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Dexamethasone Reduces the Behavioural Effects Induced by Baclofen in Mice

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Abstract

The present study examines the influence of dexamethasone on the behavioural effects induced by baclofen in mice. The behaviour elements considered were locomotor activity, motor co-ordination, catalepsy, stereotyped behaviour and antinociception.

Baclofen (1·0–4·0–6·0 mg kg^{-1}, i.p.) induced a significant reduction of all behavioural elements studied and an antinociceptive effect was recorded. Dexamethasone alone (0·1–0·5–1·0 mg kg^{-1}, i.p.) did not induce significant changes in the behaviour elements considered. On the other hand, when the steroid was injected immediately before baclofen a significant reduction of baclofen's behavioural effects was found.

Our results suggest a possible link between glucocorticoid and the GABA-ergic system.

Baclofen is a derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Baclofen appears to inhibit transmission in monosynaptic as well as in polysynaptic spinal pathways (Fukuda et al 1977). It is useful in treating spasticity associated with spinal cord lesions, as in multiple sclerosis. Chronic intrathecal infusion of the drug is sometimes beneficial, with a lower incidence of adverse effects in patients who do not respond favourably to oral administration (Penn et al 1989). An antinociceptive effect has also been reported after systemic administration of baclofen in rodents (Cutting & Jordan 1975; Levy & Proudfit 1977; Bartolini et al 1981; Hill et al 1981; Sawynok & La Bella 1982; Vaught et al 1985) and in man (Corli et al 1984). Furthermore, the antinociceptive effect exerted by baclofen is not reduced by $GABA_A$ (Bartolini et al 1981; Sawynok & La Bella 1982), opioid (Levy & Proudfit 1979; Bartolini et al 1981) or muscarinic receptor antagonists (Bartolini et al 1981). By contrast, the effects induced by baclofen are antagonized by the $GABA_B$-selective antagonists such as CGP 35348 (Malcangio et al 1991; Hammond & Washington 1993).

In our laboratories we have studied some steroid effects on opioid antinociception by using different experimental procedures. We have demonstrated that dexamethasone was able to reduce opioid antinociception in the hot-plate test (Pieretti et al 1991, 1994) and in the tail-flick test (Capasso et al 1992) and a possible influence of the corticosteroids on several neurotransmitters was discussed (Capasso et al 1993, 1994).

Numerous studies have shown that opioids exert several of their pharmacological actions by affecting GABA transmission (Yoneda et al 1976; Kuriyama & Yoneda 1978; Moroni et al 1978). Also, it has been demonstrated that the antinociceptive effect of morphine is potentiated by pretreatment with muscimol (Biggio et al 1977) or aminoxyacetic acid (Yoneda et al 1976) and reduced by pretreatment with semicarbazide and bicuculline (Yoneda et al 1976). However, there are also data indicating that potentiation of GABA transmission did not affect (Christensen et al 1978) or antagonize (Ho et al 1976; Mantegazza et al 1979) the analgesic effect of morphine.

Several studies have shown a link between corticosteroids and the GABA-ergic system, indicating that endogenous steroids may regulate the GABA-receptor complex, either agonistically or antagonistically (Miller et al 1978; Majewska et al 1985; Majewska 1987). We therefore considered it of interest to study the influence of dexamethasone on this system. In this study we have investigated the effects of dexamethasone on behavioural effects exerted by baclofen in mice.

Materials and Methods

Animals

Male Swiss mice, 20–25 g, were supplied by Charles River (Italy). The animals were housed in colony cages (ten mice each) under standard light (light on from 0700 to 1900 h), temperature (22 ± 1°C) and room humidity (60 ± 10%) conditions for at least 1 week before the experimental sessions. Food and water were freely available.

Locomotor activity

The animals were placed in the activity cage for at least a 30-min period for acclimatization before receiving injection of drugs. Temperature, sound and light conditions were maintained at a uniform level during the course of the experiments. Locomotor activity of the mice was recorded in an activity cage (Basile, Milan, Catalogue No 7400) and the sessions in the activity cage lasted 2 h. Measurements were carried out at 10-min intervals and cumulative counts were recorded.

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Motor co-ordination

Motor co-ordination of the mice was evaluated by using a rotarod apparatus (Ugo Basile, Italy) consisting of a bar with a diameter of 3·0 cm, subdivided into five compartments by a disk 24 cm in diameter. The bar rotated at a constant speed of 16 rev min^{-1} (Pieretti et al 1994). The integrity of motor co-ordination was assessed on the basis of the endurance time of the animals on the rotating rod. One day before the test, the animals were trained twice. On the day of the test, only mice able to stay balanced on the rotating rod between 70 and 120 s (cut-off time) were selected. The performance time was measured before and at 20, 40, 80 and 120 min after treatment (Malcangio et al 1991).

Stereotyped behaviour

Rearing, grooming, social response, crossing, smelling, face-washing, scratching and bar-holding were all assessed as previously reported (Hecht & Schiorring 1979). Frequency of all types of behaviour was recorded manually by one observer who did not know the treatment. The test was conducted for a period of 120 min after baclofen injection and each mouse was observed at 10–20, 40–50, 70–80 and 100–120 min post-injection.

To check social responsiveness of the treated mouse, each session contained a social response test. An untreated mouse was placed for 5 min in the experimental cage together with the drug-treated mouse. The presence or absence of common social behaviour was recorded (sniffing, play or aggression).

Catalepsy

The presence of a state of catalepsy was detected using an abnormal posture test (Fog 1972). In mice, catalepsy was quantitatively estimated by placing the forepaws of the animals on a horizontal rod which was mounted 3 cm above the floor of the experimental box. The test was regarded as positive if the animal remained in this position for at least 45 s. Latency to step-down was recorded before and at intervals (20, 40, 80 and 120 min) after drug treatment. A maximum cut-off time of 45 s was used. Cataleptic responses were calculated as a percent of the maximum possible response defined as (R-B)/(45-B) ×100, where B is the mean baseline latency, R is for post-treatment response latency, and 45 represents the cut-off time (Kiritsy-Roy et al 1989).

Nociceptive assays

The nociceptive assays performed were the hot-plate and the tail-flick tests. The hot-plate test was performed as previously described (Pieretti et al 1991). Briefly, the hot-plate (Socrel Mod. DS-37, Ugo Basile, Italy, 25 × 25 cm) was set at a temperature of 55 ± 0·5°C, to give a latency of 17–20 s in control animals. The time of hind paw licking was recorded, and measuring was terminated if the licking exceeded the cut-off time (60 s).

The tail-flick test was performed as previously described (Capasso et al 1992). Briefly, the tail-flick latency was obtained using a tail-flick unit (Socrel Mod DS-20, Ugo Basile, Italy). The animals were gently immobilized using a glove, and the radiant heat was focused on a blackened spot 1–2 cm from the tip of the tail. Beam intensity was adjusted to give a tail-flick latency of 2–3 s in control animals. Measuring was terminated if the latency exceeded the cut-off time (10 s) to avoid tissue damage. In all the experiments, mice were tested twice, 60 and 30 min before drug administration for the baseline latency determination and then 30 min after drug administration.

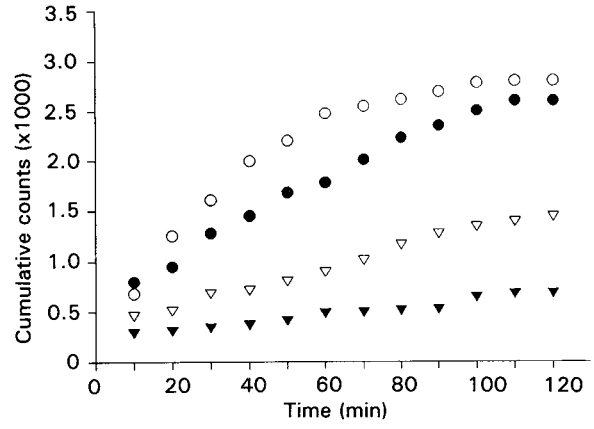

FIG. 1. Time- and dose-effect curves of baclofen (○ 0, ● 1, ▽ 4 and ▼ 6 mg kg^{-1}) on locomotor activity in mice (n = 6).

Experimental procedure

On the day of the tests, all drugs used in the experimental sessions were dissolved in saline for administration. Drugs were injected in a volume of 10 mL kg^{-1}, intraperitoneally. Dexamethasone (Sigma Chemical, USA) was administered at doses of 0·1, 0·5, or 1·0 mg kg^{-1}, intraperitoneally, immediately before saline or baclofen (Sigma Chemical, USA) injection (1·0, 4·0 or 6·0 mg kg^{-1}, i.p.). The doses were calculated as the weight of the base.

Table 1. Effect of dexamethasone on locomotor activity (cumulative counts × 1000) in mice, and on the hypoactivity induced by baclofen.

Dexamethasone (mg kg^{-1})	Baclofen (mg kg^{-1})			
	0	1	4	6
0·1	2700 ± 704	2650 ± 300	1600 ± 150	800 ± 167
0·5	2600 ± 800	2600 ± 250	1800 ± 200	900 ± 90
1·0	2800 ± 320	2750 ± 310**	2650 ± 220**	2630 ± 250**

Results are mean ± s.e.m. (n = 6). **$P < 0·01$.

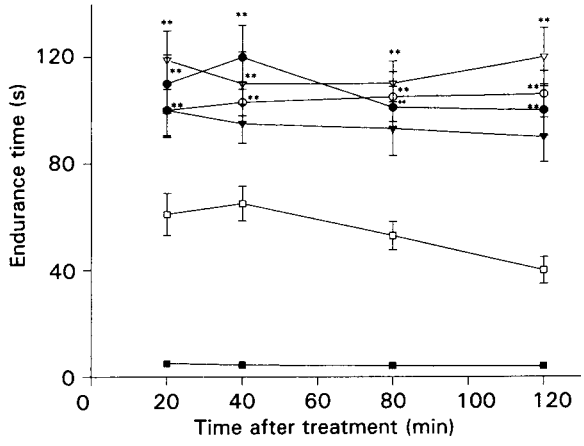

FIG. 2. Time- and dose-effect curves of baclofen on motor co-ordination in mice with and without dexamethasone treatment. Dexamethasone 1 mg kg^{-1} + baclofen 6 ▽, 1 ○ or 4 ● mg kg^{-1}; baclofen 1 ▼, 4 □ or 6 ■ mg kg^{-1} alone. Mean ± s.e.m., n = 6. $^{**}P < 0.01$.

Statistical analysis

All data (expressed as mean ± s.e.m.) were analysed by analysis of variance and Dunnett's procedure for multiple comparisons with a single control group. When the analysis was restricted to two means, Student's *t*-test (two-tailed) was used. The Fisher exact test was used to analyse the rotarod data. Significance was assumed at $P < 0.05$.

Results

Locomotor activity

The activity of saline- and baclofen-treated mice is shown in Fig. 1. Baclofen dose-dependently and significantly reduced the locomotor activity of mice. The reduction induced by baclofen is significant 10 min after administration and lasted for all the recording period (120 min).

Dexamethasone did not significantly modify the locomotor activity when the mice were challenged with doses of 0·1, 0·5 or 1·0 mg kg^{-1} (Table 1). However, when dexamethasone was used as pretreatment and baclofen as challenge,

Table 2. Effect of saline, dexamethasone (1 mg kg^{-1}), baclofen and dexamethasone (1 mg kg^{-1}) plus baclofen on the stereotyped behaviour of mice.

	Rearing	Grooming	Social response	Crossing	Smelling	Face-washing	Scratching	Bar-holding
10–20 min post-injection								
Saline	69 ± 5·3	79 ± 5·9	41 ± 3·1	57 ± 3·5	81 ± 7·9	49 ± 5·1	49 ± 5·3	45 ± 3·3
Dexamethasone	65 ± 4·9	40 ± 3·5	44 ± 3·5	50 ± 4·5	77 ± 7·3	54 ± 6·3	53 ± 4·9	46 ± 3·9
Baclofen 1 mg kg^{-1}	32 ± 2·7*	29 ± 3·3*	20 ± 1·3*	15 ± 1·2**	53 ± 6·3*	37 ± 4·1*	13 ± 2·1**	11 ± 1·9**
4 mg kg^{-1}	10 ± 1·3**	13 ± 2·9**	12 ± 0·7**	13 ± 1·7**	20 ± 2·1**	10 ± 1·5**	11 ± 1·8**	10 ± 1·1**
6 mg kg^{-1}	0**	0**	1**	1 ± 0·1**	7 ± 0·7**	0**	0**	0**
Dexamethasone								
+ baclofen 1 mg kg^{-1}	25 ± 1·2	26 ± 1·5	40 ± 3·5†	47 ± 3·7†	67 ± 5·9	35 ± 2·7	13 ± 1·6	10 ± 1·1
+ baclofen 4 mg kg^{-1}	15 ± 0·8	10 ± 1·3	35 ± 2·8†	40 ± 3·5†	40 ± 3·6†	12 ± 1·7	10 ± 1·5	10 ± 1·5
+ baclofen 6 mg kg^{-1}	0	0	34 ± 2·4†	31 ± 2·3†	55 ± 4·3†	0	0 ±	0
40–50 min post-injection								
Saline	65 ± 5·9	48 ± 2·8	47 ± 3·1	39 ± 2·7	76 ± 6·9	55 ± 4·9	43 ± 3·3	37 ± 3·9
Dexamethasone	57 ± 4·3	51 ± 3·5	50 ± 4·3	45 ± 2·3	67 ± 4·3	49 ± 5·3	45 ± 4·1	46 ± 4·5
Baclofen 1 mg kg^{-1}	30 ± 2·7*	21 ± 1·2*	27 ± 1·3*	26 ± 2·1*	47 ± 3·6*	20 ± 3·3*	21 ± 2·7*	20 ± 2·3*
4 mg kg^{-1}	11 ± 0·9**	10 ± 1·0**	14 ± 1·4**	13 ± 1·5**	10 ± 7·9**	11 ± 1·3**	12 ± 2·1**	11 ± 1·1**
6 mg kg^{-1}	0**	0**	2 ± 0·1**	0**	2 ± 0·6**	0**	0**	0**
Dexamethasone								
+ baclofen 1 mg kg^{-1}	35 ± 2·7	27 ± 1·7	34 ± 2·9	31 ± 2·3	45 ± 3·1	22 ± 2·7	19 ± 1·8	18 ± 2·3
+ baclofen 4 mg kg^{-1}	19 ± 1·5	15 ± 1·3	39 ± 2·5†	40 ± 2·1†	30 ± 2·5†	17 ± 2·3	19 ± 1·9	15 ± 2·1
+ baclofen 6 mg kg^{-1}	0	0	21 ± 1·7†	29 ± 2·2†	24 ± 2·0†	0	0	0
70–80 min post-injection								
Saline	70 ± 6·7	50 ± 4·2	49 ± 3·7	42 ± 3·3	67 ± 5·7	59 ± 4·3	45 ± 3·3	43 ± 5·6
Dexamethasone	49 ± 5·6	45 ± 3·4	47 ± 3·1	51 ± 4·5	63 ± 6·5	44 ± 3·7	51 ± 3·7	50 ± 4·8
Baclofen 1 mg kg^{-1}	25 ± 3·3**	23 ± 2·2**	30 ± 2·7**	26 ± 2·9**	40 ± 4·3*	17 ± 1·5**	12 ± 1·8**	14 ± 2·3**
4 mg kg^{-1}	12 ± 1·3**	11 ± 1·2**	10 ± 1·5**	15 ± 2·3**	10 ± 1·2**	10 ± 1·3**	11 ± 1·4**	10 ± 1·7**
6 mg kg^{-1}	0**	4 ± 0·3**	5 ± 0·3**	5 ± 0·3**	4 ± 0·6**	0**	0**	0**
Dexamethasone								
+ baclofen 1 mg kg^{-1}	30 ± 2·5	29 ± 2·1	49 ± 2·9	52 ± 4·9†	60 ± 7·4†	19 ± 2·1	11 ± 1·5	12 ± 1·9
+ baclofen 4 mg kg^{-1}	15 ± 1·7	12 ± 0·9	36 ± 2·1	39 ± 3·8†	40 ± 5·9†	11 ± 1·6	10 ± 1·6	11 ± 1·5
+ baclofen 6 mg kg^{-1}	0	0	25 ± 3·1†	20 ± 2·1†	23 ± 3·1†	0	0	0
100–120 min post injection								
Saline	68 ± 5·5	55 ± 3·3	50 ± 4·5	45 ± 3·7	65 ± 6·6	60 ± 5·7	47 ± 3·5	45 ± 3·3
Dexamethasone	50 ± 4·5	49 ± 2·3	45 ± 3·7	46 ± 3·5	56 ± 4·5	47 ± 4·5	52 ± 4·3	47 ± 4·8
Baclofen 1 mg kg^{-1}	23 ± 3·3**	25 ± 1·7**	30 ± 2·7**	30 ± 3·9**	25 ± 2·7**	20 ± 2·3**	21 ± 2·6**	20 ± 1·6**
4 mg kg^{-1}	13 ± 0·7**	10 ± 1·1**	11 ± 1·5**	16 ± 2·1**	14 ± 1·7**	17 ± 1·5**	11 ± 2·1**	14 ± 0·9**
6 mg kg^{-1}	0**	0**	0**	3 ± 0·5**	2 ± 0·8**	0**	0*	0**
Dexamethasone								
+ baclofen 1 mg kg^{-1}	29 ± 1·9	27 ± 2·1	40 ± 3·9	47 ± 3·7†	54 ± 6·1†	25 ± 2·3	20 ± 1·3	21 ± 2·6
+ baclofen 4 mg kg^{-1}	18 ± 1·3	11 ± 1·5	30 ± 2·5	35 ± 3·1†	39 ± 4·3†	15 ± 1·7†	10 ± 0·7	13 ± 1·9
+ baclofen 6 mg kg^{-1}	0	0	20 ± 1·5	23 ± 2·1†	27 ± 3·1†	0	0	0

Stereotyped behaviour is reduced by baclofen ($^{*}P < 0.05$; $^{**}P < 0.01$ vs saline). Partial normalization was seen after dexamethasone treatment (†$P < 0.05$; †$P < 0.01$ vs baclofen).

significant effects on baclofen-induced hypoactivity were observed, which depended on the dexamethasone dose used. When 0·1 or 0·5 mg dexamethasone was injected immediately before baclofen, no significant changes were observed on the locomotor hypoactivity produced by the three doses of baclofen. By contrast, concurrent administration of 1 mg dexamethasone and baclofen resulted in a significant attenuation of the hypoactivity induced by the three doses of baclofen. Dexamethasone-reduced baclofen hypoactivity was statistically significant 20–30 min after the beginning of the session and a consistent difference was recorded for the duration of the whole period (120 min).

Motor co-ordination

Baclofen at the doses used induced a significant and dose-dependent reduction of the motor co-ordination of mice on the rotarod bar when compared both with the saline-treated mice and with the respective pre-drug (Fig. 2). The reduction induced by baclofen was significant 10–20 min after administration and lasted for all the recording period (120 min). Dexamethasone did not significantly modify the motor co-ordination when the animals were challenged with 0·1, 0·5 or 1·0 mg kg^{-1} (data not shown).

When dexamethasone was injected at the dose of 0·1 or 0·5 mg kg^{-1} immediately before baclofen, no effects were observed on the motor co-ordination produced by the three doses of baclofen (data not shown). By contrast, 1 mg kg^{-1} dexamethasone was able to attenuate significantly the reduced motor co-ordination induced by the three doses of baclofen (Fig. 2). The attenuation induced by dexamethasone was significant 20–30 min after its injection and it lasted for all the observation period.

Stereotyped behaviour

The stereotyped behaviour of saline-, baclofen- and dexamethasone-treated mice is reported in Table 2.

Baclofen dose-dependently and significantly reduced all the behaviour elements of the mice considered in our study. The reduction induced by baclofen is significant 10 min after administration and lasted for all the recording period (120 min). Dexamethasone did not significantly modify the animals' behaviour when the mice were injected with 0·1, 0·5 or 1·0 mg kg^{-1}. When 0·1 or 0·5 mg kg^{-1} dexamethasone was injected immediately before baclofen, no influence was observed on the reduced behaviour elements induced by baclofen (data not shown), whereas the higher dose of dexamethasone (1·0 mg kg^{-1}) induced a significant attenuation of some of the elements (social response, crossing and smelling). Also, at this highest dose, the attenuation induced by dexamethasone was significant 20–30 min after the administration and lasted for all the recording period (Table 2).

Catalepsy

The cataleptic effects in saline-, baclofen- and dexamethasone-treated mice are reported in Fig. 3.

Baclofen was able to induce a significant and dose-dependent cataleptic effect in mice: this cataleptic effect was significant 10–20 min after the administration and lasted for all the observation period (120 min).

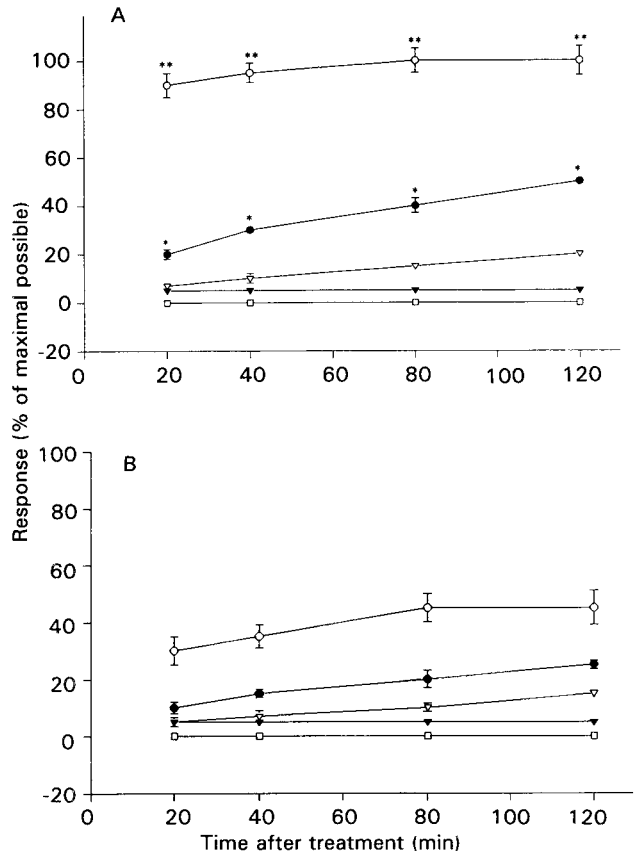

FIG. 3. Time– and dose–effect curves of baclofen catalepsy with (A) and without (B) dexamethasone treatment. A. Saline, □; dexamethasone (1 mg kg^{-1}), ▼; baclofen (1 mg kg^{-1}), ▽; baclofen (4 mg kg^{-1}), ●; baclofen (6 mg kg^{-1}), ○. B. Saline, □; dexamethasone (1 mg kg^{-1}), ▼; dexamethasone (1 mg kg^{-1}) + baclofen (1 mg kg^{-1}), ▽; dexamethasone (1 mg kg^{-1}) + baclofen (4 mg kg^{-1}), ●; dexamethasone (1 mg kg^{-1}) + baclofen (6 mg kg^{-1}), ○. Mean ± s.e.m. (n = 6), $*P < 0.05$, $**P < 0.01$.

Dexamethasone administration did not induce any cataleptic effect either at low doses of 0·1 and 0·5 mg kg^{-1} (data not shown) or at the high dose of 1·0 mg kg^{-1} (Fig. 3). Furthermore, the low doses of dexamethasone (0·1 or 0·5 mg kg^{-1}) did not affect the cataleptic effect induced by the three doses of baclofen (data not shown) whereas the high dose (1·0 mg kg^{-1}) significantly reduced the baclofen-induced catalepsy (Fig. 3); the reduction induced by dexamethasone on the cataleptic effect induced by the three doses of baclofen was significant 20–30 min after the administration and lasted for all the recording period (120 min).

Table 3. Effect of dexamethasone (0·5 mg kg^{-1}, i.p.) and baclofen (4 mg kg^{-1}) on nociceptive threshold in mice.

Treatment	Hot-plate latency (s)	Tail-flick latency (s)
Saline	15·6 ± 2·3	3·5 ± 0·5
Dexamethasone	18·1 ± 3·1	2·7 ± 0·7
Baclofen	45·6 ± 5·0[a]	7·5 ± 0·4[a]
Dexamethasone + baclofen	27·5 ± 3·2[b]	3·5 ± 0·8[b]

[a] $P < 0.05$ compared with saline control, [b] $P < 0.05$ compared with experiment without dexamethasone.

Nociceptive assays

For these tests, dexamethasone was used only at doses which did not modify the baclofen-induced reduction behaviour (0·1 and 0·5 mg kg^{-1}, i.p.) and baclofen was used only at a dose which weakly reduced animal behaviour (4 mg kg^{-1}, i.p.)

Dexamethasone at 0·5 mg kg^{-1} affected neither the hot-plate (Table 3) nor the tail-flick latency of mice, whereas baclofen (4 mg kg^{-1}, i.p.) significantly increased it. The same dose of dexamethasone injected immediately before baclofen significantly reduced baclofen antinociception both in the hot-plate and tail-flick test. Dexamethasone at a dose of 0·1 mg kg^{-1} was not able to modify baclofen antinociception (data not shown).

Discussion

The results of the present study indicate that baclofen induced a significant reduction of mouse behaviour (locomotor activity, motor co-ordination, and stereotyped behaviour), thus confirming that this compound exerts depressant effects on the central nervous system (Matsumoto 1989; Fukuda et al 1977; Hammond & Washington 1993). Also, baclofen induced antinociception as previously reported (Malcangio et al 1991).

There are no data in the literature on the effects exerted by glucocorticoids on the behavioural effects induced by baclofen in mice, and thus our data give some help in explaining the mechanism by which dexamethasone interferes with baclofen and hence, with the GABA-ergic system.

Our data show an influence of dexamethasone on behavioural effects of baclofen thus indicating and confirming an influence of corticosteroids on the GABA-ergic system (McEwen 1979).

In this respect, given the results of the present study, one would suppose that dexamethasone may interact with the GABA-ergic system, by modulating its activity. This hypothesis is supported by biochemical evidence indicating a modulatory role of glucocorticoids on GABA-ergic function as corticosterone has been reported to modulate the binding and uptake of GABA in the hippocampus (Miller et al 1978; Majewska et al 1985).

It has also has been reported that several endogenous steroids are able to modulate the GABA receptor/chloride ionophore complex.

The agonist or antagonist properties of the steroids at the GABA receptor complex correspond with their known inhibitory (Pfaff et al 1971; Gyermek & Soyka 1975), neuro-excitatory (Carette & Paulain 1984; Avanzino et al 1984; Feldman 1984) and biphasic (Dafny et al 1973) actions on neuronal firing (Riker & Sastre 1982).

In our experimental model, we cannot exclude the possibility that dexamethasone reduction of baclofen behavioural effects may be related to its ability to interact with the GABA-ergic system, thus reducing baclofen effects, nor can we exclude other (perhaps concurrent) possibilities.

It has been reported that some effects induced by baclofen may be mediated by the G-protein (Potier & Dutar 1993). Recent evidence shows that glucocorticoids may modulate the steady-state levels of G-protein subunits (Ros et al 1989). G-protein, in turn, modulates the activity of adenylate cyclase, cyclic GMP phosphodiesterase, phospholipase C and ion channels (Houslay 1987; Neer & Clapham 1988). The effects exerted by glucocorticoids on G-protein may be able to antagonize the baclofen-induced effects.

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