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Locomotor Stereotypy Produced by Dexbenzetimide and Scopolamine Is Reduced by SKF 83566, Not Sulpiride

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FRITTS, M. E., K. MUELLER AND L. MORRIS. *Locomotor stereotypy produced by dexbenzetimide and scopolamine is reduced by SKF 83566, not sulpiride.* PHARMACOL BIOCHEM BEHAV **60**(3) 639–644, 1998.—Like amphetamine, scopolamine produces locomotor stereotypy (repetitive routes of locomotion) in an open field. To determine whether locomotor stereotypy is a common behavioral effect of anticholingeric agents, several doses of the anticholinergic dexbenzetimide were tested for the ability to produce locomotor stereotypy; like scopolamine, dexbenzetimide produced locomotor stereotypy. To investigate a possible role of dopamine in anticholinergic-induced locomotor stereotypy, we tested the ability of the dopamine D_1 antagonist SKF 83566 and the D_2 antagonist sulpiride to block the locomotor stereotypy induced by scopolamine as well as dexbenzetimide. SKF 83566 blocked scopolamine- and dexbenzetimide-induced locomotor stereotypy; sulpiride did not reduce dexbenzetimide-induced locomotor stereotypy, but enhanced scopolamine-induced locomotor stereotypy. Hyperlocomotion was reduced by both dopamine antagonists. Results are interpreted in support of the notion that dopamine is the likely candidate mediating locomotor stereotypy. © 1998 Elsevier Science Inc.

Locomotor Stereotypy SKF 83566 Sulpiride Dopamine Acetylcholine Scopolamine Dexbenzetimide

THE role of dopamine (DA) in mediating the motor effects of amphetamine is well established (1). Amphetamine reliably increases locomotion and produces focused stereotypy (absence of locomotion and intense sniffing and licking/biting of a restricted area of the environment) in rats (25). Amphetamine also produces locomotor stereotypy—repetative patterns or routes of locomotion in an open field (18,25). Several studies demonstrate that amphetamine produces hyperlocomotion by increasing DA release in the nucleus accumbens and focused stereotypy by enhancing DA release in the caudate (4,13). Locomotor stereotypy has been less studied, and only recently become a focus of attention. Because locomotor stereotypy combines aspects of stereotypy and hyperlocomotion, the mechanisms underlying these behaviors may well be similar. Likewise, most amphetamine-induced behaviors are mediated by increases in either mesolimbic or nigrostriatal DA systems; these same systems are likely candidates for the mediation of locomotor stereotypy. The hypothesis is supported by findings that haloperidol, a D_2 DA antagonist, reduced amphetamine-induced locomotor stereotypy at doses that failed to affect locomotion per se (17).

If DA receptor stimulation is intimately involved in locomotor stereotypy, one would expect other DA agonists to produce this behavior in an open field. However, not all data are consistent with this hypothesis. Like amphetamine, apomorphine produces hyperlocomotion and focused stereotypy (3,19); these effects are mediated by DA receptors in the caudate and nucleus accumbens (13). Apomorphine, however, does not produce locomotor stereotypy in an open field (19), although it produces repetitive locomotion in a smaller testing arena (10). Moreover, like amphetamine, the anticholinergic scopolamine produces hyperlocomotion (23,27). Scopolamine-induced hyperlocomotion is different from amphetamine-induced locomotion (23) and appears to be mediated by different mechanisms. For instance, lesions of DA terminals block amphetamine-induced hyperlocomotion but not scopolamine-induced hyperlocomotion (12). Scopolamine has no direct action on DA receptors and produces locomotor ste-

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reotypy, but not focused stereotypy (19). Therefore, the involvement of DA in locomotor stereotypy has yet to be firmly established.

One possibility is that scopolamine produces locomotor stereotypy due to an indirect effect on DA. Numerous studies have reported that DA can inhibit the release of acetylcholine (ACh) (6,29), which points to a negative interaction between the two systems (16,28). Moreover, because the discovery that DA effects are mediated by at least two different receptors (D_1 and D_2), it has been shown that while D_2 agonists decrease, D_1 agonists increase ACh release in the striatum (2,5,8,24). If this is the case, anticholinergics like scopolamine may be producing locomotor stereotypy by indirect elevation of DA levels achieved via a reduction in ACh, and this effect may be differentially mediated by D_1 and D_2 receptors. The idea is supported by findings that haloperidol and the D_1 antagonist SCH 23390 decrease scopolamine-induced hyperlocomotion (26). Similarly, alpha-methyl-para-tyrosine reduces hyperlocomotion produced by scopolamine, benztropine, and atropine (30).

We tested the above hypothesis with scopolamine and dexbenzetimide. Dexbenzetimide is an anticholinergic that crosses the blood–brain barrier more easily than scopolamine and has a much longer duration of action than scopolamine. Therefore, if locomotor stereotypy is a property of anticholinergics in general, dexbenzetimide should be more effective than scopolamine at producing locomotor stereotypy. If this is the case, one would hypothesize an interaction between DA and ACh underlying scopolamine-induced locomotor stereotypy. To determine whether DA mechanisms might be related to anticholinergic-induced locomotor stereotypy, we tested the ability of the D_1 antagonist SKF 83566 and the D_2 antagonist sulpiride to block scopolamine- and dexbenzetimide-induced locomotor stereotypy.

METHOD

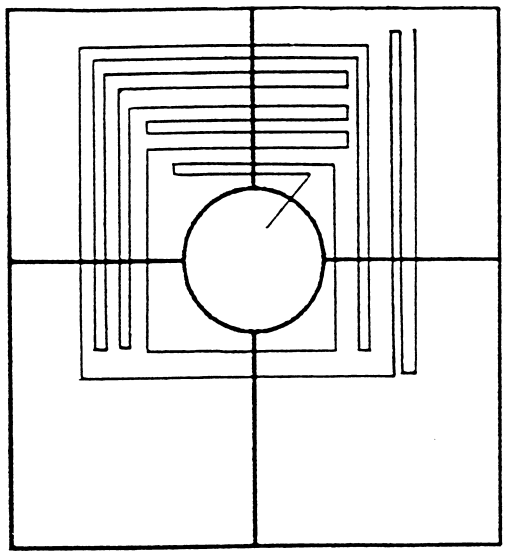
Animals

Male Wistar rats (350 to 450 g) bred in the departmental animal facilities were housed individually in standard wire-mesh cages on a 12 L:12 D cycle. Food and water were available ad lib. Rats were tested 4 h prior to lights out.

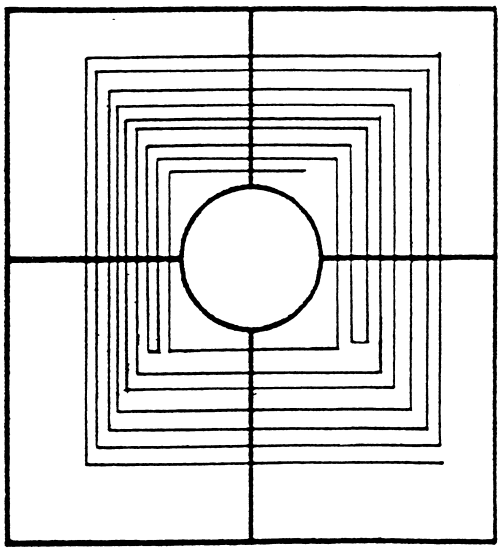
Apparatus and Data Reduction

An open field (112 × 112 × 30 cm) was divided into five equal areas (a center and four surrounding areas). A videocamera was mounted approximately 170 cm above the floor of the open field. Each animal was videotaped for 1 h; the animal's route through the open field was recorded by a videotracking system (Videomex-V, Columbus Instruments). The rat's path through the open field was then divided into a series of trips [see Fig. 1; for explanation, see (18)]. Briefly, there are five trip types. "C" designates a trip to the center area of the open field. Otherwise, trip types are defined as the number of lines crossed during a trip. Trip types range from "1" to "4," with a trip of "4" representing a complete tour of the perimeter of the open field.

The index of locomotor stereotypy, gamma, is calculated by dividing the total number of (sequentially) repeated trips by the total number of trips exhibited (18). Thus, gamma quantifies the probability that the rat will repeat the trip that it has just exhibited. Gamma values range from 0 to 1.0; higher values indicate greater locomotor stereotypy. The design was a two-factor (dose × time) ANOVA. The number of lines crossed was determined in the usual way (18). Statistically significant differences between groups were assessed with a two-factor (dose × time) ANOVA. Data were analyzed with the statistical program BMDP 2V (11).



Gamma = 0.364 LC = 24 Time: 0 to 10 min



Gamma = 0.625 LC = 33 Time: 30 to 40 min

FIG. 1. Raw data from a rat injected with 2.0 mg/kg scopolamine. In general, rats locomote near the walls. The rat's path begins near the center and spirals outward simply to facilitate the data collection process. The rats do no simply circle the perimeter of the open field in one direction; changes in direction are common. This is a rat with a high gamma score at 40 min and a high proportion of trips of "4." LC = lines crossed.

Testing

Each animal was briefly handled once a day for 5 days prior to testing. All animals were then habituated to the open field for 40 min on 2 consecutive days prior to testing. On the day of testing, each rat was injected with the anticholinergic of interest and immediately placed in the center of the open field. Each rat was tested only once. All injections were subcutaneous.

Experiments

In the first experiment, rats (n = 8 per group) were injected with various doses of dexbenzetimide (saline, 0.50, 0.80, or 1.5 mg/kg, Sigma Chemicals) and tested for dexbenzetimide-induced changes in gamma and lines crossed. Although the rats were videotaped for 1 h, most rats were asleep by the end of the first half hour. Therefore, only the data from the first 40 min are reported. In the second series of experiments (n = 8 per group) either the D_1 antagonist SKF 83566 (saline, 0.005, 0.01, or 0.03 mg/kg, Sigma) or the D_2 antagonist sulpiride (saline, 15 or 25 mg/kg, Sigma) were injected 30 min prior to injection of 2 mg/kg scopolamine hydrobromide (Sigma; dose calculated as the salt) or 1.5 mg/kg dexbenzetimide. The rats were immediately placed in the open field after the scopolamine or dexbenzetimide injection and were videotaped for 1 h. Again, little locomotion was present after 40 min; therefore, only gamma and lines crossed data from the first 40 min are presented.

RESULTS

Because gamma conveys no meaning if a rat fails to locomote, gamma data were not used if a rat failed to exhibit four or more trips during a particular time interval. These missing data' were replaced with the group mean; degrees of freedom were reduced accordingly in the statistical analyses (15).

Dexbenzetimide

Dexbenzetimide significantly induced locomotor stereotypy, $F(9, 84) = 2.91$, $p < 0.05$, for the dose × time interaction. In comparison to saline controls, dexbenzetimide-treated rats generally exhibited higher gamma scores over time (see Fig. 2a). As shown in Fig. 2b, dexbenzetimide-treated rats were hyperactive with respect to controls. Dexbenzetimide produced significant hyperlocomotion, $F(12, 108) = 3.51$, $p < 0.05$, for the dose × time interaction.

SKF 83566 plus Dexbenzetimide

SKF 83566 significantly reduced dexbenzetimide-induced locomotor stereotypy, $F(9, 75) = 2.89$, $p < 0.05$, for the dose × time interaction. In comparison with saline controls, locomotor stereotypy was reduced by higher doses of SKF 83566 (see Fig. 3a). SKF 83566 produced a dose-related reduction in hyperlocomotion (see Fig. 3b; $F(4, 46) = 3.46$, $p < 0.05$ for the dose × time interaction.

Sulpiride plus Dexbenzetimide

Sulpiride failed to consistently block dexbenzetimide-induced locomotor stereotypy (see Fig. 4a; $F(6, 72) = 1.09$, $p > 0.05$ for the dose × time interaction. Sulpiride significantly reduced dexbenzetimide-induced hyperlocomotion, $F(4, 44) = 2.39$, $p < 0.05$, for the dose × time interaction (Fig. 4b).

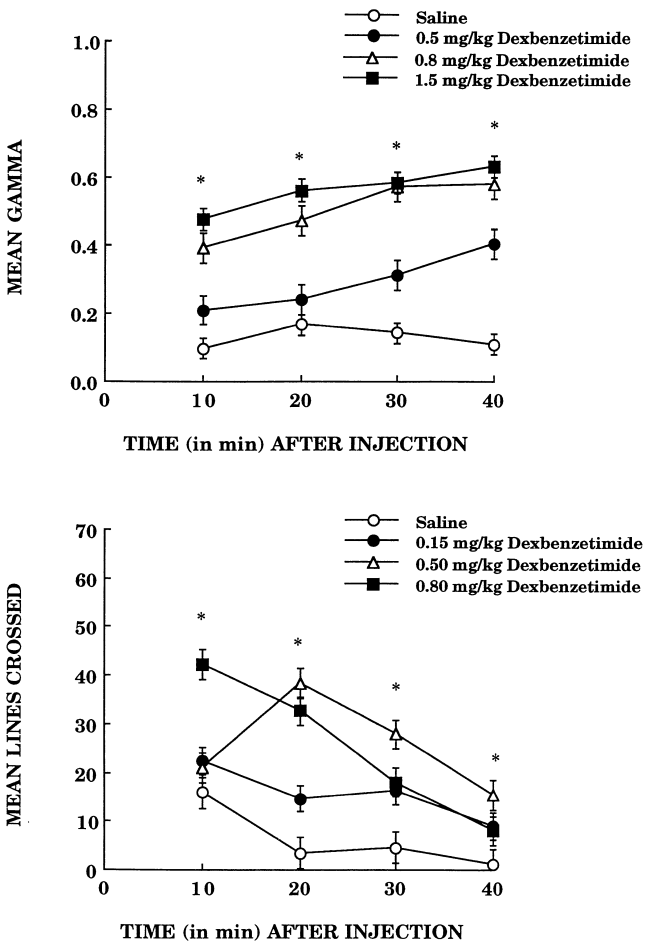


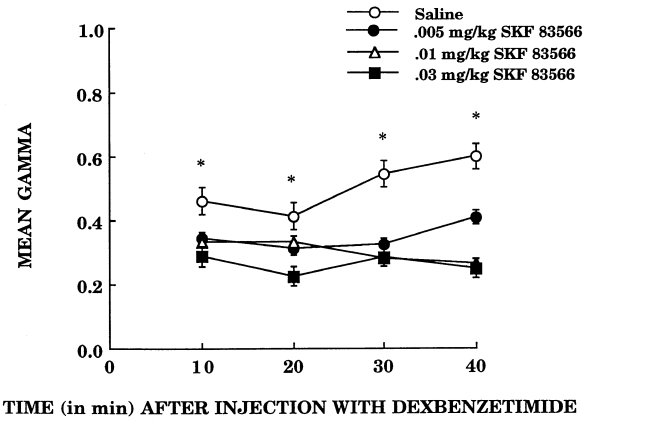
FIG. 2. Locomotor stereotypy (top) and hyperlocomotion (bottom) exhibited by saline- and dexbenzetimide-treated rats. Gamma is the index of locomotor stereotypy; higher values indicate more stereotypic or repetitive patterns of locomotion in the open field. Asterisks (*) denote significant differences between groups. Error bars indicate the standard error of the mean.

SKF 83566 plus Scopolamine

SKF 83566 significantly reduced scopolamine-induced locomotor stereotypy, $F(9, 75) = 3.19$, $p < 0.05$, for the dose × time interaction. In comparison with saline + scopolamine controls, locomotor stereotypy was reduced by higher of SKF 83566 (see Fig. 5a). As shown in Fig. 5b, SKF 83566 produced a dose-related reduction in scopolamine-induced hyperlocomotion, $F(4, 46) = 5.52$, $p < 0.05$, for the dose × time interaction. SKF 83566 was effective at reducing the number of lines crossed over time, but the effect was mainly due to the highest dose of SKF 83566.

Sulpiride plus Scopolamine

Sulpiride failed to consistently block scopolamine-induced locomotor stereotypy, $F(6, 72) = 8.31$, $p < 0.05$, for the dose × time interaction. In fact, 25 mg/kg of sulpiride actually enhanced gamma scores during the 40-min observation period (see Fig. 6a). On the other hand, sulpiride significantly reduced scopolamine-induced hyperlocomotion, $F(4, 44) = 2.93$, $p < 0.05$, for the dose × time interaction (Fig. 6b).



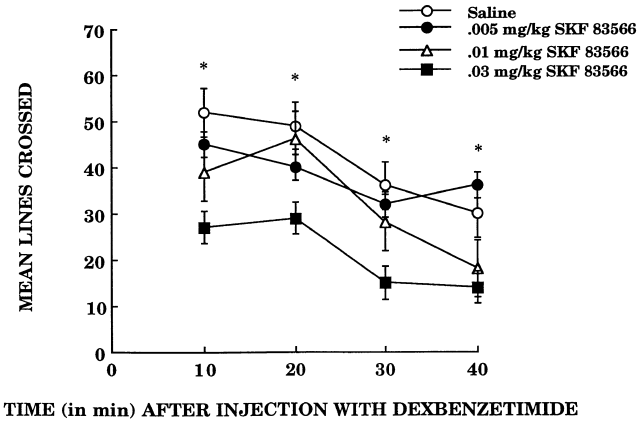
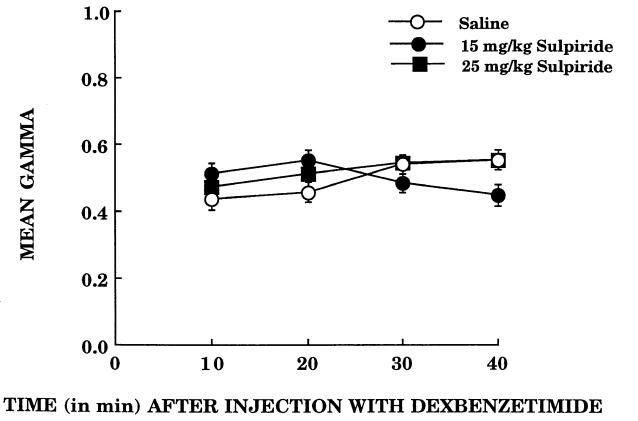


FIG. 3. The effects of the D_1 antagonist SKF 83566 on dexbenzetimide-induced locomotor stereotypy (top) and hyperlocomotion (bottom). Asterisks (*) denote significant differences between groups. Error bars indicate the standard error of the mean.



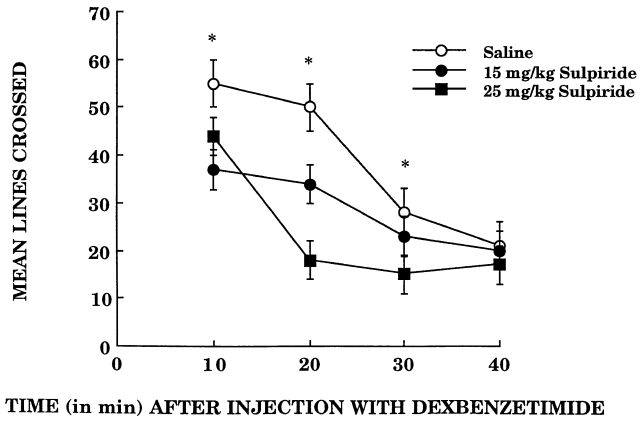


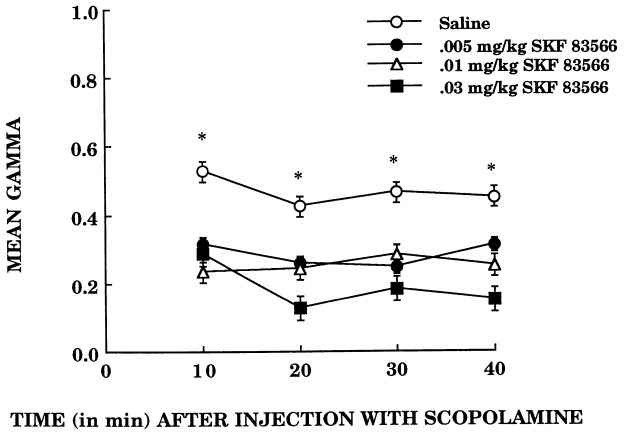
FIG. 4. The effects of the D_2 antagonist sulpiride on dexbenzetimide-induced locomotor stereotypy (top) and hyperlocomotion (bottom). Asterisks (*) denote significant differences between groups. Error bars indicate the standard error of the mean.

DISCUSSION

The purpose of the present study was to determine if locomotor stereotypy was produced by anticholinergics in general, and whether DA might play a role in anticholinergic-induced locomotor stereotypy. We expected that dexbenzetimide would produce locomotor stereotypy, and that this effect would be blocked by specific DA subreceptor antagonists. Like scopolamine, dexbenzetimide produced significant locomotor stereotypy as measured by gamma as well as hyperlocomotion. The D_1 antagonist SKF 83566 significantly blocked both scopolamine- and dexbenzetimide-induced locomotor stereotypy and hyperlocomotion, whereas the D_2 antagonist sulpiride reduced locomotion, failed to block dexbenzetimide-induced locomotor stereotypy, and enhanced the expression of scopolamine-induced locomotor stereotypy.

The ability for dexbenzetimide to produce locomotor stereotypy provides support for the hypothesis that scopolamine-induced locomotor stereotypy is related to its anticholinergic effect. Scopolamine is structurally similar to atropine, and we have seen that atropine produces locomotor stereotypy in a dose-dependent manner (unpublished data). Dexbenzetimide is, however, structurally dissimilar to atropine and scopolamine, but also produces locomotor stereotypy. Locomotor stereotypy thus appears to be a property of anticholinergics in general. Prior work has reported that anticholinergics can enhance the release of DA (28), and our findings suggest that this effect may account for the mechanism by which scopolamine, atropine, and dexbenzetimide produce similar locomotor effects as amphetamine. Interestingly, both scopolamine and dexbenzetimide have been reported to elevate mood (7); mood elevation is more commonly associated with DA agents than cholinergic agents.

The findings that SKF 83566, not sulpiride, blocked locomotor stereotypy, but both antagonists reduced hyperlocomotion, support the notion that DA subreceptors are differentially involved in the expression of anticholinergic-induced locomotor behavior. Previous work demonstrates that locomotor effects of DA agonists like amphetamine involve distinct DA subreceptors. For example, the intense grooming and gnawing observed during amphetamine-induced focused stereotypy in rats are elicited by the D_1 agonist SKF 38393, but not the D_2 agonist LY 163502 (20,21). Amphetamine-induced locomotor stereotypy is reduced by SKF 83566, not sulpiride; yet both antagonists decrease hyperlocomotion (9). Our results with SKF 83566 and sulpiride confirm prior work and extend the notion that expression of locomotor stereotypy involves the activation of D_1 receptors.



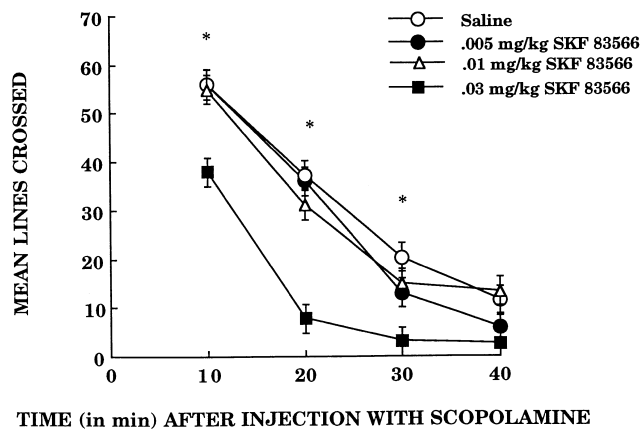
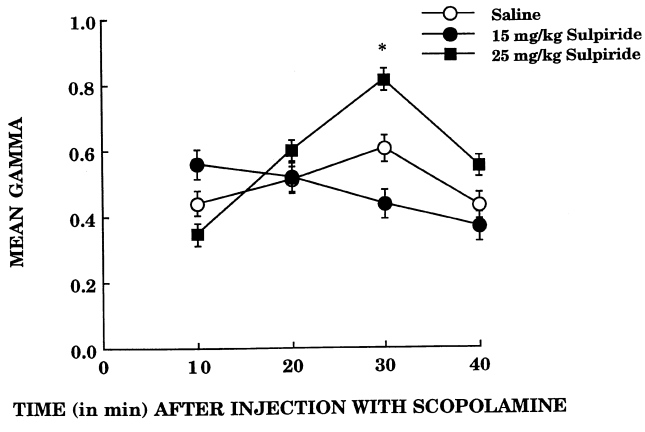


FIG. 5. The effects of the D_1 antagonist SKF 83566 on scopolamine-induced locomotor stereotypy (top) and hyperlocomotion (bottom). Asterisks (*) denote significant differences between groups. Error bars indicate the standard error of the mean.



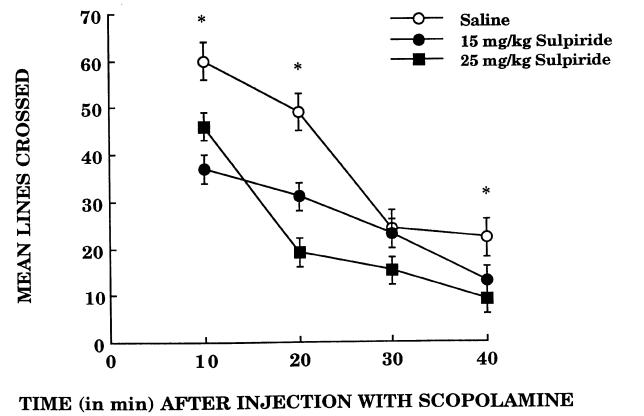


FIG. 6. The effects of the D_2 antagonist sulpiride on scopolamine-induced locomotor stereotypy (top) and hyperlocomotion (bottom). Asterisks (*) denote significant differences between groups. Error bars indicate the standard error of the mean.

The failure of sulpiride to block dexbenzetimide- and scopolamine-induced locomotor stereotypy was not surprising in light of our previous data showing that similar doses of sulpiride were ineffective on amphetamine-induced locomotor stereotypy (9). We had tested higher doses of sulpiride (45 mg/kg, 65 mg/kg), but these doses were so effective at reducing activity that insufficient locomotion remained for calculation of gamma scores (data not shown). What is interesting is that sulpiride actually enhanced scopolamine- not dexbenzetimide-induced locomotor stereotypy, and this effect was not seen previously with amphetamine (9,14). A similar paradoxical effect has been reported (22) where 20 mg/kg of sulpiride enhanced the stereotyped head movements and sniffing (i.e., focused stereotypy) induced by 2.5 and 5 mg/kg amphetamine, but reduced hyperlocomotion. Furthermore, 50 mg/kg sulpiride prolonged stereotyped head and forelimb movements produced by 2 mg/kg amphetamine (27). The differential effect of sulpiride on scopolamine and dexbenzetimide may be related to the structural differences between the two compounds. The significance of this effect in the present data is unclear, but is consistent with the general consensus that atypical neuroleptics block selective components of stereotypy (14).

One intriguing feature of the proposed DA–ACh interaction is that DA seems to exert a dual control on ACh neurons. On the one hand, many data support the view that DA, acting postsynaptically on D_2 receptors, exerts an inhibitory role on striatal ACh neurons (24). On the other hand, some data suggest a facilitation through D_1 receptors (2). Our results involving D_1 and D_2 antagonist effects on locomotor stereotypy are in agreement with the notion of differential DA subreceptor interactions with ACh. It seems likely that scopolamine and dexbenzetimide's effects were to inhibit ACh release and indirectly increase DA levels. With SKF 83566, DA could not activate D_1 receptors and, thus, no locomotor stereotypy was observed. In contrast, sulpiride-blocked DA effects on D_2 receptors and locomotor stereotypy was observed, possibly due to actions of DA on other subreceptors like D_1. Although most data involving D_2 agonists suggest an inhibitory role on striatal ACh; this effect occurs at postsynaptic DA receptors (24). Acting at presynaptic DA autoreceptors, D_2 agonists are also thought to decrease DA release, thereby removing DA inhibition of the firing rate of cholinergic neurons, leading to an increase in cholinergic release (16). It follows from these findings that sulpiride may have acted presynaptically to increase DA release and inhibit ACh, thereby resulting in the expression (or enhancement) of locomotor stereotypy with a D_2 antagonist.

No clear conception has yet been elaborated that explains the opposite effects of D_1 and D_2 subreceptors on apparently the same target ACh neurons, but it has been proposed that both mechanisms are operative in the regulation of striatal neurons (2,16,24). Although the present data cannot clarify which target areas are involved in the production of anticholinergic-induced locomotor stereotypy, they support the notion that DA systems are likely involved in its expression. The caudate and nucleus accumbens are likely sites to be investigated so as to further elucidate the mechanisms underlying this effect. Furthermore, it is likely that other DA subreceptors (D_3, D_4, or D_5) play a role in the expression of locomotor stereotypy, but this has yet to be confirmed.

ACKNOWLEDGEMENTS

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