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Dopamine Receptor Subtypes and Formalin Test Analgesia

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MORGAN, M. J. AND K. B. J. FRANKLIN. *Dopamine receptor subtypes and formalin test analgesia.* PHARMACOL BIOCHEM BEHAV **40**(2) 317–322, 1991.—The role played by dopamine D_1 and D_2 receptors in formalin test analgesia was explored by challenging D-amphetamine- and morphine-induced analgesia with mixed and selective D_1 and D_2 antagonists, and by examining the relative analgesic activity of mixed and selective D_1 and D_2 agonists. The mixed D_1/D_2 dopamine antagonist cis-flupenthixol (0.5 mg/kg), the D_2 antagonist pimozide (0.5 mg/kg), and the D_1 antagonist SCH 23390 (0.1 mg/kg) attenuated both D-amphetamine and morphine analgesia. The mixed D_1/D_2 agonist apomorphine and the selective D_2 agonist quinpirole produced dose-dependent analgesia while the selective D_1 agonist SKF 38393 was without effect. These data suggest that D_1 receptors play an "enabling" role in D_2 receptor-mediated analgesia in the formalin test.

D-Amphetamine Morphine cis-Flupenthixol SCH 23390 Pimozide Apomorphine SKF 38393 Quinpirole Analgesia Formalin test

THE formalin test (19) is a model of injury-produced pain which has pharmacological characteristics that differ from those of reflex withdrawal types of pain test such as the tail-flick test (2, 3, 16). One difference is that dopamine (DA) agonists such as D-amphetamine, cocaine and apomorphine consistently produce analgesia in the formalin test (17, 26, 30, 35) but are either without effect in the tail-flick test (20, 28, 30–32, 34, 38, 41) or produce hyperalgesia (5, 22, 39).

Morphine is now known to stimulate the release of striatal and nucleus accumbens DA in vivo (9, 12, 13) and this effect appears to be involved in the reinforcing effect of morphine and heroin in the drug self-administration and conditioned place preference paradigms (8, 21, 36, 37). Recently, we have found that DA-depleting, 6-hydroxydopamine lesions of the substantia nigra and ventral tegmental area abolish analgesia induced by D-amphetamine and morphine in the formalin test (30). This suggests that DA release in the forebrain mediates the analgesic effects of both D-amphetamine and morphine in the formalin test.

The present study explored the role of DA D_1 and D_2 receptors in formalin test analgesia by challenging D-amphetamine- and morphine-induced analgesia with the mixed and selective D_1 and/or D_2 receptor antagonists cis-flupenthixol, pimozide and SCH 23390 and, in addition, by examining the relative analgesic activity of mixed and selective D_1 and/or D_2 receptor agonists apomorphine, quinpirole and SKF 38393.

METHOD

Subjects

At least five male Long-Evans rats (300 g) were tested at each dose of drug, 367 rats in total. Between 3 and 6 doses of agonist were tested to establish each dose-response relation (15–30 rats). However, only the data points corresponding to the sharply rising portion of the dose-effect curve were used in the dose-response analysis. The numbers of rats whose data were used in the dose-response relations for each drug combination are shown in Tables 1 and 2 in the Results section. Rats were tested once only with morphine. Rats tested with dopamine agonists had received cis-flupenthixol with or without morphine 2 weeks previously.

Rats were habituated to the formalin test room and apparatus for at least 20 min on the two days preceding testing.

Apparatus

The formalin test cubicle was made of clear Plexiglas and was 32 × 32 × 32 cm in size. A mirror below the floor angled at 45 degrees allowed an unobstructed view of the rat's paws. Sterile 2.5% formalin (0.05 ml) was injected into the plantar surface of one of the rat's hindpaws.

Formalin Test Procedure

Formalin test pain was rated by a rater who was blind to the drug conditions by recording the number of seconds that the rat engaged in each of the following behaviours: walking or sitting normally (pain rating = 0); walking or sitting while the injected paw was in contact with the floor but did not bear the rat's weight (pain rating = 1); lifting the injected paw off the floor (pain rating = 2); licking or chewing the injected paw (pain rating = 3). Because pain behaviour is not stable until 20–25 min after formalin injection and begins to decline after 50–60 min

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(19), testing began at 30 min after the injection and continued for 20 min. Animals were rated for pain 2 at a time and the sessions were videotaped to record the animals' general behaviour for later analysis.

Drug Treatments

D-Amphetamine sulphate, morphine sulphate, cis-flupenthixol, SCH 23390, apomorphine, SKF 38393, and quinpirole were dissolved in physiological saline. Pimozide was dissolved in 3% tartaric acid. All doses are expressed as the salt.

DA antagonists plus D-amphetamine or morphine. On the test day each rat was given two injections: a DA antagonist or saline followed by D-amphetamine (0.5–8.0 mg/kg, IP), morphine (0.75–9.0 mg/kg, SC) or saline. The injection times of D-amphetamine or morphine and the DA antagonists were adjusted, relative to the time of formalin injection, so that the maximum effects of D-amphetamine or morphine would correspond to optimal DA receptor blockade and the period of stable formalin-induced pain. Amphetamine and morphine were administered immediately before one of the rat's hindpaws was injected with formalin. Pimozide (0.025, 0.25 or 0.5 mg/kg, IP) was administered 4 h before D-amphetamine or morphine. cis-Flupenthixol (0.25 or 0.5 mg/kg, IP) was given 1 h before, and SCH 23390 (0.01 or 0.1 mg/kg, IP) was given at the same time as D-amphetamine or morphine, immediately before formalin injection.

Apomorphine, quinpirole or SKF 38393. Rats were given intraperitoneal injections of saline, apomorphine (0.03, 0.1, or 2.0 mg/kg), SKF 38393 (1.0, and 10.0 mg/kg), or quinpirole (0.3, 1.0, or 3.0 mg/kg). Apomorphine was administered immediately before formalin injection, while SKF 38393 and quinpirole were administered 30 min before formalin injection. Rats were then placed in the formalin test cubicle.

Analysis of Data

The formalin pain score was determined for the period 30–50 min after injection as 1/1200 × the sum across rating categories of the time spent in each category (s) multiplied by the Pain Rating. The pain scores were converted to percent of Maximum Possible Effect by the formula

$$\%\text{MPE} = \frac{(\text{pain score under drug} - \text{control score})}{(\text{maximum possible analgesia score} - \text{control score})} * 100.$$

Percentage analgesia scores were plotted against log dose and a statistical estimate of the MPE_{50} and its standard error was calculated from the data for individual animals by jackknifing the regression lines and interpolated MPE_{50}'s (1). Jackknifing is a method of directly assessing the variability of statistics which offers ways to set sensible confidence limits in complex situations. It is an iterative procedure which computes pseudo-values for statistics from all possible subsets of n − 1 of the data points. The mean and variance of these pseudo-values are unbiased estimates of the statistics and their variability (33). Differences in slopes and MPE 50's were tested using 2-tailed *t*-tests.

For graphical display, dose-response regression lines were computed and plotted by Sigmaplot (Jandel Scientific, Corte Madera, CA).

RESULTS

Effects of DA Antagonists on D-Amphetamine Analgesia

SCH 23390, pimozide and cis-flupenthixol all antagonized the analgesic effect of amphetamine in the formalin test but had no effect on formalin pain in the absence of amphetamine. The dose-response curves are depicted in Fig. 1 and the estimates of MPE_{50} are shown in Table 1.

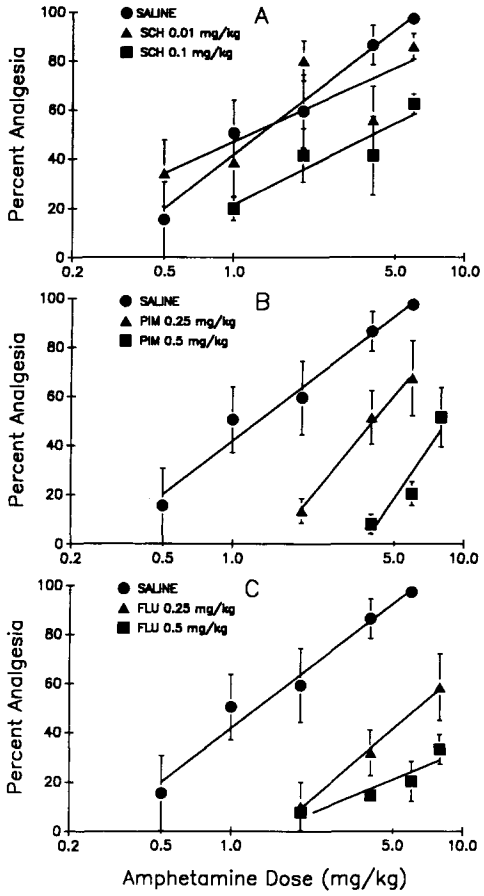

FIG. 1. Mean % formalin test analgesia produced by various doses of D-amphetamine in combination with saline or the selective D_1 dopamine receptor antagonist SCH 23390 (A), the selective D_2 dopamine receptor antagonist pimozide (B), or the mixed dopamine receptor antagonist cis-flupentixol (C). The data for amphetamine plus saline are repeated in each panel to aid comparison.

The lower dose of SCH 23390 (0.01 mg/kg) had no effect on the MPE_{50} for D-amphetamine but the higher dose raised the MPE_{50} ($t = 2.84$, $p < 0.01$). The MPE_{50}'s for both doses of pimozide were significantly greater than baseline ($t = 4.22$, $p < 0.001$; and $t = 5.86$, $p < 0.001$; respectively). Furthermore, the higher dose of pimozide (0.5 mg/kg) attenuated D-amphetamine analgesia more than the lower dose (0.25 mg/kg) ($t = 2.69$, $p < 0.02$), indicating dose-dependent antagonism of D-amphetamine analgesia by pimozide. With cis-flupenthixol the MPE_{50}'s for both doses were significantly greater than baseline ($t = 3.82$, $p < 0.001$ and $t = 3.55$, $p < 0.001$; respectively). However, the MPE_{50} for the higher dose was not significantly greater than that for the lower dose ($t = 1.27$, N.S.).

Effects of DA Antagonists on Morphine Analgesia

As can be seen in Fig. 2 and Table 1 the effects of DA antagonists on morphine-induced analgesia were complex. Figure 2A shows the effect of SCH 23390 on morphine analgesia. The lower dose (0.01 mg/kg) strongly potentiated the analgesic ef-

TABLE 1

FORMALIN TEST ANALGESIA MPE $_{50}$'s (95% CONFIDENCE INTERVALS) IN mg/kg FOR D-AMPHETAMINE AND MORPHINE IN COMBINATION WITH SALINE OR DOSES OF MIXED AND SELECTIVE D1 AND D2 DOPAMINE RECEPTOR ANTAGONISTS SCH 23390 (SCH.), PIMOZIDE (Pim.) AND FLUPENTHIXOL (Flu.)

Drug	mg/kg	D-Amphetamine	n	Morphine	n
Saline		1.34 (0.86–2.09)	25	4.34 (3.62–5.20)	15
SCH.	0.01	1.26 (0.59–2.68)†	20	1.15 (0.69–1.91)*	20
SCH.	0.10	3.85 (2.05–7.22)†	20	6.08 (5.36–6.89)†	10
Pim.	0.025	—		3.98 (2.49–6.38)	10
Pim.	0.25	3.98 (2.94–5.40)†	15	5.34 (4.28–6.65)	15
Pim.	0.5	7.94 (5.01–12.53)†	15	6.72 (5.72–7.89)†	10
Flu.	0.05	—		3.68 (2.49–5.43)‡	15
Flu.	0.25	6.38 (2.52–16.14)†	15	7.05 (4.47–11.12)‡§	16
Flu.	0.5	13.65 (3.75–49.7)†	20	10.15 (5.32–19.36)†§	16

*Significant potentiation; $p<0.01$.
†Significant antagonism; $p<0.02$.
‡Not parallel with morphine dose-response relation.
§Modified formalin pain rating—see text.
The number of rats tested for each dose-response curve is shown in the columns labelled "n."

fect of low doses of morphine. This dose of SCH 23390 combined with morphine to produce maximum possible effect (complete analgesia) at the normally marginally analgesic dose of 3.0 mg/kg morphine. The MPE_{50} was lower than that for morphine alone ($t=5.30$, $p<0.001$). When the morphine dose was increased to 6 mg/kg the analgesic effect decreased ($p<0.005$, Mann-Whitney) then rose again at 9 mg/kg. This second component of the dose-response curve (dashed line in Fig. 2A) appears to be parallel to the lower component and shifted to the right. The dose-response curve for morphine with 0.1 mg/kg SCH 23390 was also biphasic but the low dose component (not shown) did not reach 50% analgesia while the major component was clearly shifted to the right of the morphine dose response curve. The MPE_{50} (see Table 1) was significantly greater than baseline ($t=3.34$, $p<0.01$).

The higher dose of pimozide (0.5 mg/kg) raised the MPE_{50} for morphine analgesia ($t=3.96$, $p<0.001$). Only the two highest doses of morphine tested with pimozide are shown in Fig. 2. Though pimozide itself had no effect ($t<1$) the dose-response curves for morphine in combination with 0.25 or 0.5 mg/kg pimozide were flat at approximately 35% analgesia from 0.5 mg/kg to 3 mg/kg. At the higher doses of morphine the curves rose steeply and parallel to the morphine dose-response curve (Fig. 2B). Still higher doses of pimozide or morphine were not tested because animals became severely cataleptic and completely immobile.

cis-Flupenthixol at 0.05 mg/kg had no significant effect on the MPE_{50} for morphine analgesia though the slope of the dose-response relation was significantly more shallow than that for morphine alone. A dose of 0.25 mg/kg appeared to reduce the maximum effect, while 0.5 mg/kg reduced analgesia at all the doses that could be tested. With 9 mg/kg morphine and the 0.25 or 0.5 mg/kg doses of cis-flupenthixol, pain could not be confidently rated using the usual numerical scale because animals were so severely catatonic. When left undisturbed, most rats remained in a rigid posture with the hind feet splayed out. This would normally be rated as showing no pain. However, when the rats were disturbed, by gently grasping the tail to raise the hind feet and then replacing them on the floor, asymmetrical postures of the hind limbs were revealed which suggested they would protect the injured paw but were unable to move spontaneously. With 0.25 or 0.5 mg/kg cis-flupenthixol and 9 mg/kg morphine, 3/6 rats extended the injured paw posteriorly so that the plantar surface was uppermost. This behaviour was assigned a score of "2" to calculate dose-response relations. Two other rats curled up the toes of the injured paw and kept it closer to the body than the other hind paw. The sixth rat flinched and curled up the toes when the injured paw contacted the floor but stood on both feet. In these cases, where the injured paw was in contact with the floor but was not bearing weight, the behaviour was assigned a score of "1." Using this modified pain rating scale the MPE_{50} for morphine analgesia was estimated to be more than doubled by 0.5 mg/kg cis-flupenthixol. It was not possible to determine whether full analgesia could be obtained.

Analgesic Activity of Apomorphine, Quinpirole and SKF 38393

The mixed D_1/D_2 dopamine receptor agonist apomorphine produced a dose-dependent analgesia in the formalin test over a range of doses from 0.03 to 2.0 mg/kg (Fig. 3). The MPE_{50} for apomorphine analgesia in the formalin test was 0.199 (0.057–0.689) mg/kg of apomorphine. The highest dose of apomorphine (2.0 mg/kg) produced downward sniffing and licking, while the lower doses did not.

Quinpirole produced dose-dependent analgesia in the formalin test over a range of doses from 0.3 to 3.0 mg/kg. The MPE_{50} for quinpirole analgesia in the formalin test was 0.188 (0.089–0.401) mg/kg of quinpirole. The lowest dose of quinpirole (0.3 mg/kg) elicited sporadic licking and stimulated exploratory behaviour. Quinpirole (1.0 mg/kg) primarily stimulated licking, while the highest dose of quinpirole (3.0 mg/kg) elicited a more obviously stereotyped form of downward sniffing and licking.

SKF 38393 did not produce analgesia in the formalin test at a dose of 1.0 mg/kg, $F(1,10)=0.491$, N.S., or at a dose of 10.0 mg/kg, $F(1,10)=1.131$, N.S. Neither dose of SKF 38393 elicited any signs of sniffing, licking or repetitive movement. The data for DA agonists are summarized in Table 2.

DISCUSSION

The results of the present study are in line with our previous finding that 6-hydroxydopamine lesions of the SN-VTA region abolish D-amphetamine analgesia in the formalin test (30) in that

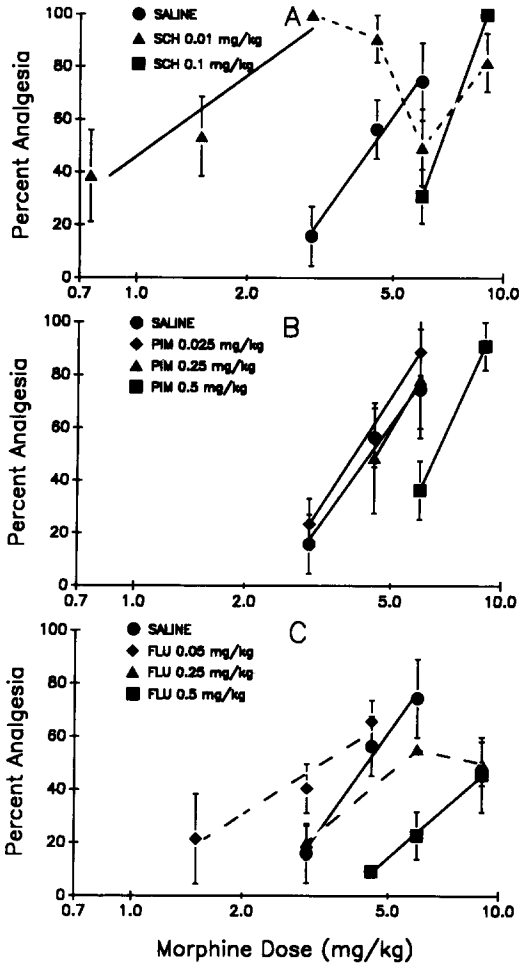

FIG. 2. Mean % formalin test analgesia produced by various doses of morphine in combination with saline or the selective D_1 dopamine receptor antagonist SCH 23390 (A), the selective D_2 dopamine receptor antagonist pimozide (B), or the mixed D_1/D_2 dopamine receptor antagonist cis-flupentixol (C). The data for morphine plus saline are repeated in each panel to aid comparison. Dashed lines represent dose-response relations that are not adequately fitted by linear regression or are not parallel to the curve for the agonist alone.

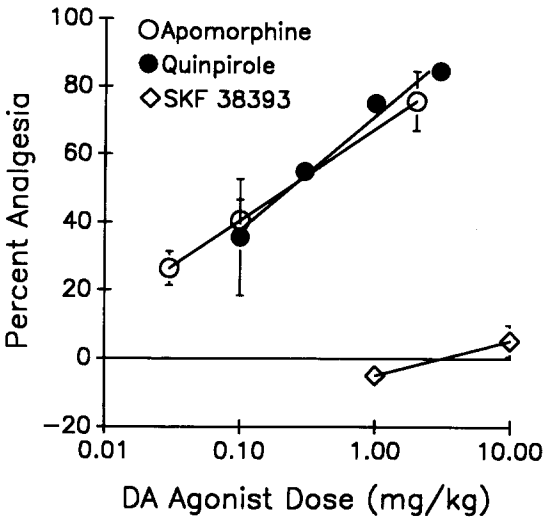

FIG. 3. Mean % formalin test analgesia produced by various doses of the mixed DA agonist apomorphine, the selective D_2 DA agonist quinpirole and the selective D_1 DA agonist SKF 38393.

both D_1 and D_2 antagonists reduced D-amphetamine analgesia in the formalin test. Pimozide, which has approximately a 1000-fold greater affinity for the D_2 receptor than the D_1 receptor (14), attenuated D-amphetamine analgesia in a dose-dependent manner. This corroborates two previous reports that selective D_2 antagonists attenuate the analgesic effect of indirect dopamine agonists in the formalin test (26,35). The mixed DA receptor antagonist, cis-flupenthixol, which has almost equal affinity for both DA receptor subtypes, and a relatively high dose of the selective D_1 receptor antagonist SCH 23390 (0.1 mg/kg), which has more than 500 times greater affinity for the D_1 receptor than the D_2 (14), also attenuated D-amphetamine analgesia. Similarly, cocaine-induced analgesia in the formalin test was attenuated by both the mixed DA receptor antagonist chlorpromazine, and SCH 23390 (0.1 mg/kg) (26). Amphetamine considerably increased locomotor activity, but it is unlikely that increased activity accounts for the lowered pain scores, since activity and pain scores are dissociable. Undrugged rats can be observed locomoting while keeping the formalin-injected paw elevated from the floor, showing that locomotion is compatible with high pain scores. Furthermore, pimozide and cis-flupenthixol virtually eliminated locomotor activity, but had no effect on pain scores. The effects of dopamine antagonists on morphine analgesia were more complex. Relatively high doses of pimozide (0.5 mg/kg), SCH 23390 (0.1 mg/kg); and cis-flupenthixol (0.5 mg/kg) attenuated the analgesic effect of morphine in the formalin test but elevated the low dose portion of the morphine dose-response relation.

Morphine produced some catalepsy and catatonia. When combined with higher doses of all three dopamine antagonists these effects were greatly increased. Despite these motor effects, rats treated with high dose morphine/DA antagonist combinations in the formalin test still exhibited pain, adopting unusual postures to protect their formalin-injected paw when catatonia was most severe. Since immobility in a standing posture would be scored as analgesia, catalepsy or catatonia would be expected to increase analgesia scores. Thus the antianalgesic effect of the DA antagonists is unlikely to be secondary to motor deficits. Taken together these results are consistent with our finding that morphine analgesia is blocked by a 6-OHDA lesion of the SN-VTA region (30). They suggest that, like D-amphetamine analgesia, morphine analgesia in the formalin test is mediated by dopamine and that both D_1 and D_2 receptors are involved.

An unexpected result was that a relatively low dose of SCH 23390 (0.01 mg/kg) synergised with low doses of morphine to produce full analgesia. This effect seems to involve a specific

TABLE 2

FORMALIN TEST ANALGESIA MPE_{50}'s (95% CONFIDENCE INTERVALS) IN mg/kg FOR APOMORPHINE, QUINPIROLE AND SKF 38393 AND THE NUMBER OF RATS TESTED IN EACH DOSE-RESPONSE CURVE

Drug	MPE_{50}	n
Apomorphine	0.199 (0.057–0.689)	15
Quinpirole	0.188 (0.089–0.401)	15
SKF 38393	>10	10

interaction with morphine because the same dose of SCH 23390 had no analgesic activity alone and did not affect D-amphetamine analgesia. Moreover, the fact that the full morphine dose-response curve was broken into two components by SCH 23390 suggests that the effect of morphine involves more than one mechanism. A search of the literature suggested two possible explanations of this effect. Although SCH 23390 is thought to be a selective D_1 receptor antagonist, there is evidence that it binds with high affinity to $5HT_2$ receptors in the brain (7) and may antagonise the effects of serotonin at $5HT_2$ receptors both centrally and peripherally (6,23). In the formalin test, lesions of the ascending 5HT systems enhance morphine analgesia (2,24), while loading with 5HT precursors antagonizes morphine analgesia (3). Thus the potentiation of morphine analgesia by a low dose of SCH 23390 may be attributable to its putative 5HT antagonist action. A second hypothesis is suggested by the fact that SCH 23390 increases dopamine release (25), possibly through increasing terminal excitability of dopamine neurons (18). Since the low dose of SCH 23390 does not block amphetamine-induced analgesia it is presumably too low to interfere with D_2-mediated effects which are sufficient to produce analgesia (see below). Thus, to the extent that morphine effects are mediated through dopamine release, they might be potentiated by a dopamine-releasing effect of SCH 23390 and the analgesic effect expressed through D_2 receptors.

The mixed D_1/D_2 DA receptor agonist apomorphine and the selective D_2 receptor agonist quinpirole produced dose-dependent analgesia in the formalin test. This is consistent with other reports that mixed DA agonists produce analgesia in the formalin test (17, 26, 30, 35) and in the clinical situation (4, 10, 27, 40). In contrast, the selective D_1 receptor agonist SKF 38393 was without effect. Likewise, apomorphine and the selective D_2 agonist RU 24213 produce analgesia in the poststimulation vocalization test while SKF 38393 is without effect (11).

Overall the results with specific antagonists suggest that both D_1 and D_2 receptors are involved in morphine and D-amphetamine analgesia in the formalin test, whereas the DA agonist results indicate that mixed and selective D_2 agonists produce analgesia in the formalin test but high doses of a D_1 agonist do not. This conflict may be explained by the suggestion that D_1 and D_2 receptors interact to control behavioral expression (14, 15, 29), and can interact in both opposing and synergistic fashions (15). In the present case, the attenuation of morphine and D-amphetamine analgesia by a high dose of SCH 23390 may result from inhibition of the "enabling" action of the D_1 receptor on the D_2 receptor while stimulation of this "enabling" activity by a D_1 agonist, in the absence of concurrent D_2 receptor stimulation, is not sufficient to produce analgesia in the formalin test.

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