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# The importance of nucleus accumbens in nicotine-induced locomotor activity

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**Abstract**—Bilateral injections of either nicotine (200 μg) or cytisine (30 or 60 μg) into the nucleus accumbens elicited locomotor hyperactivity in rats. Pretreatment with mecamylamine (2 mg $kg^{-1}$, s.c.) was effective in attenuating the stimulatory effect of either nicotine or cytisine. This study suggests that nicotinic agonists such as nicotine and cytisine produce their locomotor excitatory effects through stimulation of the mesolimbic dopaminergic pathway.

The effects of nicotine on spontaneous locomotor activity are complex. Depending on the dosage used and the duration of drug injection, nicotine can either stimulate or depress spontaneous locomotor activity (Stolerman et al 1974; Clarke & Kumar 1983; Fung & Lau 1986; Jerome & Sanberg 1987). The stimulatory effect of nicotine on locomotor activity has been suggested to be mediated through the activation of nicotinic receptors located in the nigrostriatal (striatum) and mesolimbic (nucleus accumbens) dopaminergic neuronal systems at the levels of cell bodies and terminals (Giorguieff-Chesselet et al 1979; Clarke & Pert 1985; Fung & Lau 1986). Activation of nicotinic receptors has been shown to be effective in stimulating the release of dopamine from the striatum and nucleus accumbens (Balfour 1982; Westfall et al 1983; Rowell et al 1987). Furthermore, this stimulatory effect of nicotine on dopaminergic neurons appears to be greater at the nucleus accumbens than the caudate-putamen area (Grenhoff & Svensson 1988).

It has been suggested that dopaminergic activity in the nucleus accumbens is associated with the mediation of locomotor activity while that in the striatum is involved with the initiation of stereotyped behaviour (Jackson et al 1975; Kalivas & Miller 1985). This study was designed to examine the hypothesis that the stimulation of locomotor activity induced by nicotine is mediated by the activation of the dopaminergic neuronal system in the nucleus accumbens.

## Materials and methods

*Animals.* Male Sprague-Dawley rats (Sasco, Omaha, NE), 200–230 g, were housed in groups of 3 in a temperature (23 ± 1 °C) and light controlled room 12/12 h: light/dark cycle; lights on at 0700 h) and allowed free access to food (Purina Laboratory Chow) and water.

*Bilateral injections of saline, nicotine or cytisine into the nucleus accumbens.* Preliminary studies were conducted to establish the coordinates for subsequent drug injections. This was achieved by examining the stain produced by the injection of a 10% methylene blue solution into the nucleus accumbens. Each rat was allowed to adapt to the Digiscan animal activity monitor (model RXYZCM-16, Omnitech Electronic Inc. Columbus, Ohio) for a period of 30 min, anaesthetized with a halothane/oxygen mixture and secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA). A midline incision was made in the skull and holes were drilled on each side at the coordinates of the nucleus accumbens: A 9·4; L ± 2·4 mm (Konig & Klippel 1963). The needle of a 10 μL Hamilton syringe (Hamilton Co., Reno, Nevada) was inserted at a 10 angle (to avoid puncturing the ventricles) into the holes to a depth of V = −1·0 mm. Either physiological saline, nicotine (100 or 200 μg) or cytisine (30 or 60 μg) in a volume of 0·5 μL was injected bilaterally into the nucleus accumbens over one min. The micro-syringe was left in place for an additional minute to allow for drug diffusion away from the injection needle. After the saline or drug injections, the skin incision was closed with wound clips and covered with lignocaine ointment to relieve any pain.

*Assessment of locomotor activity.* After the intra-accumbens injections, the rats usually recovered from anaesthesia within 5 min and showed no evidence of discomfort from the surgery. Ten minutes after the injection, animals were placed in Digiscan animal activity monitors and horizontal activity was measured every 10 min for a duration of 90 min. Horizontal movement sensors directed 16 beams from front to back (x-axis) and 16 beams from side to side (y-axis). Interruption of these beams generated data that were collected by an analyzer and the results printed automatically at the end of each time period. All testing was conducted between 0800 h and 1600 h in an isolated environmental room maintained at a temperature of 22 ± 1 °C.

*Drugs.* Nicotine tartrate and cytisine were purchased from Sigma Chemical Co. (St. Louis, MO). Mecamylamine hydrochloride was a gift from Merck Sharp & Dohme Research Lab. (Rahway, NJ).

*Statistics.* Data were expressed as the mean and the standard error of the mean (s.e.m.). Significant difference was evaluated using the analysis of variance (ANOVA) with repeated measures followed by a least significant difference test with a level of $P < 0.05$ being considered to be significant.

## Results and discussion

The results in Fig. 1 show that either nicotine (200 μg) or cytisine (30 or 60 μg) produced a significant increase in locomotor activity in rats. Cytisine, a potent nicotinic agonist, which is less lipophilic than nicotine (Romano & Goldstein 1980), is more effective than nicotine in producing hyperactivity in rats (Romano & Goldstein 1980).

To test the hypothesis that the hypermotility produced by either nicotine or cytisine is mediated via its interaction with nicotinic receptors in the nucleus accumbens, rats were pretreated with mecamylamine (2 mg $kg^{-1}$, s.c.) 20 min before the central injections of either nicotine or cytisine. It was found that mecamylamine, a centrally acting nicotinic receptor antagonist, markedly attenuated the hypermotility response produced by either nicotine or cytisine (data not shown). When given alone, mecamylamine had no effect on locomotor activity (Clarke & Kumar 1983). These observations suggest that the hypermotility response elicited by either nicotine or cytisine is mediated via its interaction with nicotinic receptors in the nucleus accumbens.

It has been previously shown that nicotine can release endogenous dopamine from nerve terminals in the nucleus accumbens (Rowell et al 1987) and compounds that release dopamine in the nucleus accumbens can stimulate locomotor

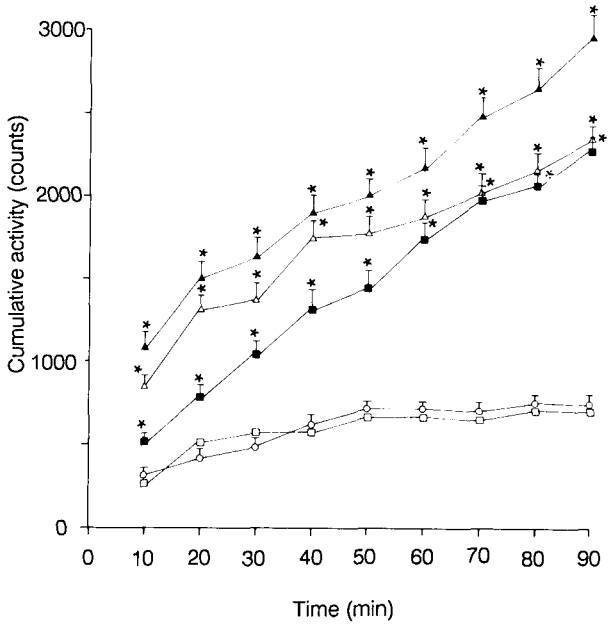


FIG. 1. Effect of nicotine or cytisine on locomotor activity of rats. Under halothane anaesthesia, rats were injected with saline, nicotine (100 or 200 μg) or cytisine (30 or 60 μg) bilaterally into the nucleus accumbens. Cumulative locomotor activity was measured at 10 min intervals for 90 min. Results are mean ± s.e.m. of 5 animals. ○——○ animals were injected with saline, □——□ animals were injected with nicotine (100 μg), ■——■ animals were injected with nicotine (200 μg), △——△ animals were injected with cytisine (30 μg), ▲——▲ animals were injected with cytisine (60 μg).

* Significantly different from saline-treated group ($P < 0.05$).

activity (Jackson et al 1975). Therefore, activation of nicotinic receptor sites in the nucleus accumbens may release dopamine, which may interact with postsynaptic dopaminergic receptors resulting in hyperactivity in these animals (Mitchell et al 1989). Our results are in agreement with a recent report showing that activation of the mesolimbic dopaminergic system mediates the locomotor stimulant effect produced by the systemic administration of nicotine (Clarke et al 1988). In addition, the locomotor stimulant effect of nicotine was abolished by the bilateral intra-accumbens injections of 6-hydroxydopamine, a drug that depletes dopamine in mesolimbic terminal areas (Clarke et al 1988). This provides further evidence of the significance of the nucleus accumbens in mediating the locomotor stimulant effect of nicotine. The doses of nicotine injected into the nucleus accumbens appeared to be high and it is possible that smaller doses of nicotine injected into the ventral tegmental area (the origin of the mesolimbic pathway) may also elicit the same hyperactivity in these animals.

In summary, this study suggests that the nucleus accumbens plays an important role in the nicotine-mediated locomotor activity.

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