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Dopamine receptor-mediated spinal antinociception in the normal and haloperidol pretreated rat: effects of sulpiride and SCH 23390

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1 Nociceptive tail flick latencies (TFL) were recorded in response to noxious thermal stimuli applied to lightly anaesthetized rats. The effects of intrathecally administered dopamine receptor agonists alone and combined with dopamine receptor antagonists were examined upon the TFL. Experiments were repeated on animals made supersensitive to dopamine following withdrawal from 28 day administration of haloperidol.

2 In untreated animals the D_2-receptor agonist LY 171555 and apomorphine produced an increase in TFL. In contrast, the D_1-receptor agonist SKF 38393 had no significant effect on TFL.

3 Following haloperidol-induced dopamine-supersensitivity, SKF 38393 produced an increase in TFL. In contrast, LY 171555 and apomorphine had minimal effects on TFL in this preparation.

4 In animals not treated with haloperidol, the dopamine receptor antagonists SCH 23390 and (±)-sulpiride both blocked the increase in TFL produced by the D_2-agonists.

5 SCH 23390 and (±)-sulpiride also blocked the increase in TFL produced by SKF 38393 in haloperidol-supersensitized animals.

6 The antinociceptive action of intrathecally administered dopamine agonists appears to be mediated via D_2-receptors. Whether the antinociception produced by SKF 38393 is exclusively contingent upon the activation of D_1-receptors in the dopamine-supersensitive animal is as yet unresolved.

Introduction

It is generally accepted that several neurotransmitter systems are involved in the modulation of nociceptive information at the level of the spinal cord (Yaksh *et al.*, 1981). There is accumulating evidence that enhancement of dopamine function produces antinociception (Saarnivaara, 1969; Paalzow & Paalzow, 1975; 1983; Barasi & Duggal, 1985; Jensen & Smith, 1982; 1983a,b; Jensen & Yaksh, 1984; Fleetwood-Walker *et al.*, 1984), whilst there are also reports of hyperalgesia following L-DOPA, apomorphine (Tulunay *et al.*, 1975) and nomifensine (Gonzalez *et al.*, 1980) treatments. However, these divergent reports appear to be dependent on the different species, routes of drug administration and noxious stimuli employed. It is of particular interest that Paalzow & Paalzow (1983) have demonstrated different effects of apomorphine on nociceptive vocalization threshold induced by electrical stimulation in rats, where low doses produced hyperalgesia and high doses antinociception, indicating the possibility of two dopamine receptor sub-types mediating these responses. In other studies electrical stimulation of the rat substantia nigra (SN) was reported to produce antinociception (Sandberg & Segal, 1978). However, Duggal & Barasi (1985) were unable to replicate this observation and concluded that the previously reported antinociceptive effects were not due to discrete activation of the SN alone but resulted from current spread to neighbouring structures. More recently electrical stimulation in the region of the A11 dopamine cell group has been shown to suppress selectively nociceptive responses recorded from dorsal horn neurones (Fleetwood-Walker & Hope, 1985); this correlates well with anatomical evidence for the origin of a descending dopaminergic pathway (Bjorklund & Skagerberg, 1979; Skagerberg & Lindvall, 1983).

In previous studies we have shown that apomorphine elevates the thermal tail flick latency (TFL) in

barbiturate-anaesthetized rats (Barasi & Duggal, 1985). Moreover it was shown that in mice the reputed D_2-agonist LY 141865 (Stoof & Kebabian, 1981) produced antinociceptive activity after intracerebroventricular injection whilst the D_1-agonist SKF 38393 (Setler *et al.*, 1978) was inactive (Ben-Sreti *et al.*, 1983a). The lack of effect of SKF 38393 on the nociceptive threshold might be explained by the idea that this compound may stimulate only supersensitive dopamine receptors (Setler *et al.*, 1978). Furthermore in chronically morpine-treated rats undergoing withdrawal, which is a model of dopaminergic supersensitivity (Lal, 1975; Sicuteri *et al.*, 1980), SKF 38393 produced an overall intensification of the withdrawal syndrome as shown by the increased incidence of dopamine mediated withdrawal signs (Ben-Sreti *et al.*, 1983b).

The present study examines the effects of the dopamine agonists apomorphine, SKF 38393 and LY 171555 (the laevorotatory isomer of LY 141865) on nociceptive sensitivity in naïve rats and in rats with haloperidol-induced dopamine supersensitivity. In addition, the reputedly specific dopamine antagonists SCH 23390 (Hyttel, 1983) and sulpiride (Elliott *et al.*, 1977; Woodruff *et al.*, 1980) were used to characterize the dopamine receptor type mediating changes in nociception produced by the dopamine agonists. Preliminary results have been presented to the British Pharmacological Society (Barasi *et al.*, 1985a,b).

Methods

Animals and environment

Male Wistar rats (UWIST breeding stock) weighing between 200–300 g were used in all experiments. They were allowed free access to standard rat and mouse breeding diet (Grain Harvesters, Wigham, Kent) and tap water, both being withdrawn 2 h before experimentation. Animal house and laboratory conditions were maintained on a 12 h light-dark cycle at a constant temperature of 21°C.

Drugs and injections

All drug solutions were made up immediately before injection. The following drugs were dissolved in apyrogenic 0.9% (w/v) sodium chloride: LY 171555 (trans-(−)-4aR-4,4a,5,6,7,8,8a, 9-octahydro-5-propyl-2H-pyrazolo [3,4-g] quinoline monohydrochloride, Eli Lilly); apomorphine hydrochloride (Sigma). SKF 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine) was dissolved in sterile water for injection. Sulpiride (Ravizza), haloperidol (Searle) and SCH 23390 ((R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hemimaleate) (Schering) were dissolved in 1% tartaric acid and the pH was adjusted to approximate neutrality. A commerical preparation of pentobarbitone (Saggital, May and Baker) was used as anaesthetic. Anaesthesia was maintained by injecting small (approx. 0.02ml) volumes of dilute barbiturate ($12\,mg\,ml^{-1}$) at appropriate intervals throughout the experiment.

Two routes were used for drug administration. Peripheral injections via the femoral vein in a volume of 0.2 ml were administered over a period of 2 min. Similarly intrathecal injections were made into the lumbar subarachnoid space at 15 µl dose volume followed by 10 µl of 0.9% saline to flush the cannula. Animals were subjected to a post-mortem examination to determine the location of the intrathecal cannula.

Earlier studies from this and other laboratories (Jensen & Smith, 1982; Jensen & Yaksh, 1984; Barasi & Duggal, 1985) have demonstrated the dose-related nature of the effect of the currently used dopamine agonists on tail flick latencies following spinal administration. On the basis of these previous studies, appropriate doses of agonist were selected.

Nociceptive testing

Nociceptive threshold in rats lightly anaesthetized with pentobarbitone were determined as tail flick latencies (TFL) in seconds elicited in response to noxious radiant heat (D'Amour & Smith, 1941; Barasi & Duggal, 1985). Briefly, radiant heat was applied by means of a 75W projector bulb to the underside of the tail which had previously been blackened with Indian ink. After establishing a steady nociceptive baseline latency (ranging from 1.5 to 2.5 s) TFLs were determined at 4 min intervals following drug administration. A cut-off latency of 6 s was imposed after which the stimulus was terminated, and that particular site of stimulus was excluded from further study. The noxious stimulus was applied to successive sites along the middle 5 cm of the tail in order to reduce any changes in the sensitivity of cutaneous nociceptors following repeated exposure to the radiant heat. In previous studies simultaneous recordings of femoral arterial blood pressure and tail-skin temperatures showed that with this technique the increases in nociceptive sensitivity detected were not related to changes in tail blood flow (Barasi & Duggal, 1983).

Intravenous and intrathecal cannulations

The femoral vein was cannulated to enable dilute anaesthetic and drugs to be injected. To reduce dead space a three-way tap was not used. An intrathecal cannula was introduced as described previously (Barasi & Duggal, 1985) and the spinal location checked by post mortem examination. Briefly, a

7.5 cm length of Portex PP10 tube was inserted through a small slit in the atlanto-occipital membrane. Drugs were introduced by a manual injection system.

Induction of dopamine supersensitivity

Dopamine supersensitivity was induced by the method of Muller & Seeman (1978) whereby haloperidol was administered in tap water (50 mg litre^{-1}) as the sole source of fluid intake for 28 days. Experiments on nociceptive sensitivity were performed 4 days after withdrawal from haloperidol. Based on the average fluid consumption of each animal, the daily intake of haloperidol per rat ranged between 3 mg kg^{-1} at the start of the schedule to approximately 12 mg kg^{-1} at the end of the schedule. To check the degree of dopamine supersensitivity which had been achieved, a group of rats was challenged with apomorphine 0.25 mg kg^{-1} i.p. four days after haloperidol withdrawal. The incidence of stereotype behaviour was assessed by use of the rating scale devised by Creese & Iversen (1973).

Assessment of data

Comparison of the nociceptive sensitivity of different treatment groups was achieved by converting tail flicks latencies to an Index of Analgesia (IA) as follows;

$$IA = \frac{TFL - \text{mean control TFL}}{\text{max TFL} - \text{mean control TFL}}$$

Calculations of statistical significance were performed using the Mann-Whitney U-test (Siegel, 1956).

Results

Effect of dopamine agonists on tail flick latency in untreated rats

Apomorphine (75 μg kg^{-1}) and LY171555 (75 μg kg^{-1}) injected intrathecally (i.t.) were found to significantly increase the TFL for periods between 20 to 30 min. Initially the responses exceeded the 6 s cut-off, gradually returning to the vehicle control baseline latencies (Figure 1). In contrast to these responses, administration of SKF38393 (150 μg kg^{-1}, i.t.) produced no significant change from the control TFL. There was a statistically insignificant reduction in the TFL following injection of the D_1-agonist.

Effect of dopamine agonists on TFL in dopamine-supersensitive rats

Administration of SKF38393 (75 μg kg^{-1}, i.t.) to rats withdrawn from chronic haloperidol treatment

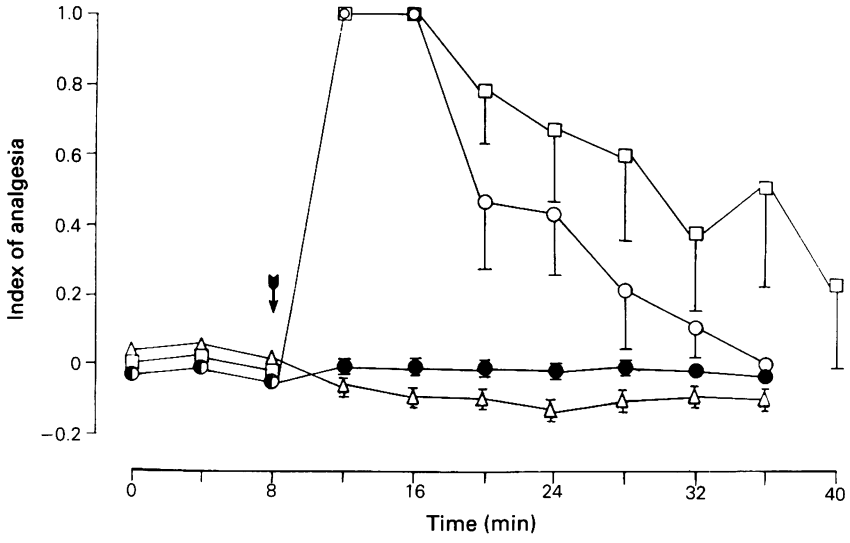

Figure 1 The effects of intrathecal (i.t.) injections of dopamine agonists on tail-flick latencies expressed as Index of Analgesia in vehicle pretreated (i.e. dopamine normosensitive) rats. After establishment of a steady baseline the following agents were injected at time = 8 min; apomorphine (75 μg kg^{-1} i.t.) (□), LY171555 (75 μg kg^{-1}, i.t.) (○), SKF38393 (150 μg kg^{-1}, i.t.) (△) and 0.9% w/v saline (15 μl per rat, i.t.) (●).

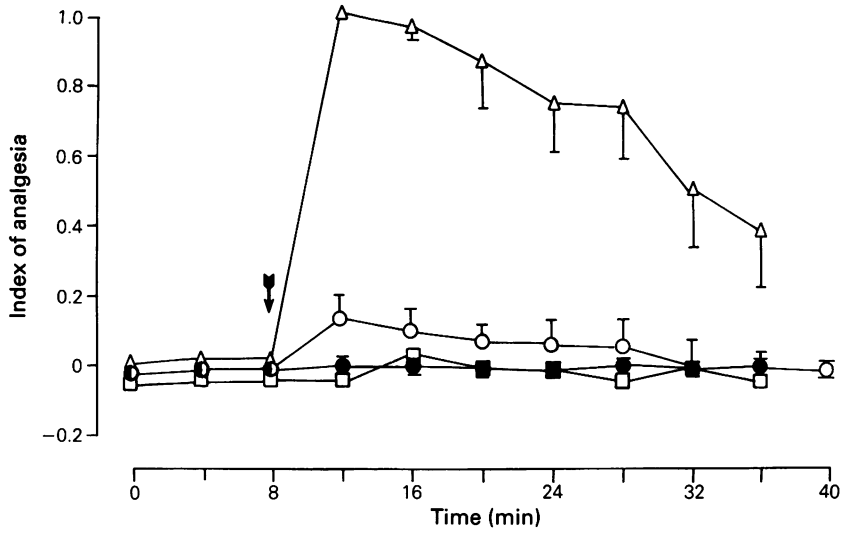

Figure 2 The effects of intrathecal (i.t.) injections of dopamine agonists on tail-flick latencies (expressed as Index of Analgesia) in rats with haloperidol-induced dopamine supersensitivity. After establishment of a steady baseline the following agents were injected at time = 8 min; SKF38393 (75 $\mu g\,kg^{-1}$, i.t.) (△), LY171555 (75 $\mu g\,kg^{-1}$, i.t.) (○), apomorphine (75 $\mu g\,kg^{-1}$, i.t.) (□) and 0.9% w/v saline (15 μl per rat) (●).

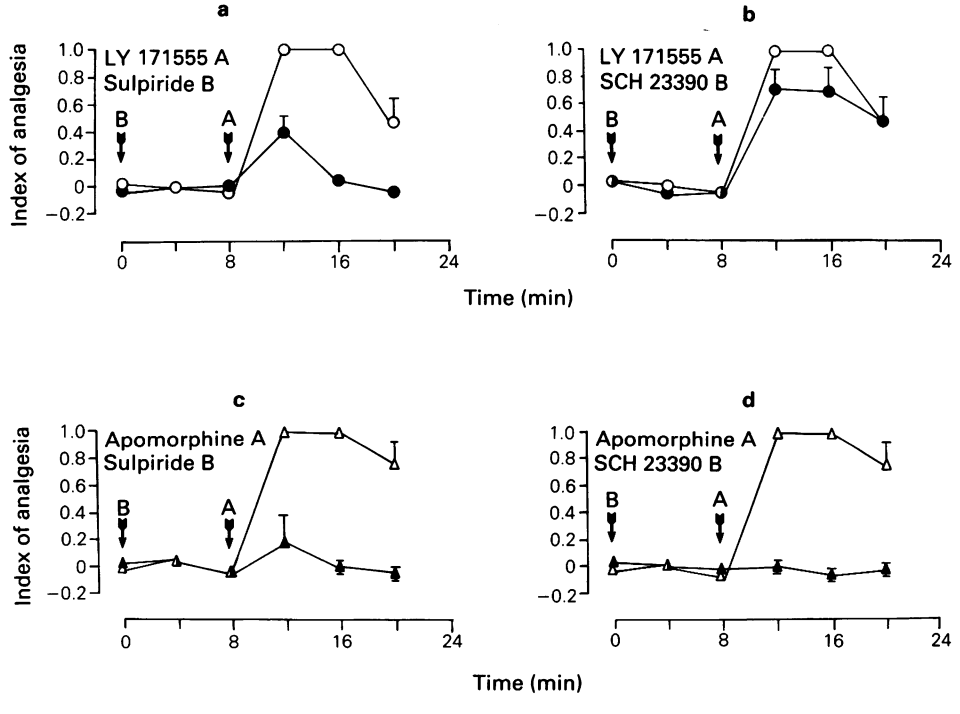

Figure 3 The effects of intrathecal (i.t.) injections of LY 171555 (75 $\mu g\,kg^{-1}$) or apomorphine (75 $\mu g\,kg^{-1}$) alone (open symbols) or in combination with intravenous (i.v.) injections of sulpiride (10 $mg\,kg^{-1}$) or SCH23390 (250 $\mu g\,kg^{-1}$) (closed symbols) on tail-flick latencies in vehicle pretreated (dopamine normosensitive) rats.

produced a significant elevation of TFL compared to the control baseline (Figure 2). The first TFL reading after injection of SKF 38393 attained the cut-off value and subsequently diminished over the duration of the experiment. This contrasts with the lack of effect when examined in untreated rats. In addition, the effect of LY 171555 (75 $\mu g\,kg^{-1}$, i.t.) on TFL was substantially reduced in the dopamine supersensitized animals compared with the cut-off response in dopamine naïve rats. Similarly, administration of apomorphine (75 $\mu g\,kg^{-1}$, i.t.) produced no change in TFL and response latencies were of the same order of magnitude as those of vehicle controls (Figure 2).

Effects of sulpiride and SCH 23390 on the apomorphine and LY 171555 elevated TFL responses in dopamine-naïve rats

The effects of intravenous administration of the dopamine antagonists sulpiride and SCH 23390 at doses corresponding to those used by ourselves and other workers (Gonzalez *et al.*, 1985; Pugh *et al.*, 1985) were examined on the protracted increase in TFL produced by apomorphine and LY 171555 in dopamine-naïve rats (Figure 3). Both sulpiride (10 $mg\,kg^{-1}$, i.v.) and SCH 23390 (250 $\mu g\,kg^{-1}$, i.v.) blocked the increased TFL produced following the i.t. administration of LY 171555 (75 $\mu g\,kg^{-1}$). The blockade produced by sulpiride was almost complete whilst that associated with SCH 23390 was considerably less extensive although it achieved statistical significance (Figure 3a,b). Furthermore, in subsequent experiments, treatment with either sulpiride or SCH 23390 (doses as above) totally abolished the increase in TFL produced by i.t. administration of apomorphine (Figure 3c,d). In the presence of either of these blockers the response to apomorphine was comparable to that produced by vehicle treatment.

Effects of sulpiride and SCH 23390 on the increase in TFL produced by SKF 38393 in dopamine-supersensitive rats

The effects of intravenous administration of sulpiride and SCH 23390 were examined on the increase in TFL produced by SKF 38393 in rats with haloperidol-withdrawal-induced dopamine supersensitivity (Figure 4). Administration of both sulpiride (10 $mg\,kg^{-1}$, i.v.) and SCH 23390 (250 $\mu g\,kg^{-1}$, i.v.) completely blocked the TFL responses produced by SKF 38393 (75 $\mu g\,kg^{-1}$, i.t.). In the presence of the antagonists the SKF 38393 response had returned to the baseline control level (Figure 4).

Assessment of maximum dopamine supersensitivity

Following withdrawal from haloperidol, rats became progressively more sensitive over a period of several days in terms of certain behavioural effects. By challenging the animals with apomorphine (0.25 $mg\,kg^{-1}$, i.p.) following four haloperidol-free days, it was noted that maximal stereotyped gnawing, licking and yawning was observed between 40 and 80 min after the agonist was injected. Thus in experiments with sensitized animals, drug studies were performed on the fourth day after haloperidol treatment had been discontinued.

Discussion

Chronic administration of haloperidol and other neuroleptics is an established method for inducing supersensitivity in dopaminergic systems, though supersensitivity in other aminergic systems has also been shown (Muller & Seeman, 1978). The schedule employed in the present study involving 28 day

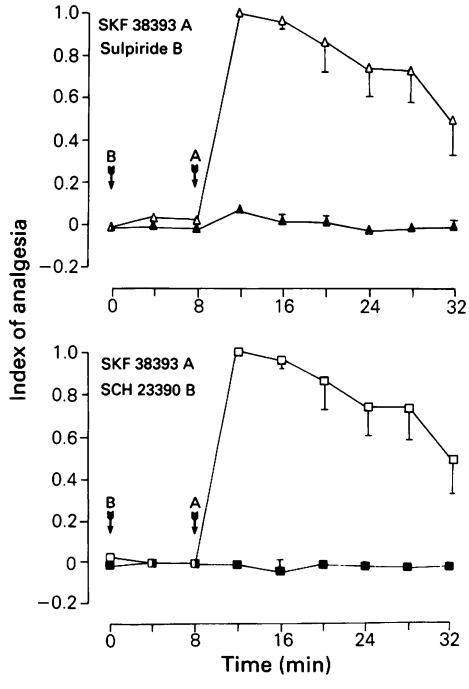

Figure 4 The effects of intrathecal (i.t.) injections of SKF 38393 (75 $\mu g\,kg^{-1}$, i.t.) alone (open symbols) or in combination with intravenous injections (i.v.) of either sulpiride (10 $mg\,kg^{-1}$) or SCH 23390 (250 $\mu g\,kg^{-1}$) (closed symbols) on tail-flick latencies in rats with haloperidol-induced dopamine-supersensitivity.

administration of haloperidol in the drinking water and the subsequent 4 day drug-free period before testing was shown to induce a characteristic pattern of stereotypic behaviour after apomorphine challenge. This demonstrates that the haloperidol dosing produced a measurable and marked degree of functional dopamine supersensitivity which accords with a 40% increase in D_2-binding sites (Mackenzie & Zigmond, 1985).

The present results clearly highlight the ability of different groups of dopamine agonists to influence spinal nociceptive reflexes. These antinociceptive profiles are correlated with the presence or absence of functional dopamine receptor supersensitivity. Thus it has been demonstrated that the putative D_2-agonists apomorphine and LY 171555 (Kebabian & Calne, 1979; Stoof & Kebabian, 1981) produced a significant elevation of the TFL in untreated naïve rats. In addition, under identical conditions the agonist SKF 38393, which is reputedly specific for D_1-receptors (Stoof & Kebabian, 1981), produced a marginal but insignificant hyperalgesia manifested by a reduction in TFL. In contrast to these results, following withdrawal from chronic exposure to haloperidol, SKF 38393 produced a pronounced elevation of the TFL whereas in untreated rats no such increase in the nociceptive response latency was recorded. Likewise in these supersensitive rats the antinociceptive response produced by LY 171555 was substantially reduced whilst that of apomorphine was abolished completely. The data obtained with untreated rats are in agreement with other reports concerning the effects of the application of dopamine agonist drugs to the spinal cord and their modification of nociceptive responses. For example, in studies by Jensen & Smith (1982, 1983a,b) using spinalized rats or following pretreatment with 5-hydroxytryptamine receptor or noradrenoceptor blocking drugs, apomorphine was found to produce an antinociceptive effect. These authors noted that apomorphine had no effect on TFL in untreated rats; the effects of the anaesthetic used in the present study may be analogous to the spinalised preparation used by Jensen & Smith. The ability of SKF 38393 to produce an antinociceptive response in the dopamine-supersensitive but not the untreated rats appears to reflect the specificity of SKF 38393 for supersensitive dopamine receptor sites as previously suggested by Setler and co-workers (1978). These authors reported SKF 38393 to produce contralateral rotation in rats with nigrostriatal lesions but not in the intact animal. In other studies it was shown that SKF 38393, which was inactive behaviourally, exacerbated withdrawl signs in chronically morphine-treated rats (Ben-Sreti *et al.*, 1983b). This state of opioid withdrawal is believed to be associated with dopamine-supersensitivity (Lal, 1975).

From the results of dopamine receptor-binding studies the benzazepine derivative SCH 23390 has been characterized as a selective antagonist at D_1-receptors (Hyttel, 1983; Christensen *et al.*, 1984). The results of the present studies with SCH 23390 and sulpiride may suggest a possible lack of dopamine receptor selectivity in the mechanisms of the antinociceptive responses produced by the dopamine agonists used. Both dopamine antagonists blocked the increase in TFL evoked by LY 171555 and apomorphine in untreated rats and also that of SKF 38393 in the supersensitive model. However, in recent publications it has been shown that SCH 23390 antagonizes amphetamine-induced locomotor activity and selected apomorphine stereotypes, behaviours associated with D_2-receptor stimulation (Christensen *et al.*, 1984; Molloy & Waddington, 1984; Arnt, 1985a). It is not surprising therefore that SCH 23390 effectively blocks the antinociceptive effect produced by apomorphine in this study (Figure 3). In pharmacokinetic studies (Schulz *et al.*, 1985), it has been shown that whilst SCH 23390 was cleared rapidly from the periphery, high levels were maintained in the CNS for comparatively long periods of time, in contrast to other neuroleptics. However, it has been observed that ligands which interact specifically with D_1-receptors may influence the expression of dopamine-mediated behaviours with a possible functional interaction between D_1- and D_2-receptors (Arnt, 1985a,b). In the light of the present results the possibility exists that SCH 23390 may influence the expression of D_2-mediated suppression of nociception. The predominantly D_2-dopamine receptor antagonist sulpiride, which was found to block the increased TFL produced by SKF 38393 in chronic haloperidol-withdrawn rats, may also block the activation of supersensitive dopamine receptor sites by D_1-agonists. In a recent report, sulpiride has been resolved into stereoisomers with the (−)-isomer showing a marked selectivity for D_2-receptors (Leff *et al.*, 1984). It may be possible using the (−)-isomer to determine whether blockade of D_1-sites by sulpiride contributes towards the overall antagonism of the SKF 38393 response produced in the supersensitive model.

The results of this study provide further evidence that the antinociceptive action of intrathecally administered dopamine agonists in lightly anaesthetized rats is mediated via D_2-receptors. D_1-agonists appear to have no antinociceptive activity in normal rats. In complete contrast, D_2-agonists have minimal antinociceptive activity in rats with supersensitive dopamine receptors. It must be added that in addition to the well characterized dopamine supersensitivity following chronic neuroleptic treatment, the antidopamine effect of brief exposure to haloperidol may persist for several weeks (Campbell *et al.*, 1985), and this may account for the apparent lack of effect of D_2-agonists in the supersensitive animal. However, in

these animals the D_1-agonist SKF 38393 increases TFL, but whether this antinociception is exclusively contingent upon the activation of D_1-receptors in the neuroleptic pretreated rats is as yet unresolved.

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