Effects of SCH23390 Injection into the Dorsal Striatum and Nucleus Accumbens on Methamphetamine-induced Gnawing and Hyperlocomotion in Rats

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Abstract

The effects of SCH23390, a selective D1 receptor antagonist, injected into either the dorsal striatum or nucleus accumbens on methamphetamine-induced stereotyped gnawing and hyperlocomotion in rats were investigated. SCH23390 injected into the dorsal striatum did not alter the gnawing induced by both methamphetamine and apomorphine. However, SCH23390 injected into the nucleus accumbens significantly reduced methamphetamine-induced gnawing without altering the effects of apomorphine. Injection of SCH23390 into the nucleus accumbens reduced the hyperlocomotion produced by methamphetamine more markedly than injection of SCH23390 into the dorsal striatum.

Introduction

Sulpiride, a specific dopamine 2 (D2) receptor antagonist, has been reported to potentiate apomorphine- and methamphetamine-induced oral stereotypy when injected into the dorsal striatum\cite{1-4}. A small but significant increase of apomorphine-induced oral stereotypy has also been reported upon injection of a specific D1 receptor antagonist, SCH23390, into the same site\cite{2}. However, the effect of D1 receptor blockade in the dorsal striatum on methamphetamine-induced oral stereotypy is not known. The present study sought to determine whether injection of SCH23390 into the dorsal striatum potentiates methamphetamine-induced oral stereotypy. To support the regional differences in function within the areas of dopaminergic neuron terminals, SCH23390 was also injected into another dopaminergic terminal area, the nucleus accumbens. Hyperlocomotion produced by methamphetamine after intracerebral injection of SCH23390 was also measured to test the hypothesis that the nucleus accumbens more effectively generates methamphetamine-induced hyperlocomotion via D1 (as well as D2\cite{3}) receptors than the striatum.

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Materials and Methods

1. Animals and surgery

Male Wistar rats (180~220 g) were anesthetized with sodium pentobarbital (50 mg/kg, i. p.). Bilateral guide cannulae (0.70 mm o. d., 0.30 mm i. d.) were implanted stereotaxically in the dorsal striatum (ant. 7.8~8.4, vert. 1.0~1.5, lat. 2.0~2.5) and nucleus accumbens (ant. 9.0~9.4, vert. -0.5~1.5, lat. 0.8~1.4) according to the atlas of KÖNIG and KLIPPEL[5]. The nucleus accumbens cannulae were angled at 8° from the mid-sagittal plane to avoid the ventricular system. The animals were not used until at least 1 week after surgery, at which time they were temporarily restrained for bilateral intracerebral injection of either SCH23390 (1 μg in 0.5 μl of saline) or saline (0.5 μl) from Hamilton microsyringes over a 30-s period, and the cannulae were left in situ for 30 s after completion of the injections. The injection sites were verified by macroscopic examination using cryostat sections (100 μm) at the end of the experiments. If injections were localized outside the defined regions, the results concerned were omitted from data analysis.

2. Behavioral methods

To observe behavior, pairs of rats were placed in rectangular activity boxes (40 x 27 x 20 cm) with perspex sides and wire-mesh floors at least 1 h before the start of the experiment. The rats received intraperitoneal injections of either methamphetamine (5 or 10 mg/kg) or apomorphine (1 or 2 mg/kg) 10 min after the intracerebral injection. Gnawing behavior was observed for 5 min every 15 min for 1.5 h. The numbers of rats showing continuous gnawing during each observation period were expressed as percentages of the total. To facilitate observation, the cages were raised on 30-cm legs and the animals were viewed from below.

For the measurement of locomotor activity, rats were placed singly in experimental boxes 1 h before the start of the experiment. Methamphetamine (3 mg/kg) was injected i. p. 10 min after intracerebral injection of either SCH23390 or saline, and locomotor activity was measured with a battery of infra-red photocells (Opto-Varimex, Columbus Instruments Ltd.) for 1.5 h.

The drugs used were methamphetamine HCl (Dainippon Pharmaceutical Co. Ltd.), apomorphine HCl (Sigma) and SCH23390 (Schering Co.).

3. Statistical analysis

The results from the locomotor experiments were analyzed by two-tailed Student’s t test and the gnawing data were analyzed by Fisher’s exact probability test.

Results

1. Effects of intracerebral SCH23390 on methamphetamine-induced gnawing

Only a few (6-11%) of the rats previously injected (10 min before) with saline into the dorsal striatum displayed stereotyped gnawing after methamphetamine (5 mg/kg) injection (data are from KOSHIKAWA et al.[10]). SCH23390 (2 and 4 μg) injected into the dorsal striatum instead of saline did not alter the gnawing after methamphetamine (Fig. 1). Methamphetamine (10 mg/kg) caused stereotyped gnawing in rats previously injected with saline into the nucleus accumbens. The
percentages of rats exhibiting gnawing were between 63% and 79% from 45 to 90 min after methamphetamine injection. This gnawing was significantly (P<0.05) inhibited by prior injection of SCH23390 (2 μg) instead of saline into the nucleus accumbens at 45 and 60 min after methamphetamine injection (Fig. 2).

Fig. 1 Percentages of rats displaying gnawing behavior. Methamphetamine (5 mg/kg i. p.) was given 10 min after injection into the dorsal striatum of saline (——, n=18), SCH23390 2 μg (●, n=12) or SCH23390 4 μg (△, n=12). Data in saline group are from KOSHIKAWA et al[4].

Fig. 2 Percentages of rats displaying gnawing behavior. Methamphetamine (10 mg/kg i. p.) was given 10 min after injection into the nucleus accumbens of saline (——, n=24) or SCH23390 2 μg (●, n=12). *P<0.05, differences from appropriate saline controls.
2. Effects of intracerebral injection of SCH23390 on apomorphine-induced gnawing

Apomorphine (1 mg/kg) did not induce stereotyped gnawing in rats previously (10 min before) injected with saline into the dorsal striatum. SCH23390 (2 μg) injected into the dorsal striatum instead of saline produced no significant increase of gnawing after apomorphine (1 mg/kg) (Table 1).

In rats previously (10 min before) injected with saline into the nucleus accumbens, apomorphine (2 mg/kg) rapidly induced gnawing, the peak effect occurring at 30 min then falling to zero by 75 min. SCH23390 (2 μg) given instead of saline tended to reduce this gnawing (Table 1). However, this apparent reduction in gnawing was not statistically significant (P > 0.05).

3. Effects of intracerebral SCH23390 on methamphetamine-induced hyperlocomotion

SCH23390 (4 μg) injected into the dorsal striatum significantly reduced (P <
0.05) the locomotor activity produced by methamphetamine (3 mg/kg) from 80 to 90 min after methamphetamine injection (Fig. 3). A smaller dose of SCH23390 (2 μg) into the same site did not alter the hyperlocomotion produced by methamphetamine (Fig. 3).

Injection of SCH23390 (2 μg) into the nucleus accumbens significantly reduced (P<0.05) locomotor activity from 80 to 90 min after methamphetamine (3 mg/kg) injection (Fig. 4).

**Discussion**

SCH23390 injected into the dorsal striatum did not facilitate gnawing induced by either methamphetamine (5 mg/kg) or apomorphine (1 mg/kg). Facilitatory effects of sulpiride injected into the same site on gnawing induced by methamphetamine and apomorphine suggested the importance of D2 (but not D1) receptor blockade in the dorsal striatum[4]. However, a small increase of apomorphine-induced oral stereotypy has also been reported by D1 receptor blockade with SCH23390 in the dorsal striatum[2]. Our results contradict those of the latter study[2], which suggested the involvement of D1 (as well as D2) receptor blockade in the dorsal striatum on apomorphine-induced oral stereotypy. The discrepancy between our results and those of the other authors may be partly due to differences in experimental conditions such as the dose employed, and method used for assessing the stereotyped gnawing.

SCH23390 injected into the nucleus accumbens inhibited methamphetamine-induced gnawing but did not significantly affect the gnawing induced by apomorphine. These effects of SCH23390 are of interest because blockade of D2 receptor
in the nucleus accumbens by sulpiride also blocked the gnawing induced by methamphetamine without altering the effects of apomorphine\cite{3}, and also because the nucleus accumbens is not thought to affect dopamine-mediated stereotypy\cite{6}. The suggestion that the nucleus accumbens might be involved is supported by another study in which several putative dopamine agonists induced stereotyped gnawing after their administration into the nucleus accumbens\cite{7}. Our results cannot be explained by diffusion of injected SCH23390 from the nucleus accumbens to the adjacent ventral striatum, which is considered to mediate stereotypy\cite{4,8}, because apomorphine still evoked gnawing after SCH23390 had been injected into the nucleus accumbens, similar to that obtained in rats given saline instead of SCH23390. Other authors have also reported that sulpiride injected into the nucleus accumbens does not block apomorphine-induced stereotypy, although sulpiride injected into ventral striatum is effective\cite{2}. Taken together with these previous studies using sulpiride\cite{3,4}, both D₁ and D₂ receptors in the nucleus accumbens are suggested to mediate the gnawing induced by methamphetamine administration.

SCH23390 (2 μg) injected into the nucleus accumbens reduced methamphetamine-induced hyperlocomotion whereas the same dose of SCH23390 injected into the dorsal striatum had no effect. Only a high dose (4 μg) of SCH23390 could reduce the hyperlocomotion induced by methamphetamine. A much greater reduction of methamphetamine- and apomorphine-induced hyperlocomotion was also produced by sulpiride injected into the nucleus accumbens rather than into the dorsal striatum\cite{3}. These results support the general idea that the nucleus accumbens more effectively generates dopamine-mediated locomotion than the striatum\cite{6} and suggest the involvement of both D₁ and D₂ receptors in the generation of locomotion in rats.

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**References**


