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Hypothermia induced by baclofen, a possible index of $GABA_B$ receptor function in mice, is enhanced by antidepressant drugs and ECS

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1 Intraperitoneal injection to mice of the γ-aminobutyric $acid_B$ ($GABA_B$) receptor agonist (±)-baclofen induces a dose-dependent decrease in rectal temperature.

2 Injection of (−)-baclofen intracerebroventricularly at doses that had no effect when given peripherally induced a marked hypothermia. (+)-Baclofen was without effect.

3 The decrease in rectal temperature induced by (−)-baclofen when injected intraperitoneally was highly correlated with an increase in sedation.

4 Repeated administration of amitriptyline (10 mg kg^{-1} daily for 14 days) resulted in mice displaying an enhanced temperature and sedation response to injection of (±)-baclofen (5 mg kg^{-1}) 24 h after the last dose of antidepressant.

5 An enhanced hypothermic response was also seen following repeated administration of zimeldine, mianserin or desipramine (all 10 mg kg^{-1} daily for 14 days) or repeated electroconvulsive shock (ECS; 5 ECS over 10 days) 24 h after the last treatment.

6 A single administration of any of the antidepressant drugs or ECS or repeated administration of the anxiolytic drug flurazepam (20 mg kg^{-1} daily for 14 days) did not alter the baclofen-induced hypothermic response.

7 Administration of (±)-baclofen (5 mg kg^{-1}) daily for 5 or 14 days attenuated the baclofen-induced hypothermic response. However, one pretreatment dose did not alter the response.

8 It has previously been reported that repeated baclofen administration decreases $GABA_B$ receptor number in the brain while repeated administration of antidepressant drugs and ECS increases the density of this receptor. The current data therefore suggest that baclofen-induced hypothermia may provide a simple index of $GABA_B$ receptor function in the brain and strengthens the evidence that $GABA_B$ receptor function is enhanced by antidepressant drugs and ECS.

Introduction

γ-Aminobutyric acid (GABA) receptors in the brain have been classified as $GABA_A$ and $GABA_B$. The $GABA_A$ receptor is linked to the benzodiazepine-chloride ionophore receptor complex and is antagonized by bicuculline (see Paul *et al.*, 1981) while the $GABA_B$ receptor is insensitive to bicuculline and baclofen is a selective agonist at the site (Bowery *et al.*, 1980).

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Recently Lloyd and colleagues (1985) have reported that the number of $GABA_B$ receptors in the frontal cortex of rats is increased following repeated administration of a diverse range of antidepressant drugs or electroconvulsive shocks (ECS). A similar increase in $GABA_B$ receptor density has also been observed in mouse frontal cortex following repeated amitriptyline administration (Suzdak & Gianutsos, 1986). However it should also be noted that Cross & Horton (1986) have been unable to confirm a change in $GABA_B$ receptor density following desipramine or zimeldine administration to rats.

Serrano *et al.* (1985) observed that large doses of GABA induced hypothermia in rats and that this

response was bicuculline-insensitive suggesting the possible involvement of a $GABA_B$ receptor.

Preliminary experiments in this laboratory demonstrated that baclofen produced a decrease in rectal temperature in mice. This paper describes the partial pharmacological characterization of this response and the effect upon it of administration of antidepressant drugs and ECS. Data suggest that this change might be useful as an *in vivo* index of the function of $GABA_B$ receptors and that the response is enhanced by administration of antidepressant treatments.

Methods

Male C57B16 mice (Olac, Bicester) were housed in groups of eight 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 41B pellets and tap water.

Measurement of temperature and sedation

Temperature was measured with a rectal probe inserted 2.5 cm and a digital thermometer, the mice being lightly restrained during measurement. All measurements were made in a room with an ambient temperature of 20°C ± 0.5°C. Since rectal temperature tends to rise after initial handling three measures were made at 5 min intervals, the third measure being taken as the first recorded measure prior to baclofen injection. Because the temperature response to baclofen tended to vary from experiment to experiment, every investigation of the response in treated animals was undertaken with a control group and a treatment group studied simultaneously.

Sedation was scored by measuring a group of behavioural changes (passivity, tactile responsiveness, posture, gait and body sag) on a 0–3 scale for each behaviour at 10 min intervals over a 60 min period. Results are given as the mean of the total score (maximum response being 15) at each observation time. This technique has been described in detail elsewhere (Heal *et al.*, 1981).

For measurement of sleeping time after pentobarbitone, mice were injected with sodium pentobarbitone (40 mg kg^{-1}) and the time taken from injection to loss of righting reflex measured. The animals were then laid on their backs and the time taken until they rolled over spontaneously and regained normal posture was measured (referred to as 'sleeping time').

Intracerebroventricular injection of baclofen and lesioning of 5-HT pathways in the brain

Baclofen was injected intracerebroventricularly (i.c.v.) by use of a stereotaxic apparatus recently described in detail elsewhere (Heal, 1984). Animals were briefly anaesthetized with halothane (ICI Pharmaceuticals) during the procedure.

Depletion of 5-hydroxytryptamine (5-HT) in the brain was similarly achieved by injection (i.c.v.) of 5,7-dihydroxytryptamine (5,7-DHT; 50 μg in 2 μl saline containing 0.1% ascorbic acid). This technique has previously been shown to deplete the content of 5-HT in the cortex by an average of 70% (Heal *et al.*, 1985).

Drugs and electroconvulsive shock administration

Drugs were obtained from the following sources (in parentheses). Amitriptyline (Merck, Sharp and Dohme, Hoddesdon), desipramine, (±)-baclofen, (−)-baclofen and (+)-baclofen (Ciba-Geigy, Horsham), mianserin (Organon, Oss, Holland), zimeldine (Astra Alab, Sodertalje, Sweden), sodium pentobarbitone (May and Baker, Dagenham), flurazepam (Roche Products, Welwyn Garden City), 5,7-dihydroxytryptamine (5,7-DHT; Sigma, Poole). All drugs were dissolved in 0.9% w/v NaCl (saline) and injected intraperitoneally, except where stated otherwise.

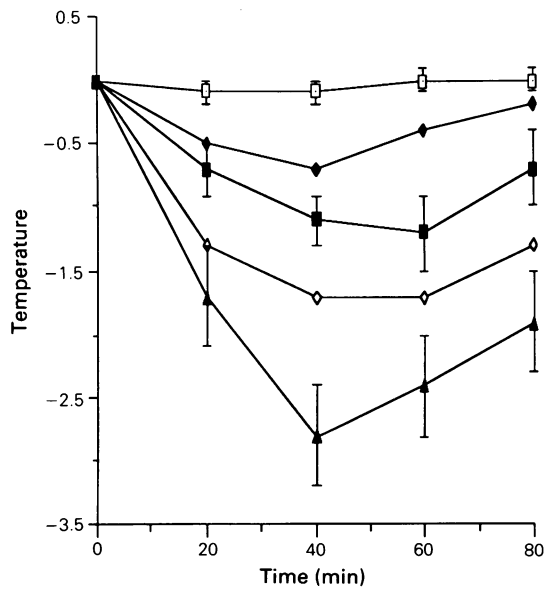

Figure 1 The effect of (±)-baclofen (2.5 − 10 mg kg^{-1}) on rectal temperature in mice. The mean response in the 60 min following intraperitoneal injection is shown after administration of saline (□); (±)-baclofen, 2.5 mg kg^{-1} (◆), 5 mg kg^{-1} (■), 7.5 mg kg^{-1} (◇) and 10 mg kg^{-1} (▲). Results shown as mean with s.d. shown by vertical lines except that some s.d. values have been omitted for clarity.

Electroconvulsive shocks were administered to animals anaesthetized with halothane through ear-clip electrodes by use of a Theratronics small animal electroplexy unit (90 V, 1 s, 50 Hz sinusoidal). Control animals received halothane alone. For repeated treatment, animals were given 5 ECS spread out over 10 days (Mon, Wed, Fri, Mon, Wed).

Statistics

Data were log transformed before subjection to 2-way analysis of variance (ANOVA).

Results

Effect of intraperitoneal injection of baclofen on rectal temperature

Injection of (±)-baclofen produced a dose-dependent decrease in rectal temperature with a nadir around 40 min after injection (Figure 1). Injection of (+)-baclofen (5 mg kg^{-1}) was without effect on rectal temperature (data not shown). The temperature change was always more variable than in our study on 8-OH-DPAT-induced hypothermia (Goodwin *et al*; 1985a), and varied somewhat from week to week. Control and treatment groups were therefore always studied simultaneously in subsequent experiments.

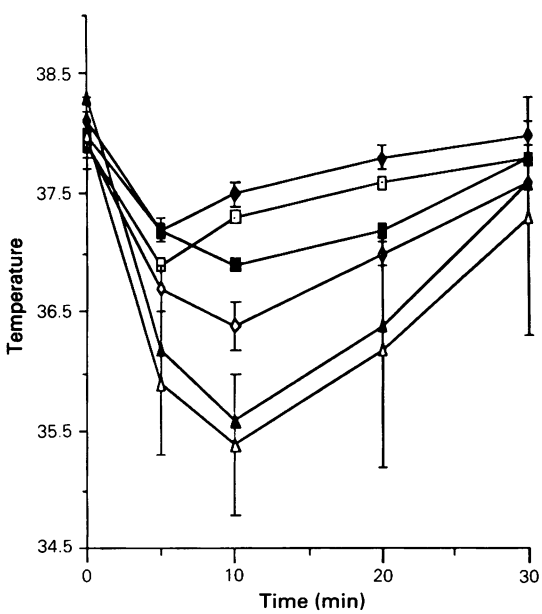

Figure 2 The effect of baclofen injected intracerebroventricularly on rectal temperature in mice. Results show the mean temperature with s.d. shown by vertical lines (some s.d. omitted for clarity) at various times following injection of saline (□); (+)-baclofen, 5 ng (◆); (−)-baclofen, 0.5 ng (■); 5 ng (◇); 20 ng (▲) and 50 ng (△), all given in 2 μl.

Effect of intracerebroventricular injection of baclofen on rectal temperature

Injection of saline (2 μl) intracerebroventricularly under anaesthesia induced a small decrease in rectal temperature in the 10 min immediately following administration. A similar small effect was observed following injection of (+)-baclofen (5 ng) (Figure 2). In contast (−)-baclofen injection produced a sustained and dose-dependent decrease in rectal temperature at doses from 0.5 ng–50 ng (Figure 2).

The sedative effect of baclofen

Injection (i.p.) of baclofen was observed to induce a sedation response somewhat similar to that observed after clonidine injection (see Heal *et al.*, 1981). It could be quantified readily by a behavioural assessment score of several parameters (see Methods and Heal *et al.*, 1981).

Following injection of (−)-baclofen (5 mg kg^{-1}), mice showed an increasing degree of sedation which coincided with the fall in rectal temperature (Figure 3a) and was correlated closely with it (Figure 3b). No sedation was observed after injection of (+)-baclofen (5 mg kg^{-1}).

Effect of a 5,7-DHT lesion on the baclofen-induced hypothermia

We have previously shown that hypothermia can be induced in mice by the 5-HT$_{1A}$ agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) and that this response is attenuated by a 5,7-DHT lesion (Goodwin *et al.*, 1986). Since baclofen can decrease 5-HT release in at last some regions of the brain (Bowery *et al.*, 1980; Schlicker *et al.*, 1984; Gray & Green, 1987a) we investigated whether baclofen was producing hypothermia through an action on presynaptic 5-HT function. Accordingly the effect of injection of (±)-baclofen (5 mg kg^{-1}) on rectal temperature was examined in mice where brain 5-HT content had been depleted by previous injection of 5,7-DHT (see Methods).

Baclofen injection produced a similar hypothermic response in both sham and 5,7-DHT lesioned mice (Table 1). In contrast, and in confirmation of earlier findings (Goodwin *et al.*, 1986a) hypothermia in the lesioned mice following 8-OH-DPAT (0.5 mg kg^{-1} s.c.) was markedly attenuated (Table 1), thereby confirming the effectiveness of the lesion.

Table 1 Effect of a 5,7-dihydroxytryptamine lesion in mouse brain on the hypothermic response to either (±)-baclofen (5 mg kg^{-1}) or 8-hydroxy-2-(di-*n* propylamino) tetralin (0.5 mg kg^{-1})

Treatment	Injected:	*Temperature change* (±)-*Baclofen*	*8-OH-DPAT*
Sham lesioned		− 0.6 ± 0.4 (6)	− 1.2 ± 0.2 (6)
Lesioned		− 0.7 ± 0.5 (6)	− 0.2 ± 0.3 (6)*

Response shown as mean temperature change ± s.d. either 40 min after baclofen (5 mg kg^{-1} i.p.) or 20 min after 8-OH-DPAT (0.5 mg kg^{-1} s.c.) in the same animals. *Different from sham lesioned, $P < 0.01$. There was no difference in the basal temperature between the two groups before drug administration.

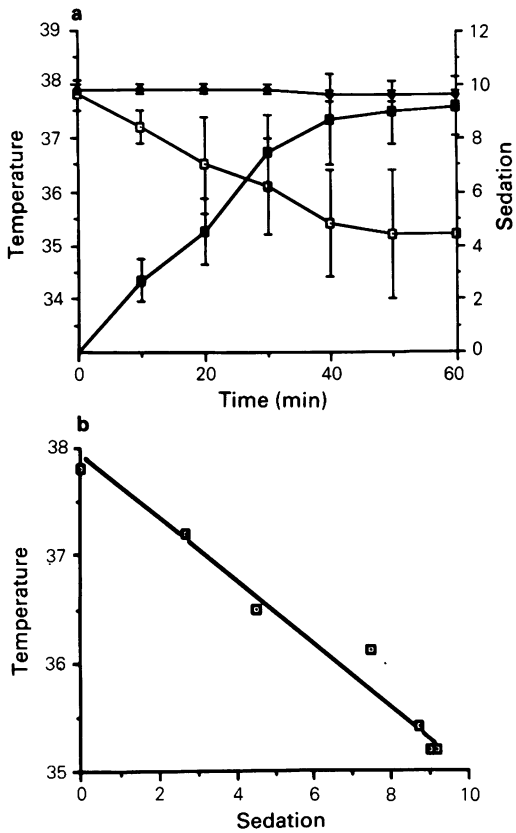

Figure 3 Effect of (+)-baclofen and (−)-baclofen on temperature and sedation: (a) shows the rectal temperature following injection of (+)-baclofen, 5 mg kg^{-1} (◆) and (−)-baclofen, 5 mg kg^{-1} (□) and the sedation response following (−)-baclofen, 5 mg kg^{-1} (■). The sedation score is the sum of the scores of each behavioural parameter (see Methods), each of the 5 behaviours being rated on a 0–3 scale. No sedation was seen following (+)-baclofen, 5 mg kg^{-1}. Results shown as mean with s.d. indicated by vertical lines ($n = 6$). (b) Shows the correlation between the mean value for temperature and sedation (taken from data in top panel) at each time point following (−)-baclofen.

Effect of repeated amitriptyline administration on baclofen-induced hypothermia.

Mice were treated once daily with either saline (controls) or amitriptyline (10 mg kg^{-1} i.p.) for 14 days.

Twenty four hours after the final dose both groups were injected with (±)-baclofen (5 mg kg^{-1}) and rectal temperature measured over the next 60 min. Basal temperature was not significantly different in amitriptyline-treated and control animals (data not shown). However, animals treated with amitriptyline showed an enhanced hypothermic response to baclofen at all time points (Figure 4). The sedation response was also measured and was found to be increased in the amitriptyline-treated animals (Figure 4).

No enhancement of the hypothermic response was observed when the mice were examined either 3 or 5 days after the final dose of amitriptyline (data not shown).

Effects of other antidepressant drugs on baclofen-induced by hypothermia.

Mice were treated once daily for 14 days with mianserin, zimeldine or desipramine (10 mg kg^{-1}, i.p. of each). Control animals received saline.

Twenty four hours after the last dose the hypothermic response to (±)-baclofen (5 mg kg^{-1}) was markedly enhanced in the antidepressant-treated mice (Figure 5). Basal temperature was not significantly different in antidepressant drug treated mice compared with the saline injected control animals.

Effects of repeated administration of ECS on baclofen-induced hypothermia

Mice were given ECS during halothane anaesthesia 5 times over 10 days and the hypothermic response to baclofen measured 24 h after the last treatment. Control mice received halothane anaesthesia only. The ECS treated mice showed an increased hypothermic response to baclofen (Figure 5).

Effects of a single treatment with antidepressant drugs or ECS on baclofen induced hypothermia

Mice were injected with saline or antidepressant drug (mianserin, zimeldine, desipramine or amitriptyline) and the temperature response to baclofen tested 24 h later.

Further groups were either anaesthetized with halothane or anaesthetized and given a single ECS and the baclofen hypothermic response measured 24 h later.

None of the treatments examined altered the temperature response to (±)-baclofen (5 mg kg^{-1}) following a single administration (Table 2).

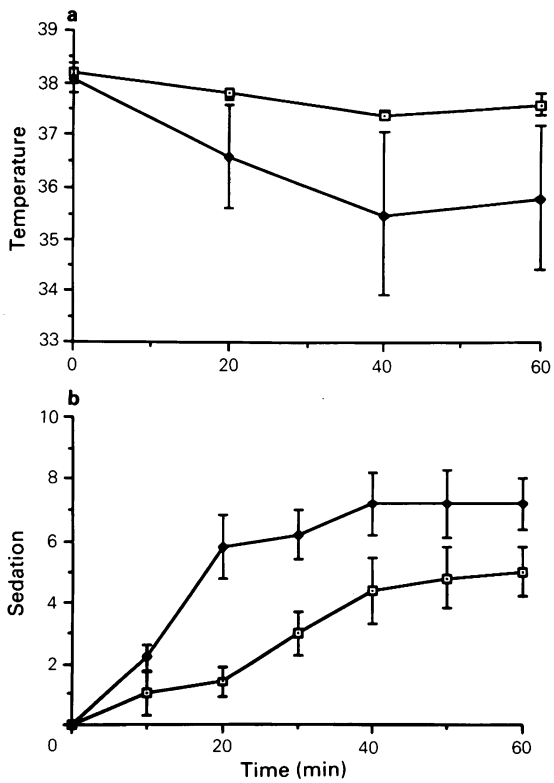

Figure 4 The effect of (±)-baclofen (5 mg kg^{-1}) on rectal temperature and sedation following 14 days treatment with amitriptyline (10 mg kg^{-1} once daily) 24 h after the last dose: (a) shows temperature change and (b) shows sedation score in mice treated with saline (□) or amitriptyline (◆) in the 60 min following baclofen injection. Results shown as mean ± s.d. of group of 6–8 animals. Amitriptyline group different from saline-injected controls ($P < 0.01$) from 20 min onwards.

Effects of repeated amitriptyline administration on the hypothermic and sedative response to sodium pentobarbitone

In view of the increased hypothermic and sedative responses to baclofen observed after antidepressant treatments, we felt it important to see if a similar change in the response occurred to another drug which produces both hypothermia and sedation. For this purpose we used sodium pentobarbitone, a drug which has not been reported to have any affinity for the $GABA_B$ receptor.

A similar degree of hypothermia to that induced by the challenge dose of (±)-baclofen (5 mg kg^{-1}) used in this study could be produced by pentobarbitone (25 mg kg^{-1} i.p.). However, the sedation produced by the barbiturate was not the same as that seen after baclofen and could not therefore be quantified by using the behavioural assessment score. We therefore measured the sleeping time, and the time to loss of righting reflex following a dose of pentobarbitone of 40 mg kg^{-1}, i.p.

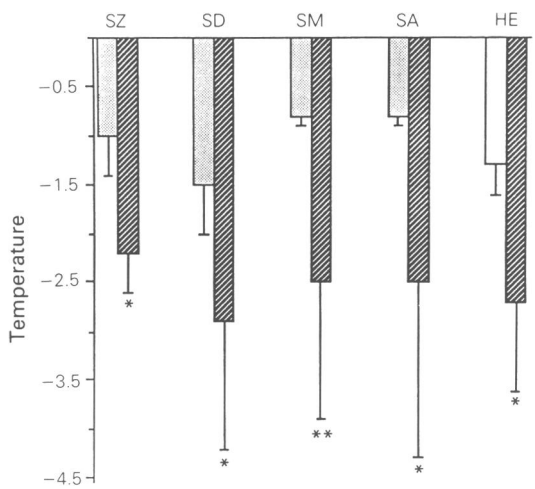

Figure 5 Temperature decreases in groups of mice given (±)-baclofen (5 mg kg^{-1}) 24 h after the last of the 14 doses (once daily over 14 days) zimeldine (Z), desipramine (D), mianserin (M), or amitriptyline (A), all given at a dose of 10 mg kg^{-1} or appropriate saline controls (S). Also shown is the temperature response in groups of mice either given 5 ECS during halothane anaesthesia over 10 days (E) of 5 halothane exposures (H), also 24 h after the last treatment. Results in groups of 6–8 mice shown as mean and s.d. (vertical lines) of temperature change 40 min after injection of baclofen. Treated groups different from the appropriate control group, $^*P < 0.05$; $^{**}P < 0.01$. There was no difference in the basal temperature before baclofen injection between any of the two groups (data not shown except for amitriptyline in Figure 4).

Table 2 Effect of acute administration of antidepressant drugs and electroconvulsive shock (ECS) on the hypothermia elicited by baclofen

Treatment	*Decrease in temperature (°C)*
Saline	-1.2 ± 0.4 (6)
Amitriptyline	-1.2 ± 0.7 (6)
Zimeldine	-0.9 ± 0.4 (6)
Mianserin	-1.3 ± 0.7 (6)
Desipramine	-1.4 ± 0.7 (6)
Halothane	-1.4 ± 0.7 (6)
Halothane/ECS	-1.2 ± 0.2 (6)

Mice were injected with either saline or the antidepressant drugs (10 mg kg^{-1}) on day 1 or anaesthetized with halothane or given a single ECS during halothane anaesthesia. On Day 2, 24 h after treatment all groups were injected with (±)-baclofen (5 mg kg^{-1} i.p.) and the temperature measured 40 min later. Results shown as mean temperature change after baclofen ± s.d. (*n*). There were no significant changes seen in either the temperature before baclofen injection or the decrease in temperature induced by baclofen.

Mice were injected daily with either saline or amitriptyline (10 mg kg^{-1}, i.p.) for fourteen days. Twenty four hours after the last dose both groups were divided into 2. Group 1 had their temperature response measured over the 40 min following injection of pentobarbitone (25 mg kg^{-1}) while group 2 were assessed for the hypnotic response following injection of pentobarbitone (40 mg kg^{-1}).

No difference was observed in either the hypothermic or the hypnotic response (Table 3) after antidepressant treatment compared with saline-treated controls.

Effects of flurazepam on baclofen induced hypothermia.

To strengthen the view that changes in $GABA_B$ receptor function had some selectivity towards antidepressant treatments we treated mice for 14 days with the anxiolytic drug flurazepam (20 mg kg^{-1}).

Twenty four hours after the last dose the hypothermic response to (±)-baclofen (5 mg kg^{-1}) was the same in both groups ($\Delta t\,(t_{40} - t_0)$ saline group : -1.3 ± 0.2°C, $n = 6$; flurazepam group : -1.3 ± 0.4°C, $n = 6$).

Effects of repeated treatment with baclofen on baclofen-induced hypothermia

When (±)-baclofen (5 mg kg^{-1}) was given 24 h after an initial dose of (±)-baclofen (5 mg kg^{-1}) there was no alteration in the temperature decrease observed either 20 or 40 min later (Table 4). However, following treatment daily for 4 days the response on the fifth was considerably attenuated (Table 4). Little further attenuation was observed on the fifteenth day after 14 days administration (Table 4). Appropriate control groups were tested in these studies being given either 1, 4 or 14 days of saline injection before the baclofen challenge but no differences were observed between any of these groups and animals given a single dose of baclofen (Table 4).

Discussion

Several of our findings point to the possibility that the hypothermia induced by baclofen may be used as an index of the function of $GABA_B$ receptors in the brain. Thus the response is dose-dependent and when induced by central injection of the drug is seen at doses far below those necessary to induce a response when given peripherally (5 ng = 2 μg kg^{-1}). Furthermore,

Table 3 Effect of chronic amitryptyline on the hypnotic and hypothermic responses of mice to pentobarbitone administration

	Hypnotic response		*Hypothermic response*
Treatment	*Loss of righting(s)*	*Sleeping time (min)*	$\Delta t\,(T_{30} - T_0)$
Saline	612 ± 30 (6)	26.0 ± 1.5 (6)	1.3 ± 0.3 (6)
Amitriptyline	624 ± 48 (6)	26.0 ± 1.5 (6)	1.3 ± 0.2 (6)

Mice were injected with saline or amitriptyline (10 mg kg^{-1}) for 14 days. Twenty-four hours after the last treatment they were injected with pentobarbitone at either 25 mg kg^{-1} (for hypothermic response) or 40 mg kg^{-1} (for hypnotic response). The hypothermic response was measured at 10 min intervals over 40 min but table shows only the change in temperature (Δt) 30 min (T_{30}) after injection at T_0, the nadir of the response. No significant changes were seen at any time. Results show mean response ± s.d. with number of observations in parentheses.

Table 4 Effect of repeated baclofen administration on the hypothermic response to a further dose of baclofen

Time	Pretreatment	Temperature decrease (°C) t_{20}	t_{40}
Day 1	—	− 0.7 ± 0.1	− 1.3 ± 0.3
Day 2	Saline	− 0.6 ± 0.2	− 1.3 ± 0.3
	Baclofen	− 0.7 ± 0.4	− 1.0 ± 0.2
Day 5	Saline	− 0.8 ± 0.2	− 1.6 ± 0.5
	Baclofen	− 0.5 ± 0.3	− 0.8 ± 0.3*
Day 14	Saline	− 0.7 ± 0.1	− 1.2 ± 0.3
	Baclofen	− 0.4 ± 0.1	− 0.7 ± 0.3*

Mice were injected with either saline of (±)-baclofen (5 mg kg^{-1} i.p.) for various numbers of days as shown. The temperature decrease is shown 20 min (t_{20}) and 40 min (t_{40}) after injection and is shown as mean response ± s.d. ($n = 8$). *Different from control group pretreated with saline; $P < 0.05$.

the hypothermic response is highly stereoselective, (+)-baclofen being devoid of effect at a dose of 5 mg kg^{-1}. However, in the absence of an effective $GABA_B$ antagonist it is not possible to state unequivocally that the effect is through a $GABA_B$ receptor.

Despite the observations that $GABA_B$ receptors can be located presynaptically as heteroceptors on 5-HT neurones in both rats (Bowery *et al.*, 1980; Schlicker *et al.*, 1984) and mice (Gray & Green, 1987a) and that the $5\text{-}HT_{1A}$ agonist 8-OH-DPAT is hypothermic in mice (Goodwin *et al.*, 1985a) the baclofen-induced hypothermia does not appear to be via a serotoninergic mechanism since a 5,7-DHT lesion, while abolishing the 8-OH-DPAT mediated hypothermia had no effect on baclofen-induced hypothermia. Furthermore, repeated antidepressant administration has previously been found to attenuate 8-OH-DPAT-induced hypothermia (Goodwin *et al.*, 1985b) but, as shown in this study, this treatment enhances baclofen-induced hypothermia.

Fung *et al.* (1985) have demonstrated a weak interaction of baclofen with α_2-adrenoceptors. In this regard it is interesting that the α_2-adrenoceptor agonist clonidine induces both hypothermia and a very similar sedative response to that seen after baclofen. Studies have previously observed that both the sedation (Heal *et al.*, 1981; 1983) and hypothermic responses (Von Voigtlander *et al.*, 1978; Pilc & Vetulani, 1982) to clonidine are attenuated by repeated administration of ECS or antidepressant drugs. In contrast however, when induced by baclofen, both these responses are enhanced after antidepressant treatments. For this reason it seems unlikely that baclofen is acting through the same mechanism as clonidine to produce hypothermia and sedation.

Repeated administration of baclofen attenuated its own hypothermic response. Similar tolerance to the hypolocomotor (or sedative) effects of baclofen in rats has been reported by Gianutsos & Moore (1979). It is possible that the tolerance to baclofen seen after repeated administration might be due to decreased density of $GABA_B$ receptor as has been demonstrated by Suzdak & Gianutsos (1986). Baclofen is largely excreted unchanged via the kidneys (Faigle & Keberle, 1972). After repeated administration of baclofen there is no change in its plasma half-life (Faigle & Keberle, 1972) or any evidence of hepatic enzyme induction (Gianutsos & Moore, 1979). These findings make a kinetic explanation for the tolerance to repeated baclofen seem unlikely.

The ligand receptor binding data of Lloyd *et al.* (1985) showing that $GABA_B$ receptor number is increased in some areas of the brain by a diverse range of antidepressant drugs and ECS has been supported by our *in vitro* observations on the effect of baclofen on 5-HT release from frontal cortex slices (Gray & Green, 1987b) and now gains further support from the current *in vivo* functional test. Administration of diverse antidepressant drugs or ECS resulted in an enhanced hypothermic effect of baclofen. This response appears to require repeated antidepressant administration since it was not seen after one day of treatment but was evident after 2 weeks. This is again consistent with the binding data of Lloyd *et al.* (1985) and Suzdak & Gianutsos (1986).

It seems unlikely that the enhanced temperature response to baclofen following antidepressants is due to some direct interaction of baclofen with antidepressant drugs since the enhanced response was also seen after repeated ECS, a treatment involving no drug administration. It is also a change that has been shown to have some selectivity to antidepressant treatments; repeated administration of the anxiolytic drug flurazepam did not alter the hypothermic response to baclofen.

A final consideration is the possibility that the results reflect a generalised increase in the responsiveness of mice to sedative and hypothermic agents following antidepressant treatments rather than a selective change in $GABA_B$ function. We would suggest that there are several indications which render such a proposal unlikely. First is our finding that chronic amitriptyline administration had no effect on the hypothermic or hypnotic responses to pentobarbitone, a drug which enhances $GABA_A$ function through an action at the $GABA_A$-benzodiazepine-chloride ionophore (Haefely, 1971; Leeb-Lundberg *et al.*, 1980; Paul *et al.*, 1981). This is consistent with the earlier observation that the hypnotic effect of pentobarbitone is unaltered by ECS in rats (Green *et al.*, 1977). Other evidence against a non-specific increase in hypothermic and sedative responsiveness after

antidepressant treatments comes from the previously quoted observations that both the hypothermic and sedative responses to clonidine are attenuated by antidepressant drugs and ECS as is the hypothermic response to 8-OH-DPAT.

In conclusion therefore we propose that the hypothermic response following administration of baclofen to mice may provide a simple *in vivo* index of $GABA_B$ receptor function. The enhancement of this response following antidepressant drugs and ECS strengthens the evidence that these treatments may increase $GABA_B$ receptor function.

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