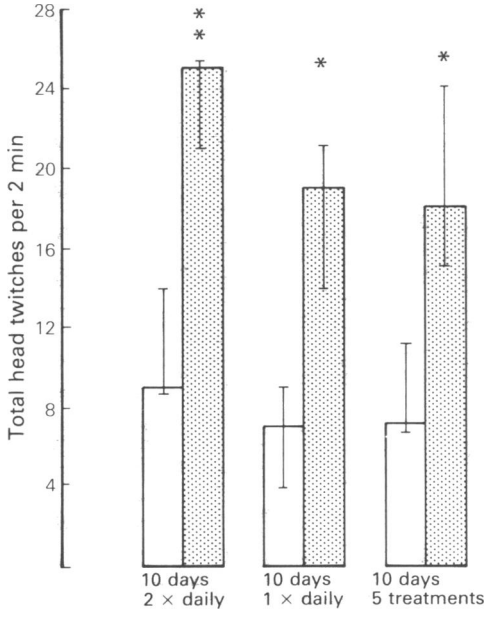

Figure 2 Effect of progabide administration on 5-hydroxytryptophan (5-HTP)-induced head-twitch. Mice were treated for 10 days with progabide (400 mg kg^{-1}, i.p.) either twice daily, once daily or 5 times over the 10 days, and the head-twitch behaviour assessed 24 h after the last dose as described in Methods and caption to Figure 1. Results show median head-twitch and bars the interquartile ranges in vehicle (open columns) and progabide (stippled columns) treated groups of at least 8 animals per group. Different from control: $*P<0.05$; $**P<0.01$.

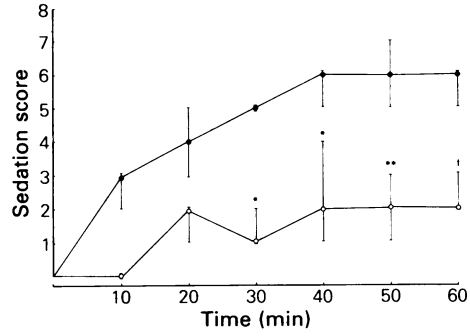

Figure 3 Effect of progabide (400 mg kg^{-1}, i.p.) twice daily for 14 days (○) or saline (●) on the sedation response to clonidine (0.15 mg kg^{-1}, i.p.) in mice. The sedation response was measured as described in the Methods section. Points show median sedation response and bars the interquartile ranges. Different from the vehicle-treated mice at the same time point: $*P<0.05$; $\dagger P<0.025$; $**P<0.01$, with at least 8 mice in each group.

Table 2 Characteristics of the 5-hydroxytryptamine$_2$ (5-HT$_2$) receptor in frontal cortex and β-adrenoceptor in the rest of the cerebral cortex following repeated administration of three anticonvulsant drugs to mice

	5-HT$_2$ receptor			*β-Adrenoceptor*		
	B_{max}	K_D	n	B_{max}	K_D	n
Control	188 ± 8	2.40 ± 0.32	4	64.7 ± 1.0	0.78 ± 0.09	4
Progabide	253 ± 9**	1.47 ± 0.34	4	57.2 ± 6.0	0.97 ± 0.20	4
Control	243 ± 8	1.95 ± 0.60	4	75.0 ± 3.6	1.08 ± 0.19	4
Na valproate	343 ± 35*	1.98 ± 0.02	3	68.9 ± 4.1	0.88 ± 0.08	4
Control	216 ± 12	2.12 ± 0.34	3	–	–	
Diazepam	314 ± 13*	1.85 ± 0.42	3	–	–	

β-Adrenoceptor characteristics were measured using [^{3}H]-dihydroalprenolol binding and 5-HT$_2$ receptor characteristics using [^{3}H]-spiperone. Mice were treated twice daily with progabide (400 mg kg^{-1}), sodium valproate (400 mg kg^{-1}), or diazepam (1.25 mg kg^{-1}), or appropriate vehicle for 14 days. Twenty-four hours after the last dose binding was performed on frontal cortex. Results are expressed as mean ± s.e. mean with number of Scatchard analysis determinations shown (*n*). Different from appropriate control: $*P<0.05$; $**P<0.01$. B_{max} expressed in fmol mg^{-1} protein and K_D in nM.

Effect of progabide on apomorphine-induced locomotion and clonidine-induced sedation

Administration of progabide (400 mg kg^{-1}) twice daily for 14 days did not affect the apomorphine-induced locomotor response 24 h after the last dose (Table 1). However, this treatment did result in a marked attenuation of the sedative response to clonidine (0.15 mg kg^{-1}, i.p.) over the 60 min period following administration of the α_2-adrenoceptor agonist (Figure 3).

Effect of progabide on 5-hydroxytryptamine$_2$ receptor and β-adrenoceptor number

Twenty-four hours after the last injection of progabide (400 mg kg^{-1}, twice daily for 14 days) the mice were killed and the cerebral cortex was dissected for measurement of the 5-HT$_2$ receptor or β-adrenoceptor binding characteristics. Progabide administration increased the number of 5-HT$_2$ receptor sites (B_{max}) in the frontal cortex but produced no change in the dissociation constant (K_D) (Table 2). In contrast, no

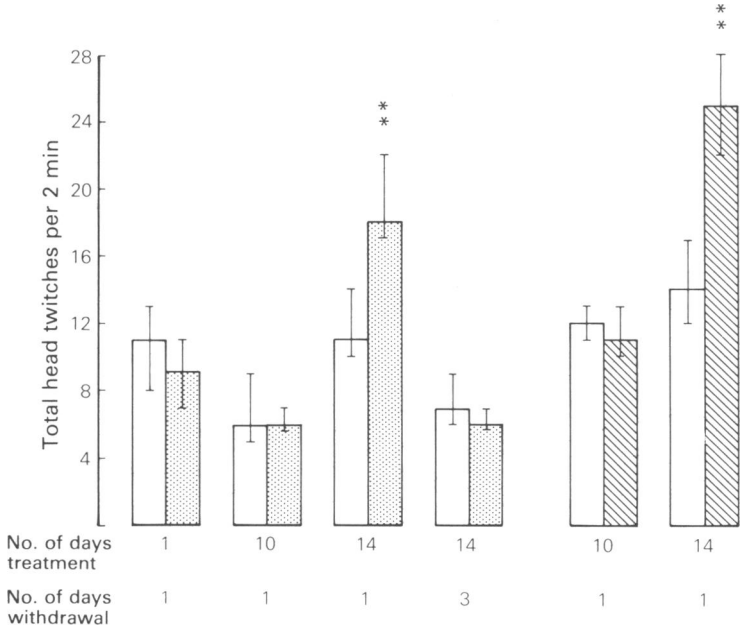

Figure 4 Effect of valproate (400 mg kg^{-1} i.p., stippled columns) or diazepam (1.25 mg kg^{-1} i.p., hatched columns) given twice daily for 1, 10 or 14 days on the head-twitch response following carbidopa and 5-hydroxytryptophan. Methods as described in the Methods section and caption to Figure 1. Points show median sedation response and bars the interquartile ranges. Different from appropriate control: $**P<0.01$; with at least 8 mice in each group.

changes were found in β-adrenoceptor number or affinity in the rest of the cortex (Table 2).

Effect of sodium valproate 5-hydroxytryptophan-induced head-twitch

Sodium valproate (400 mg kg^{-1}) was given twice daily for 14 days. Twenty-four hours after the last dose the mice showed enhanced 5-HTP-induced head-twitch response compared with the saline-injected controls (Figure 4). No enhancement was seen after either 1 or 10 days' administration or 3 days after the last dose of 14 days' treatment (Figure 4).

Effect of sodium valproate on apomorphine-induced locomotion and clonidine-induced sedation

Mice were injected with valproate for 14 days as described above. Twenty-four hours after the last dose they displayed the same locomotor response to apomorphine (1 mg kg^{-1}) as the control animals (Table 1) but showed a markedly decreased sedation response to clonidine (0.15 mg kg^{-1}) (Figure 5).

Effect of sodium valproate on 5-hydroxytryptamine$_2$ receptor and β-adrenoceptor number

After 14 days' treatment with valproate there was an increase in the number of 5-HT$_2$ receptor binding sites in frontal cortex but no change in the affinity (Table 2). There was no difference in the binding characteristics of the β-adrenoceptors in the frontal cortex (Table 2).

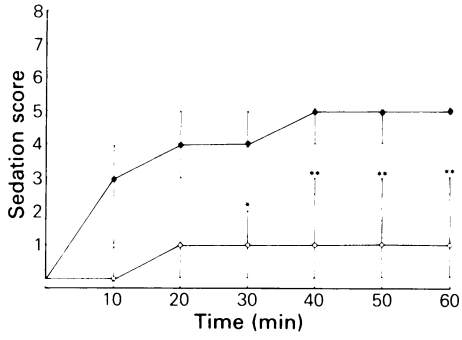

Figure 5 Effect of valproate (400 mg kg^{-1}, i.p.) twice daily for 14 days (○) or saline (●) on the sedation response to clonidine (0.15 mg kg^{-1}, i.p.) in mice. The sedation response was measured as described in the Methods section. Points show median sedation response and bars the interquartile ranges. Different from the vehicle-treated mice at the same time point; $*P<0.05$; $**P<0.001$, with at least 8 mice in each group.

Effect of carbamazepine and phenytoin on 5-hydroxytryptophan-induced head-twitch and clonidine-induced sedation.

Mice were injected with either carbamazepine (20 mg kg^{-1}) or phenytoin (40 mg kg^{-1}) daily for 14 days. Twenty-four hours after the last dose they were injected with carbidopa and 5-HTP and the subsequent head-twitch response measured. Neither drug altered the head-twitch response compared with the appropriate vehicle-treated animals (Table 3) nor did either drug alter the sedation response following clonidine (Table 3).

Effect of diazepam on 5-hydroxytryptophan-induced head-twitch

Mice were given diazepam (1.25 mg kg^{-1}) twice daily for 14 days. Twenty-four hours after the last dose the diazepam-treated mice showed an enhanced response compared with the vehicle-treated animals (Figure 4). No difference between the head-twitch responses of control and diazepam-treated mice was observed when the diazepam was given twice daily for 10 days' (Figure 4).

Table 3 5-Hydroxytryptamine (5-HT)-mediated head-twitch response and clonidine-induced sedation score in mice given repeated doses of carbamazepine, phenytoin or diazepam

	Median number of head-twitches per 2 min	*Mean total sedation score per 60 min*
Control	9 [7–12] (7)	19.1 (8)
Carbamazepine	11 [6–14] (8)	18.8 (8)
Control	7 [5–7] (10)	27.3 (8)
Phenytoin	8 [8–13] (9)	25.1 (8)
Control	13 [10–15] (8)	28.4 (8)
Diazepam	24 [19–27] (10)*	28.2 (8)

Mice were injected for 14 days with either carbamazepine (20 mg kg^{-1}), or phenytoin (40 mg kg^{-1}) once daily, daizepam (1.25 mg kg^{-1}), twice daily, or appropriate vehicle. On day 15 the head-twitch response was measured following carbidopa/5-HTP (see Methods) or the sedation response following clonidine (0.15 mg kg^{-1}) (see Methods). Results show median head-twitch response over a 2 min period 30 min after 5-HTP with the inter-quartile range in square brackets, or the mean sedation score determined by additions of the mean sedation score of each 10 min observation during 60 min (see, for example, Figure 3 for a typical control response). Number of observations for each determination shown in parentheses. There were no significant differences between control and experimental groups in any experiment except the head-twitch response after diazepam.

Effect of diazepam on apomorphine-induced locomotion and clonidine-induced sedation

Fourteen days' treatment with diazepam ($1.25\ mg\ kg^{-1}$, twice daily) failed to alter the response of the mice either to apomorphine (Table 1) or clonidine (Table 3).

Effect of diazepam on 5-hydroxytryptamine$_2$ receptor binding

Repeated (twice daily for 14 days) treatment with diazepam ($1.25\ mg\ kg^{-1}$) produced a significant increase in 5-HT$_2$ receptor number in the frontal cortex but no change in the dissociation constant (Table 2).

Discussion

Effects of anticonvulsants on monoamine biochemistry and function

Perhaps the first comment to be made is that we acknowledge that high doses were used in this study. They were chosen as they are doses which have been used to demonstrate the anti-convulsant action of the drugs (Nutt *et al.*, 1981). However, further investigation is clearly necessary to establish whether lower doses produce similar changes. The indications with progabide are clearly that they will, given that intermittent dosing (5 doses of $400\ mg\ kg^{-1}$, spaced over 10 days) had an effect on the head twitch response. One major investigation of progabide showed that it had remarkable specificity for the GABA receptor (Lloyd *et al.*, 1982) and data obtained in the current study will, therefore, be discussed in the light of this observation.

As mentioned above, of the various drugs examined, progabide produced the most pronounced changes in monoamine function insofar as it altered 5-HT-mediated behaviour even when given intermittently and progabide-induced changes will, therefore, be discussed in the greatest detail.

Progabide is a specific GABA-mimetic drug. It is metabolized to the corresponding acid and both progabide and the acid can be metabolized to form GABA in the brain (Worms *et al.*, 1982) as well as the acid having GABA receptor agonist properties itself (Lloyd *et al.*, 1982). Following repeated administration of this drug over 14 days the 5-HTP-induced head-twitch response was increased. This change could also be elicited by 10 days' drug administration and even when the drug was given just 5 times over 10 days, even though this drug has a short half-life (Worms *et al.*, 1982). In this regard it showed a similar profile to repeated ECS which enhances 5-HT-mediated behaviour in mice not only when given daily but also when given 5 times over 10 days (Lebrecht & Nowak, 1980; Green *et al.*, 1983b). A further similarity came with the observation that repeated progabide administration increased the number of 5-HT$_2$ binding sites, since this also occurs after repeated ECS (Vetulani *et al.*, 1981; Kellar *et al.*, 1981; Green *et al.*, 1983a) and data suggest that the increased behaviour response and increased in 5-HT$_2$ receptor number are associated (Green *et al.*, 1983a). An increase in 5-HT$_2$ receptor number in frontal cortex after repeated progabide administration has also been reported to occur in rats (Langer *et al.*, 1984).

Previous studies have demonstrated that a single ECS increases GABA concentration in specific brain regions (Bowdler & Green, 1982), increases GABA function and raised seizure threshold (Nutt *et al.*, 1981). Progabide injection produces the same changes (Worms *et al.*, 1982) and it is therefore possible that repeated progabide alters GABA function in the same way as repeated ECS, although this has yet to be studied. Certainly, the indications are that blocking the change in GABA concentration which occurs after repeated ECS prevents the changes in monoamine function (Green *et al.*, 1982) and therefore changes in GABA function occurring in specific brain regions after repeated ECS may be associated with changes in monoamine function.

Progabide does decrease 5-HT synthesis in specific brain regions both following acute and longer term administration (Scatton *et al.*, 1982; Langer *et al.*, 1984). It is possible that the enhanced behaviour and [^{3}H]-spiperone binding result from a decrease in synthesis leading to an increase in postsynaptic receptor number, and while Evans *et al.* (1976) and Modigh (1976) were unable to detect a change in the rate of 5-HT synthesis in whole brain 24 h after repeated ECS, a decrease was observed after a single seizure (Evans *et al.*, 1976) analogous to that observed after progabide.

A further change produced by progabide was the attenuation of the sedative response to clonidine. This behaviour has been linked to presynaptic α_2-adrenoceptor function (Drew *et al.*, 1979; Heal *et al.*, 1981) and the attenuation of the sedation may reflect a decrease in α_2-adrenoceptor number resulting from an increase in noradrenaline turnover (and release) caused by progabide and for which there is some evidence (Scatton *et al.*, 1982). However, no evidence was found for a change in β-adrenoceptor number which might also have been expected to occur, although evidence is now accumulating that this change, at least following antidepressant drugs, is not simply a consequence of an increase in synaptic cleft noradrelanine concentration (Brunello *et al.*, 1982; Janowsky *et al.*, 1982). Langer and colleagues (1984) have also observed that β-adrenoceptor number does not change in the frontal cortex of rats after repeated progabide administration.

Interestingly, whilst acute progabide administration

alters dopamine metabolism (Scatton *et al.*, 1982), longer term administration failed to alter dopamine-mediated behavioural responses. In this regard, progabide is quite different from repeated ECS which markedly enhances dopamine-mediated behaviour (Modigh, 1975; Evans *et al.*, 1976; Green *et al.*, 1983b).

Valproate administration produced the same changes in monoamine function as those seen after progabide although the changes might be said to be less robust, the administration having to be more often and for longer to produce the 5-HT change at least, although again like progabide it has a short half-life in plasma (Nau & Löscher, 1982). Like progabide, valproate can also produce a rapid and modest increase in GABA concentration (see, for example, Nau & Löscher, 1982) and has also been reported to decrease GABA synthesis (Cremer *et al.*, 1978). The much greater effect of progabide may reflect the GABA-mimetic properties of the drug which valproate does not possess.

To our knowledge this is the first report that a benzodiazepine, following repeated administration, enhances 5-HT-mediated head-twitch and increases 5-HT_2 receptor number. Benzodiazepines have been reported both to decrease 5-HT synthesis (Biswas & Carlsson, 1977; Saner & Pletscher, 1979) and decrease 5-HT utilization (Pratt *et al.*, 1984) and for the reasons discussed earlier, this may be the reason for the longer term changes in postsynaptic 5-HT function. Diazepam did not, however, change the clonidine sedation response. Whilst benzodiazepines, like progabide and valproate, are anticonvulsant and enhance GABA function, they do not do so by altering GABA concentration or metabolism (Costa, 1979).

Neither phenytoin nor carbamazepine are thought to produce their anticonvulsant effect through GABAergic mechanisms and neither altered the behaviours examined. However, it should be emphasized that data of this nature cannot be regarded as demonstrating a lack of effect with great authority since several doses and times of administration should be examined.

Implications for the action of antidepressant treatments

Repeated ECS increases 5-HT_2 receptor number, increases the head-twitch response and decreases clonidine-induced sedation (see Introduction) and progabide administration produced all of these changes. However, ECS also increases dopamine-mediated behaviour (Modigh, 1975; Evans *et al.*, 1976; Green *et al.*, 1983b) and decreases β-adrenoceptor number (Pandey *et al.*, 1979; Bergstrom & Kellar, 1979).

The relevance of the enhanced head-twitch response to the antidepressant effect of ECS is unclear since many antidepressant drugs decrease this behavioural change (Ogren *et al.*, 1979; Goodwin *et al.*, 1984). Furthermore, diazepam, which is not an antidepressant, has now also been found to increase the head-twitch response and [^{3}H]-spiperone binding, thereby tending to rule out a crucial role for this change in any antidepressant effect. One could argue that since diazepam and ECS have this effect in common, ECS might have a specific anxiolytic action. However, a recent investigation did not demonstrate this (File & Green, 1984).

A decrease in the clonidine-induced sedation response has been observed with several antidepressant treatments (Heal *et al.*, 1981; 1983, and references therein); however, β-adrenoceptor number also decreases with most antidepressant treatments, whilst others decrease noradrenaline-sensitive adenylate cyclase activity (see Green & Nutt, 1983 for review) and progabide did not produce either change (this paper; Zivcovic *et al.*, 1982; Langer *et al.*, 1984). Such observations become important in any theories on antidepressant drug action if the preliminary evidence that progabide is an antidepressant (Lloyd *et al.*, 1983) is strengthened.

There are clearly many questions remaining unanswered in this study. However, progabide is a most useful tool in the continuing investigations into the mode of action of ECS and other antidepressant treatments.

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