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EFFECTS OF DOPAMINE RECEPTOR AGONISTS AND ANTAGONISTS ON BACLOFEN-INDUCED ANTINOCICEPTION IN FORMALIN TEST

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ABSTRACT

In this study, the influence of dopamine receptor agonists and antagonists on antinociception induced by baclofen has been examined in the formalin test. The GABA-B agonist baclofen induced antinociception in both phases of the formalin test in mice. The dopamine receptor agonists SKF 38393 and quinpirole also induced antinociception in both phases of the test. SKF 38393 but not quinpirole potentiated the response to baclofen in the first phase of the test. The dopamine receptor antagonists SCH 23390 and sulpiride increased the response to baclofen in the first phase. Both drugs induced antinociception in the first phase of the fornalin test. However, low doses of sulpiride increased the pain response in the second phase. The peripheral dopamine receptor antagonist domperidone did not alter the effect of the test by itself. Dopamine receptor mechanisms appear to interact with baclofen-induced antinociception.

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INTRODUCTION

Baclofen is a derivative of γ-aminobutyric acid (GABA), which is an inhibitory neurotransmitter in the vertebrate central nervous system.[13] GABA receptors in the brain have been classified as $GABA_A$ and $GABA_B$.[7,8] While $GABA_A$ receptors are directly associated with Cl^- channels, $GABA_B$ receptors are coupled to Ca^{++} or K^+ channels as second messenger systems.[5] A third class of GABA-binding sites, $GABA_C$ sites, have also been observed.[14] These receptors appear to be relatively simple ligand-gated Cl^- channels with a distinctive pharmacology, in that they are not blocked by bicuculline.[22]

Baclofen is the prototype $GABA_B$ agonist.[6] The drug has major clinical use as an antispastic agent,[41] reduces pain associated with spasticity[29] and is useful in the treatment of trigeminal neuralgia.[16] Baclofen produces analgesia in a variety of available tests.[32,42,45] The analgesic action of the agent is mediated through both spinal and supraspinal sites.[32]

An involvement of brain dopaminergic systems in the modulation of nociceptive mechanisms has been demonstrated by several studies.[33,37] The pharmacological activation of dopaminergic systems increases the stimulus-produced analgesia,[2] while lesions of the nigrostriatal pathway abolish morphine-induced analgesia.[30] On the other hand, electrical stimulation of the substantia nigra produces stimulus induced analgesia in the rat.[34]

In a previous study, we showed that two different D_1 and D_2 dopamine receptor subtypes may decrease or increase morphine-induced antinociception in the tail-flick test respectively.[43]

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Interactions between GABAergic and dopaminergic systems have been shown previously. Anatomical evidence indicates that GABAergic neurons in the rat neostriatum receive dopaminergic inputs.[25] Dopaminergic activation has been shown to exert an inhibitory effect on GABA release in the rat caudate putamen,[9,10,12,39] and substantia nigra.[24] Dopaminergic afferents to the rat striatum exert an inhibitory control over striatal GABAergic interneurons.[17] It has been shown that baclofen depresses the firing rate of dopaminergic nigral neurons. It also inhibits firing of dopamine neurons in the ventral tegmental area[28] and reduces the turnover of brain dopamine.[18] Baclofen potentiates dopamine-induced behaviours in mice.[4] There is also evidence showing that both noradrenergic and dopaminergic systems are involved in baclofen antinociception.[32] Our previous study showed that dopaminergic agents may influence baclofen-induced antinociception in the tail-flick test.[45] Since dopamine may be the neurotransmitter involved in baclofen antinociception, the effects of the dopamine agonists and antagonists on baclofen antinociception in both phases of the formalin test have been examined in the present study.

MATERIAL AND METHODS

Animals

Male albino mice weighing 22-29g were used in the experiments. The animals were housed in groups of 10 in conditions of constant temperature (21±2°C) and light controlled room (light period, 07:00-19:00). Animals had free access to food and water except during the experiments.

Drugs

The chemicals used were baclofen (Ciba-Geigy, Switzerland), SKF 38393, quinpirole, domperidone, SCH 23390 and sulpiride (Research Biochemical Inc., USA). SCH 23390 or sulpiride were dissolved in a drop of glacial acetic acid, made up to the required volume with distilled water. The other drugs were dissolved in saline. The drugs were prepared immediately before use and injected in a volume of 10 mL/kg.

Antinociception recording

Mice were allowed to acclimatize for 30 min before formalin injection. Twenty-five µL formalin (0.5%) was injected subcutaneously into the dorsal surface of the right hind paw of the mouse using a microsyringe with a 26-gauge needle.

Immediately after formalin injection, animals were placed individually in glass cylinders (20 cm wide, 25 cm long) on a flat glass floor and a mirror was arranged in a 45° angle under the cylinder to allow clear observation of the animals.

The total time (seconds) spent licking and biting the injected paw during periods of 0-5 min and 20-40 min were measured as an indicator of pain.

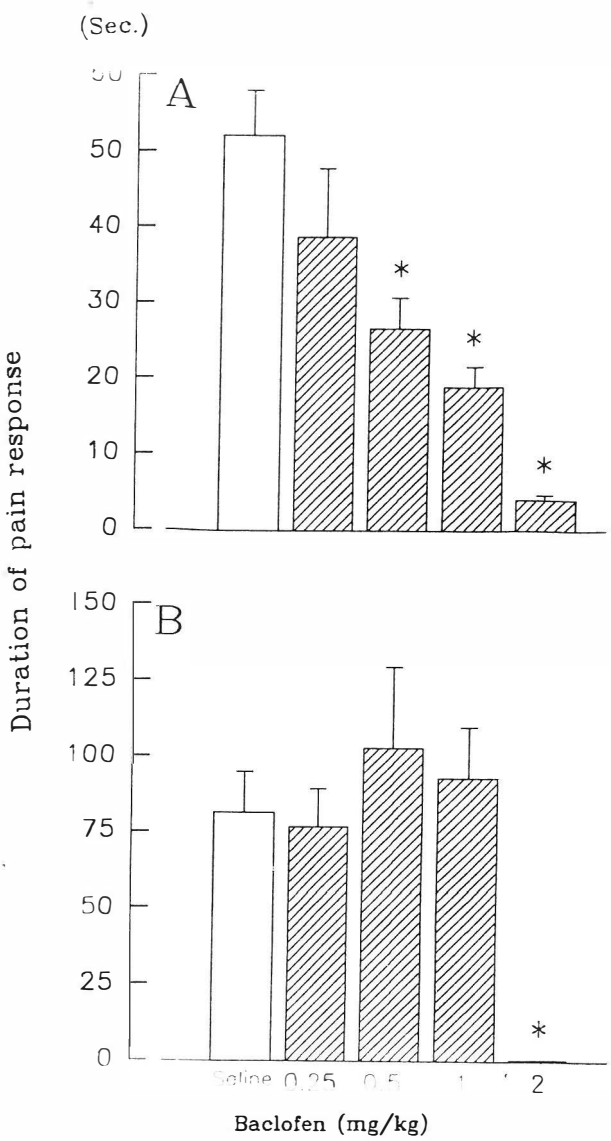

Fig. 1. Antinociceptive effect of different doses of baclofen in the formalin test in mice. Saline (10 mL/kg) or different doses of baclofen (0.25, 0.5, 1 and 2 mg/kg) was injected intraperitoneally (IP) 15 min before formalin administration to mice. Formalin (25 µL of 0.5%) was injected subcutaneously (SC) in the right hind paw and the time (seconds) spent licking and biting the injected paw during 0-5 min (panel A: first phase) and 20-40 min (panel B: second phase) after formalin injection was recorded. Each point is the mean ±SEM of 9 mice. *$p<0.01$ compared to saline control group.

Locomotor activity measurement

Locomotor activity of each animal was measured individually with an acitivity meter, Animex, type S (LKB Farrad). Each animal was placed in a plastic cage for 20 min

Table I. Effects of the D_1 agonist SKF 38393 on baclofen-induced antinociception.

Drug	Dose (mg/kg)	Early phase 0-5 min	Late phase 20-40min
Saline	10 mL/kg	49.2 ±7.7	79.6 ±12.9
SKF 38393	4	28.0 ±4.3**	26.3 ±4.7**
SKF 38393	16	24.2 ±4.2**	15.9 ±4.8**
SKF 38393	32	28.0 ±5.1**	48.4 ±8.5*
Saline+baclofen	10	25.0 ±3.8	99.0 ±13.4
SKF38393+bacl	4	19.4 ±2.1	7.6 ±2.4**
SKF38393+baclofen	16	51.1 ±4.0**	17.1 ±4.2**
SKF38393+baclofen	32	51.6 ±4.9**	55.1 ±14.2*

Animals were treated intraperitoneally with saline (10 mL/kg) or baclofen (0.5 mg/kg) 15 min before formalin injection. Saline and SKF 38393 (4-32 mg/kg) were injected 5 min prior to baclofen administration. Formalin (25 µL of 0.5%) was injected subcutaneously (SC) in the right hind paw and the time (seconds) spent licking and biting the injected paw during 0-5 min and 20-40 min after formalin injection was recorded. Each point is the mean ±SEM of 7 mice. *p<0.05, **p<0.01, different from respective control group.

to acclimatize to the environment. Counts were made for 5 min, at the appropriate time for antagonists.

Statistical analysis

Data were expressed as the mean ± S.E.M. One-way and two-way ANOVAs followed by Tukey test were used for analysis of the data. Differences between means were considered statistically significant if p<0.05.

RESULTS

Antinociception induced by baclofen in the formalin test

Intraperitoneal (IP) injection of baclofen (0.25, 0.5, 1 and 2 mg/kg) induced a dose-dependent antinociception in the first phase (one-way ANOVA, $F(4,30)=11.9$, $p<0.0001$) and second phase [$F(4,30)=6.0$, $p<0.001$] of the formalin test. The maximum response was obtained with 2 mg/kg of the drug. The effect in the late phase is not dose-dependent, but the highest dose (2 mg/kg) of the drug produced a complete antinociceptive response (Fig. 1).

Effects of dopamine agonists on baclofen-induced antinociception

Animals were treated intraperitoneally (IP) with the dopamine receptor agonist SKF 38393 (4, 16 and 32 mg/kg), 5 min prior to the administration of the $GABA_B$ agonist baclofen (0.5 mg/kg IP) (Table I). Analysis of the data with two-way analysis of variance (two-way ANOVA) showed that SKF 38393 has antinociceptive properties in the early phase [$F(3,48)=4.91$, $p<0.01$] and the late phase [$F(3,48)=22.14$, $p<0.0001$]. Baclofen induced antinociception in the first phase [$F(1,48)=3.9$, $p<0.05$] but not in the second phase [$F(1.48)=0.39$, $p>0.05$. There was also a significant interaction in the first phase [$F(3,48)=13.96$, $p<0.0001$] but not in the second phase of the formalin test [$F(3,48)=1.4$, $p>0.05$].

When the D_2 agonist quinpirole (0.01-0.3 mg/kg, IP) was administered to mice 5 min before baclofen injection, a significant interaction was found in the first phase (two-way ANOVA; [$F(4,60)=12.1$, $p<0.0001$]) but not in the second phase (two-way ANOVA; [$F(4,60)=1.0$, $p>0.05$]) of the test. The effect of quinpirole alone was significant in the first phase [$F(4,60)=69.37$), $p<0.0001$] and the second phase [$F(4,60)=50.37$, $p<0.0001$] (Table II).

The effect of baclofen was significant in the first phase [$F(1,60)=19.01$, $p<0.0001$] but not in the second phase [$F(1,60)=0.14$, $p>0.05$]. Further analysis did not indicate any difference between the response of quinpirole alone with that of quinpirole+baclofen. It seems that treatment with quinpirole masks the antinociceptive effect of baclofen.

Effects of dopamine antagonists on baclofen antinociception

Administration of the D_1 antagonist SCH 23390 (0.05 and 0.1 mg/kg IP), 30 min before either saline or baclofen (0.5 mg/kg) showed that SCH 23390 induces an antinociceptive response in the first phase [$F(3,48)=5.56$, $p<0.01$] but not in the second phase [$F(3,48)=1.33$, $p>0.05$]. Baclofen induced antinociception in the early phase [$F(1,48)=85.28$, $p<0.0001$] but not in the late phase [$F(1,48)=0.36$, $p>0.05$)]. There was a significant interaction between the two drugs in the early phase [$F(3,48)=5.46$, $p<0.01$] but not in the late phase [$F(3,48)=1.59$, $p>0.05$] (Table II).

When animals were pretreated (IP) with sulpiride 90 min prior to baclofen injection, an interaction was observed between the two drugs in the early [$F(3,48)=3.9$, $p<0.05$] but not in the late phase of the formalin test [$F(3,48)=2.0$, $p>0.05$]. The D_2 antagonist sulpiride induced antinociception in the early [$F(3,48)=34.61$, $p<0.0001$] and the late phase [$F(3,48)=85.14$, $p<0.0001$] by itself. However, the low dose of sulpiride alone increased formalin pain in the late phase. Baclofen induced antinociception in the early phase [$F(1,48)=16.52$, $p<0.001$] but not in the late phase [$F(1,48)=4.02$, $p>0.05$]. Domperidone pretreatment did not change the baclofen response, but caused antinociception in the first phase [$F(2,36)=29.1$, $p<0.0001$].

Effects of dopamine antagonists on locomotor activity

Animals were treated with saline (10 mL/kg, IP), SKF 38393 (4 and 32 mg/kg, IP), quinpirole (0.01 and 0.3 mg/kg, IP), SCH 23390 (0.01, 0.05 and 0.1 mg/kg, IP), sulpiride (25, 50 and 100 mg/kg, IP) or domperidone (5 and 10 mg/kg, SC) and locomotor activity was measured 30 min and 60

Table II. Effects of the D_2 agonist quinpirole on baclofen-induced antinociception.

Drug	Dose (mg/kg)	Early phase 0-5 min	Late phase 20-40 min
Saline	10 mL/kg	51.6±3.5	88.9±2.6
Quinpirole	0.01	14.8±2.3**	27.4±7.3**
Quinpirole	0.03	13.4±2.2**	31.4±7.0**
Quinpirole	0.1	5.7±1.2**	7.7±3.0**
Quinpirole	0.3	3.8±1.3**	1.0±0.7**
Saline+baclofen	10	25.0±3.8	100.1±12.1
Saline+baclofen	0.01	12.1±1.9**	22.0±6.4**
Quinpirole+baclofen	0.03	13.3±3.1**	23.7±4.7**
Quinpirole+baclofen	0.1	5.8±1.9**	13.3±2.9**
Quinpirole+baclofen	0.3	0.9±0.4**	0.0±0.0***

Mice received saline or baclofen (o.5 mg/kg) intraperitoneally 15 min prior to formalin injection. Saline or quinpirole was administered 5 min before baclofen. Antinociceptive effect was recorded as Table I. Each point is the mean±SEM of 7 mice. **p<0.01, ***p<0.001, different from respective control animals.

Table III. Effects of the D_1 antagonist SCH 23390 on baclofen-induced antinociception.

Drug	Dose (mg/kg)	Early phase 0-5 min	Late phase 20-40 min
Vehicle	10 mL/kg	54.6±2.5	27.6±3.9
SCH 23390	0.01	30.7±3.5**	15.0±3.5
SCH 23390	0.05	40.4±7.0*	19.0±3.8
SCH 23390	0.1	51.7±4.2	7.6±6.1
Vehicle+baclofen	10	26.7±4.3	20.4±4.2
SCH 23390+baclofen	0.01	23.3±1.9	26.0±8.6
SCH 23390+baclofen	0.05	14.9±1.8*	12.3±3.5
SCH23390+baclofen	0.1	14.7±1.8*	21.4±3.5

Animals were pretreated intraperitoneally with saline or baclofen (0,5 mg/kg), 15 min before formalin injection. Saline or SCH 23390 was injected 5 min prior to baclofen. Antinociceptive response was recorded as Table I. Each point is the mean±SEM of 7 mice. *p<0.05, **p<0.01, different from respective control group.

min after drug injection. A significant difference was shown 30 min [$F(12,75)=19.8$, $p<0.01$] and 60 min [$F(12,75)=24.5$, $p<0.01$] after drug administration. Further analysis indicated that SKF 38393 and quinpirole increased while SCH 23390, sulpiride and domperidone decreased locomotion (Table V).

DISCUSSION

The formalin test is a model of injury produced pain, which was introduced by Dubuisson and Dennis.[15] The test measures the response to a long-lasting nociceptive stimulus and resembles clinical pain.[1,27] Two distinct periods of high licking activity can be identified, an early phase lasting the first 5 min and a late phase with prolonged pain starting from

Table IV. Effects of sulpiride or domperidone on baclofen-induced antinociception.

Drug	Dose (mg/kg)	Early phase 0-5 min	late phase 20-40 min
Vehicle	10mL/kg	48.1±3.9	46.3±9.8
Sulpiride	25	21.0±3.0**	100.4±9.4**
Sulpiride	50	11.7±4.0**	12.3±1.7**
Sulpiride	100	14.9±4.1**	6.0±2.5**
Vehicle+baclofen	10	28.1±2.9	17.1±2.5
Sulpiride+baclofen	25	14.0±2.5**	98.3±12.3**
Sulpiride+baclofen	50	13.0±3.2**	11.7±2.4
Sulpiride+baclofen	100	4.4±1.9**	0.0±0.0**
Vehicle	10	51.1±2.4	47.0±5.0
Domperidone	5	18.7±2.5**	41.0±7.9
Domperidone	10	13.4±5.0**	55.6±9.6
Vehicle+baclofen	10	11.1±1.9	31.6±8.3
Domperidone+baclofen	5	7.6±1.3	16.4±2.7
Domperidone+baclofen	10	13.2±1.5	22.3±7.8

Animals were treated intraperitoneally with vehicle or baclofen (0.5 mg/kg) 15 min before formalin injection. Sulpiride was administered intraperitoneally 90 min and domperidone was injected 15 min before baclofen administration. Antinociceptive response was recorded as Table I. Each point is the mean± SEM of 7 animals. **p<0.01, different from vehicle respective group.

Table V. Effects of dopamine agents on locomotion.

		Counts/5 min (SEM)	
Drug	Dose (mg/kg)	30 min	60 min
Saline	10 mL/kg	105.3±17.2	85.1±16.4
SKF 38393	4	199.0±7.9**	165.0±13.6**
SKF 38393	32	207.7±5.7**	164.6±6.9**
Quinpirole	0.01	196.0±8.9**	74.0±20.8
Quinpirole	0.3	147.0±16.3**	59.0±14.2
SCH 23390	0.01	58.6±10.7*	33.8±4.8*
SCH 23390	0.05	96.8±15.0	62.0±9.0
SCH 23390	0.1	58.5±9.3*	26.2±6.1**
Sulpiride	25	130.9±3.2	91.4±7.6
Sulpiride	50	34.2±6.9**	30.3±5.4*
Sulpiride	100	12.3±1.5**	17.4±3.6**
Domperidone	5	138.6±9.8	32.6±10.3*
Domperidone	10	100.3±10.8	15.8±5.4**

Animals were treated intraperitoneally with saline or dopamine agonists and antagonists, and locomotor activity was counted 30 and 60 min after drug administration. Each value is mean±SEM of 7 animals.
*p<0.05, **p<0.01, different from respective control group.

20-40 min after formalin injection.[19] It has been reported that the action of analgesics differs in the early phase and late phase.[19,20]

In the present work, the influences of dopaminergic agents on baclofen-induced antinociception in both phases of the formalin test have been studied. This study demonstrates that the intraperitoneal injection of baclofen in mice produces a dose-dependent antinociceptive effect in the first phase of the formalin test. The $GABA_B$ agonist baclofen[6] is known to interact with a number of neurotransmitter systems.[8] There is evidence indicating that alteration in catecholamine function at supraspinal sites may be involved in the antinociceptive effect of baclofen.[31] Morphine induces an antinociceptive response in both phases of the formalin test[19,40] indicating that the responses of both drugs are not the same and possibly are not mediated through the same mechanism(s). This also can be supported by our previous work[42] showing that naloxone could not prevent baclofen's effect. However, the first phase of the test has been suggested to be related with substance P and morphine also may have effect attributed to substance P.[35]

There is evidence showing that the second phase of the formalin test may be associated with the peripheral action of drugs.[35] This may be in agreement with reports[32] showing that baclofen induces antinociception centrally.

The existence of two dopamine receptor subtypes, D_1 and D_2 in the brain is well established. The D_1 receptor is defined as being positively linked to adenylate cyclase while the D_2 sites are negatively linked or uncoupled to this enzyme.[23] The present data indicate that the pure D_1 agonist SKF 38393[36] causes a decrease in baclofen antinociception in the early phase, which may show that the dopamine agonist interacts with baclofen response centrally. Considering ANOVAs' results and since a single injection of SKF 38393 induced antinociception in both phases, it seems possible that increase in the antinociception of baclofen plus SKF 38393 in the second phase may be due to the D_1 agonist effect itself. However, the results obtained with SKF 38393 are not consistent with that of Morgan and Franklin[26] in which the D_1 dopamine receptor agonist showed no response in the formalin test.

The combination of baclofen with the D_2 dopamine receptor quinpirole[3,38] did not potentiate the $GABA_B$ agonist effect. The data may show that quinpirole, similar to SKF 38393, has no effect on baclofen antinociception in the first phase. The response of a combination of quinpirole plus baclofen may be due to quinpirole alone. This can be predicted from the antinociceptive effect of a single injection of quinpirole in the formalin test and can be in agreement with the report[26] showing that quinpirole induces antinociception in the formalin test.

In the present work, locomotor activity of the animals was increased by the dopamine agonists. The increase in locomotion by the drugs has been shown previously.[44] The increase in locomotor activity does not appear to influence antinociception.

The D_1 antagonist SCH 23390 also increased the baclofen response in the first phase,[21] suggesting that the D_1 antagonist may abolish the negative influence of endogenous dopamine on baclofen's effect, and in turn increases the drug response. This also shows that endogenous dopamine may exert a negative influence on antinociception.

Single administration of low doses of the D_1 dopamine receptor antagonist also shows an antinociceptive effect in the first phase. The effects are in agreement with our previous work,[44] where D_1 dopamine receptor blockade can decrease locomotor activity of the animals, which may influence or change the antinociception by the drug.

The central D_2 dopamine antagonist sulpiride,[11] in combination with baclofen, increased the baclofen effect in the early phase and caused additive antinociception in the late phase. Single doses of the D_2 dopamine receptor antagonist also showed antinociceptive response in both phases of the test. However, the low dose of the antagonist alone and in combination with baclofen caused an increase in pain response. The two opposite responses of sulpiride with different doses of the drug in late phase may be associated with the pre- and postsynaptic effects of the D_2 antagonist or it may be due to central and/or peripheral mechanism(s). However, the peripheral D_2 antagonist domperidone did not alter the baclofen response. The antinociception induced by sulpiride may be due to the blockade of the D_2 dopamine receptors at presynaptic sites, which in turn may induce antinociception. We have no explanation of the response induced by single administration of the D_2 receptor antagonist domperidone in the early phase of the test at the moment, although this may be due to high doses of the drug which may penetrate into the brain or may be mediated through a peripheral mechanism.

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