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Is the dopaminergic system involved in the central effects of nicotine in mice?

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Abstract. Pretreatment with ineffective doses of the D_1 antagonist SCH23390 but not the D_2 antagonist sulpiride reduced hyperactivity induced by nicotine in mice habituated to the test cage. On the other hand, the D_1 and D_2 antagonists were ineffective in blocking nicotine-induced hypoactivity in naive mice. Finally, SCH23390 and sulpiride did not block the antinociception induced by nicotine. Our data indicate that the dopamine receptors D_1 and D_2 are not involved in all the central effects of nicotine in mice, but seems to be a substrate for locomotor activation induced by nicotine under specific experimental conditions.

Key words: Nicotine – Dopamine antagonists – Hypoactivity – Hyperactivity – Antinociception – Mice

Nicotine produces a wide range of behavioral changes in rodents, in particular the action on locomotor activity and pain perception. It has been shown that a single systemic injection of nicotine can produce either a depressant or a stimulant effect on locomotor activity (Morrison and Armitage 1967; Clarke and Kumar 1983; Martin et al. 1990). The effects on locomotor behavior depend on the dosage used, the duration of drug injection and time of day (Stolerman et al. 1973; Clarke and Kumar 1983). Both effects of nicotine are antagonized by mecamylamine but not hexamethonium, suggesting that the effects are mediated by central nicotinic receptors (Clarke and Kumar 1983; Martin et al. 1990). Nicotine has been shown to produce antinociception centrally in both mice and rats (Phan et al. 1973; Tripathi et al. 1982; Martin et al. 1990).

Several lines of evidence point to an interaction between central nicotinic and dopaminergic systems. In vitro and in vivo studies show nicotine can enhance the release of dopamine in the ventral tegmental area, striatum, and nucleus accumbens (Balfour 1982; Imperato et al. 1986; Rapier et al. 1988). Recent evidence suggests that the activation of the mesolimbic dopamine system induced by nicotine underlies the reinforcing and stimulant effects of this drug (Clarke 1990). Furthermore, Corrigall and Coen (1991) showed that selective dopmine antagonists D_1 and D_2 reduce nicotine self-administration in rat. In the present experiments, we investigated the potential roles that D_1 and D_2 dopamine receptors might play in the central effects of nicotine on locomotor activity (stimulant and depressant effects) and in the production of antinociception in mice.

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Materials and methods

Animals and drugs. Male ICR mice (20–25 g) obtained from Harlan Laboratories (Indianapolis, IN) were used throughout the study. They were housed in groups of six and had free access to food and water. (–)-Nicotine ditartrate was prepared from nicotine (Aldrich Chemical Company, Milaukee, WI). SCH23390 HCl, SKF38393 HCl, quinpirole HCl and sulpiride were purchased from RBI (Natick, MA). All drugs were dissolved in physiological saline (0.9% sodium chloride) and injected subcutaneously (SC). All doses refer to the bases of the drug.

Behavioral assays. For the depressant effect of nicotine, mice were placed into individual photocell activity cages (28 × 16.5 cm) immediately after SC administration of either 0.9% saline or nicotine. They were allowed to acclimate for 10 min. Interruptions of the photocell beams were recorded for the next 10 min. Either antagonists or saline was administered 30 min before nicotine, except for sulpiride (45 min).

In order to evaluate for stimulant effects, mice were acclimated for 90 min in the test cages. They were removed from the test cages and injected with either 0.9% saline or a dopamine antagonist. After a 20 min period, mice received either 0.9% saline or nicotine and were placed directly into the test cages. Interruptions of the photocell beams were recorded for the next 60 min.

Nicotine-induced antinociception in mice was measured by the tail-flick procedure (D'Amour and Smith 1941; Dewey et al. 1970). A control response (2–4 s) was determined for each animal before treatment. A maximum latency of 10 s was imposed in order to prevent damage to the tail. Mice were retested 5 min after SC administration of either saline or nicotine. Antinociceptive response was calculated as % MPE, where % MPE = [{(test-control)/(10-control)] × 100]. Either antagonists or saline was administered 30 min before nicotine except for sulpiride (45 min).

Statistical analysis. Data were analyzed statistically by an analysis of variance followed by Fisher PLSD multiple comparison test. The null hypothesis was rejected at the 0.05 level.

Results

Nicotine dose dependently decreased spontaneous activity in mice with an ED_{50} of 0.65 mg/kg (0.45–1.0). Pretreatment with SCH23390 (0.005 mg/kg), a selective D_1 dopamine receptor antagonist, did not reduce nicotine-induced hypomotility at the dose of 1 mg/kg (ED_{84}%), nor did sulpiride (8 mg/kg), a selective D_2 antagonist (Fig. 1A). Pretreatment with SKF38393 (5 mg/kg) and quinpirole (0.05 mg/kg), selective D_1 and D_2 receptor agonists, respectively, have no significant effect on nicotine-induced hypomotility. The doses of agonists and antagonists used did not significantly reduce spontaneous activity in mice.

Nicotine at a dose of 0.2 mg/kg produced a 55% increase in spontaneous activity in mice habituated to the test for 90 min prior to injection. However, this increase was not dose-dependent because nicotine injected at 0.02 and 1.2 mg/kg induced decreases of 35 and 69%, respectively, in spontaneous activity. SCH23390 (0.00125 mg/kg) significantly reduced nicotine's stimulant effect [$F(5.50) = 5.79$, $P < 0.05$)] (see Fig. 1B). Sulpiride did not attenuate nicotine-induced locomotor stimulation. Higher doses of SCH23390 and sulpiride had significant effects themselves (data not shown) which precluded their evaluation at these doses.

Nicotine produced a dose-dependent increase in tail-flick latency with an ED_{50} of 0.90 mg/kg (0.75–1.5). Dopamine antagonists were evaluated for their effects on nicotine-induced antinociception in mice. The tail-flick response (%MPE, mean±SEM) for the antagonists studies with nicotine (1.5 mg/kg) and dopamine antagonists is as follows: saline-saline: 5±1; saline-nicotine (1.5 mg/kg: 75 ±12; SCH23390-saline (0.05 mg/kg): 3±2; sulpiride-saline (20 mg/kg); 1±1; SCH23390-nicotine: 72±18; sulpiride-nicotine: 66±17). Neither D_1 or D_2 receptor antagonists had a significant effect on nicotine-induced antinociception.

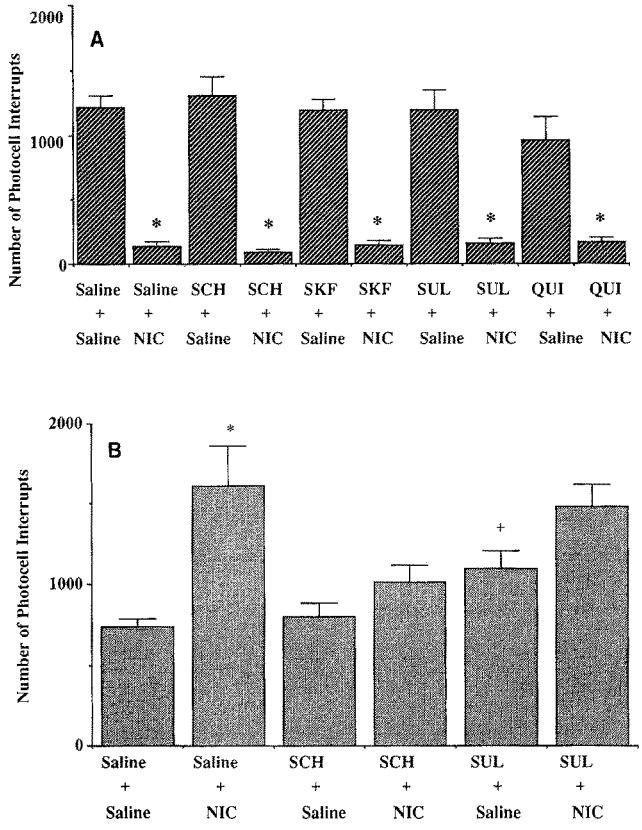

Fig. 1.A Effects of pretreatment with SCH23390 (0.005 mg/kg), sulpiride (8 mg/kg), SKF38390 (5 mg/kg) and quinpirole (0.05 mg/kg) on locomotor hypoactivity induced by nicotine (1 mg/kg) in naive mice. Results are expressed as mean (± SE) number of photocell interrupts. $^*P < 0.05$ for treatment versus saline, $^+P < 0.05$ for treatment versus nicotine. (*SCH*) SCH23390; (*SUL*) Sulpiride; (*SKF*) SKF38390; (*QUI*) quinpirole; (*NIC*) nicotine. **B** Effects of pretreatment with SCH23390 (0.00125 mg/kg), sulpiride (2 mg/kg) on locomotor hyperactivity induced by nicotine (0.20 mg/kg) in mice habituated to the test cage. Results are expressed as mean (±SE) number of photocell interrupts. $^*P < 0.05$ for treatment versus saline, $^+P < 0.05$ for treatment versus nicotine (*SCH*) SCH23390; (*SUL*) sulpiride; (*NIC*) nicotine

Discussion

Previous studies on the effect of acute nicotine injection on locomotion in rodents have yielded conflicting results. Some authors have reported that the drug increases locomotor activity, others report decreased levels of activity (Morrison and Armitage 1967; Clarke and Kumar 1983; Martin et al. 1990). These apparent contradictions may be explained by the environmental experience of the animal prior to nicotine injection and/or the different species used in the experiments. Following acute injection, nicotine induced hyperactivity in mice that had been habituated to the test cage but decreased locomotion in mice not previously exposed (or for a short period of time) to the test environment. It has been suggested that the high levels of activity displayed in a novel environment may mask the stimulant effect of a drug by a "ceiling effect" (Robbins 1977). The stimulant effect of nicotine on locomotor activity in mice is not dose-related and needs a long experimental acclimation time. On the contrary, nicotine induced hypoactivity in mice is a dose-dependent phenomenon.

The selective dopamine D_1 receptor antagonist SCH23390 significantly reduced nicotine-induced hyperactivity. The dose of SCH23390 used had no effect on spontaneous activity in mice suggesting a specific antagonist action of this drug and not a sedative effect. On the other hand, sulpiride, a specific D_2 receptor antagonist, had no significant effect on nicotine-induced hyperactivity. Nicotine-induced hyperlocomotion implicates dopaminergic mechanisms, and it has been suggested to be mediated through the activation of nicotinic receptors located in the striatum and mesolimbic system at the levels of cell bodies and terminals (Clarke and Pert 1985). Activation of nicotinic receptors has been shown to be effective in stimulating the release of dopamine from the striatum and the nucleus accumbens (Balfour 1982; Rapier

et al. 1988). It appears likely that nicotine stimulates release of brain dopamine which in turn stimulates D_1 receptors and increases locomotion. However, the involvement of the D_2 subtype in nicotine-induced hyperlocomotion showed by several authors (Museo and Wise 1990; Corrigall and Coen 1991; O'Neill et al. 1991; Kita et al. 1992) was not seen in our experiments. This lack of effect may be due to that fact that sulpiride, a substituted benzamide, does not readily pass the blood-brain barrier (Waddington and O'Boyle 1989). Interestingly, the D_1 antagonist SCH23390, but not the D_2 antagonist sulpiride, inhibited hyperactivity induced by cocaine in mice (Cabib et al. 1991).

However, the dopaminergic system is unlikely to be involved in nicotine-induced depression of locomotion, because D_1 and D_2 receptor antagonists at the doses used failed to reduce the hypoactivity induced by nicotine in mice, even at doses higher than those used in the hyperactivity model. Lower doses did not reduce nicotine's effect either (data not shown). Also, relatively high doses of these antagonists (inactive alone in the tail-flick procedure) did not block the antinociceptive effect of nicotine, suggesting that the dopaminergic system is not involved in nicotine-induced analgesia.

These findings suggest that for the locomotor activity, depending on the environmental stimuli, nicotine may be activating different subtypes of central nicotinic receptors or different locations of receptors (either pre- or postsynaptic). Another explanation is that the depressant effect of nicotine is due to a system other than the dopaminergic system. Nicotine could, for example, increase the release of GABA in the nucleus accumbens, a structure strongly involved in the control of locomotor activity. An increase in the release of GABA in the ventral striatum due to cholinergic stimulation has been demonstrated in anesthetized rats (Girault et al. 1986). Stimulation of GABA receptors in nucleus accumbens by GABA or GABA agonists induces hypoactivity and blocks the hyperactivity induced by systemic injection of *d*-amphetamine (Pycok and Horton 1979).

In conclusion, our data indicate that D_1 and D_2 dopamine receptors are not apparently involved in all the central effects of nicotine in mice, but seem to be a substrate for stimulation of locomotor activity induced by nicotine in specific experimental conditions. Other dopamine receptors, such as the D_3 and D_4 could be involved in nicotine central effects.

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