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Dopaminergic D-1 receptors: essential role in morphine-induced hypermotility

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Abstract. Administration of morphine HCl (20 mg/kg SC) to male C57Bl/6 mice evoked hypermotility. Pretreatment with low doses of the specific D-1 antagonist SCH 23390 (0.006, 0.012, 0.025 mg/kg SC) dose-dependently inhibited morphine-evoked hypermotility. The results suggest that dopamine is the essential mediator of opiate hypermotility and indicate that D-1 receptors play an important role in this effect.

Key words: Morphine – Dopamine – Hyperactivity – D-1 receptor – SCH 23390 – Mouse

An important property of morphine and related narcotic analgesics is the ability to stimulate motor activity (Oliverio and Castellano 1974), an effect hypothesized to depend on brain dopamine (DA) (Carroll and Sharp 1972; Di Chiara et al. 1977). Recently, however, this hypothesis has been challenged and alternative mechanisms have been proposed (Vaccarino et al. 1986).

In order to provide a further test of the DA hypothesis of the stimulant effects of morphine, we have used a potent and specific antagonist of D-1 DA receptors, the benzazepine derivative SCH 23390 (Hyttel 1983). We report the effect of SCH 23390 on morphine-induced hypermotility in C57Bl/6 mice, an inbred strain known to be particularly sensitive to the motor stimulant effects of morphine (Oliverio and Castellano 1974).

Materials and methods

Male C57Bl/6 mice (Charles River, Calco, Italy) weighing 20–25 g were used. The mice were housed in cages of 20 for at least 3 days upon arrival in controlled conditions of temperature (21 ± 1° C), relative humidity (60–65%) and light/dark cycle (lights from 7 a.m. to 7 p.m.).

The day of the experiment mice were placed in the motility cages (4 × cage) for 2 h and than injected subcutaneously with two injections of saline or drug 30 min apart. Motility counts were taken for 2 h before as well as after saline or drug administration.

Motility was measured with photocell motility meters (M/P_{40} Fc, Motron Products, Stockholm, Sweden) kept in sound and light proof boxes.

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Morphine HCl and SCH 23390 (Essex-Schering, Milano, Italy) were dissolved in saline and given subcutaneously in a volume of 1 ml/100 g. Statistical significance of the cumulated counts was evaluated by Dunnett's *t*-test.

Results

Figure 1 shows the time-course of motor activity in C57Bl/6 mice administered with morphine (20 mg/kg SC) and 30 min later with different doses of SCH 23390 (0.006, 0.012, 0.025 mg/kg SC). SCH 23390 dose-dependently reduced morphine-induced motor stimulation, with a significant effect even at the lowest dose tested (0.006 mg/kg SC). A dose of 0.025 mg/kg SC of SCH 23390 was effective in completely blocking the stimulation of motor activity induced by morphine. Under the present test conditions these doses of SCH 23390 failed to significantly influence spontaneous motor activity (saline, 17550 ± 2300; SCH 23390 0.025 mg/kg SC, 12800 ± 1900, total counts in 120 min, means ± SEM of results obtained in four groups of four mice each). Metergoline, a potent antagonist of $5HT_1$ and $5HT_2$ receptors, failed to affect morphine-induced hypermotility (saline: 18320 ± 2600; morphine 20 mg/kg SC: 98340 ± 11300; metergoline 0.12 mg/kg SC 30 min before morphine: 16450 ± 1900; metergoline + morphine: 99450 ± 12500; means ± SEM of activity counts cumulated for 120 min after morphine in four groups of four mice each).

Discussion

The present results demonstrate the extraordinary potency and efficacy of SCH 23390 in reducing the hypermotility induced by morphine in C57Bl/6 mice: a dose as low as 0.006 mg/kg SC reduced the effect of morphine by about 50% while 0.025 mg/kg SC blocked it completely.

The receptors for which SCH 23390 has the greater affinity are the D-1 DA-receptors (Hyttel 1984). Although SCH 23390 has moderately high affinity for 5HT receptors (Hyttel 1983) these are unlikely to play a role in the effects of SCH 23390 reported here, especially in view of the ineffectiveness of doses of metergoline about 5 times higher than the ED_{50} for antagonism of 5HT-mediated head shakes (Arnt et al. 1984), on morphine-induced hypermotility (see Results). An action via other receptor types (noradrenergic, histaminergic, opioid etc. etc.) is excluded by

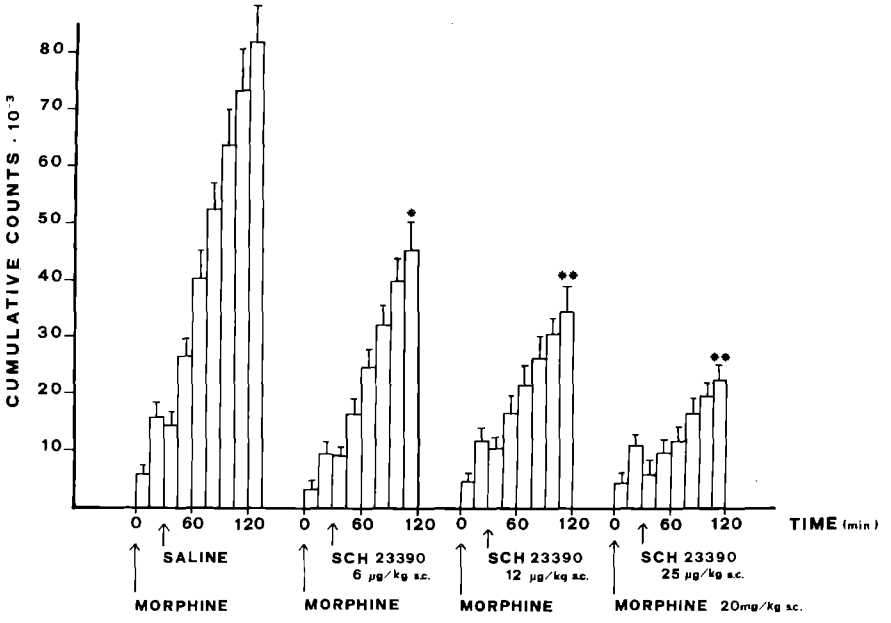

Fig. 1. Effect of increasing doses of SCH 23390 on the hypermotility induced by morphine (20 mg/kg SC) in C57Bl/6 mice. SCH 23390 was given 30 min after morphine. Count accumulation was restarted after the second administration of drug (saline or SCH 23390). Results are means ± SEM of the counts obtained in four groups of four mice. $*P<0.05$; $**P<0.001$ as compared to morphine + vehicle

the low affinity of SCH 23390 for these receptors (Hyttel 1983; Billard et al. 1984). On the other hand, non-specific effects seem to be excluded by the fact that up to the highest dose used (0.025 mg/kg SC) SCH 23390 failed to reduce spontaneous activity in control mice.

Our results therefore provide evidence for an essential role of D-1 receptors in the motor stimulant actions of morphine. Since neuroleptics with preferential activity towards D-2 receptors also block morphine-induced hypermotility (Carroll and Sharp 1972), it appears that both D-1 and D-2 receptors are essential for the expression of the morphine stimulant effects; this in turn is in keeping with the recent proposal that D-1 receptors exert a permissive-facilitatory role in the behavioural expression of D-2 mediated responses (Longoni et al. 1987).

We have recently reported that systemically administered morphine-like opiates preferentially stimulate DA-release in the limbic system at doses which induce behavioural stimulation in rats (Di Chiara et al. 1986). These results, together with the present observation that blockade of D-1 receptors by SCH 23390 antagonizes the behavioural stimulation induced by systemic morphine are in keeping with the hypothesis that the motor stimulant properties of systemic opiates are related to a preferential stimulation of the activity of a limbic subpopulation of DA neurons. Such mechanism might also apply to the rewarding effects of morphine, which are also antagonized by SCH 23390 (Leone and Di Chiara 1987).

Our results therefore indirectly contradict the suggestion that DA does not play a primary role in the opiate-induced stimulation of locomotion (Vaccarino et al. 1986). Our results also suggest that, although opiates can evoke DA-independent hypermotility from certain brain areas such as the n. accumbens (Pert and Sivit 1977), this mechanism does not account for the hypomotility elicited by their systemic administration, which, in contrast with that elicited from the accumbens (Pert and Sivit 1977) is strictly DA dependent.

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