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Behavioral Effects of a Dimethylsulfonium Analog of Dopamine After Injection into the Nucleus Accumbens and the Striatum

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BOLDRY, R , Y CHANG, D D MILLER AND N J URETSKY *Behavioral effects of a dimethylsulfonium analog of dopamine after injection into the nucleus accumbens and the striatum* PHARMACOL BIOCHEM BEHAV **24**(2) 223–228, 1986 —We have previously synthesized a chemical analog of dopamine (DA) in which the amine group has been replaced by a permanently charged dimethylsulfonium group In the present study, we have determined whether this compound can exert DA agonist activity in the nucleus accumbens by comparing its effects with those of DA When DA was injected into the nucleus accumbens of rats pretreated with nialamide, a monoamine oxidase inhibitor, there was marked stimulation of locomotor activity Similarly, after intraaccumbens injection, the sulfonium analog also produced a marked stimulation of locomotor activity, and this effect was inhibited by the DA receptor antagonist, haloperidol (0 2 mg/kg, IP) However, the sulfonium analog did not stimulate locomotor activity when rats were pretreated with saline instead of nialamide In addition, the stimulation of locomotor activity produced by the sulfonium analog in rats pretreated with nialamide was completely inhibited by the DA synthesis inhibitor, α-methyl-p-tyrosine These results suggest that the stimulation of locomotor activity by the sulfonium analog is mediated indirectly through the release of DA The sulfonium analog was able to produce marked contralateral circling after it was injected into the striatum of rats on the side of the brain in which DA nerve terminals were previously destroyed with 6-hydroxydopamine Similarly, the sulfonium analog produced a marked stimulation of locomotor activity after it was injected into the nucleus accumbens of rats that were previously injected into this region with 6-hydroxydopamine These results suggest that the sulfonium analog of dopamine can exert direct as well as indirect DA agonist activity

Dopamine Sulfonium analog of dopamine Nucleus accumbens Striatum Locomotor activity

ABNORMALITIES of dopaminergic neurotransmission in the CNS have been implicated in several disease states including Parkinson's disease, schizophrenia, Huntington's chorea, and tardive dyskinesia [10] Consequently, there has been considerable interest in developing dopaminergic agonists to use in producing animal models of these conditions and in treating diseases caused by an impairment in dopaminergic neurotransmission

We have been studying the relationship between the molecular structure of dopamine (DA) and DA agonist activity In order to determine whether the nitrogen atom of DA is required for DA agonist activity, we have synthesized an analog of DA, 2-(3,4 dihydroxyphenyl)-ethyl-dimethylsulfonium iodide In this compound, the amine group of DA is replaced by a charged dimethylsulfonium group (sulfonium analog) [1]

The sulfonium analog is permanently charged and probably does not cross the blood brain barrier Therefore, this compound was tested for dopaminergic activity using two different models in which the drug was injected directly into the brain In a behavioral model, the sulfonium analog and DA were injected unilaterally into the striatum of rats on the same side of the brain in which dopaminergic nerve terminals were previously destroyed with 6-hydroxydopamine It was found that under these conditions, both the sulfonium analog as well as DA were able to produce contraversive circling behavior [1] In an in-vitro model, it was found that the sulfonium analog, like DA, was able to inhibit the depolarization-induced release of ^{3}H-acetylcholine from striatal slices [12] These in-vivo and in-vitro effects were blocked by a DA receptor antagonist suggesting that the actions of the sulfonium analog were mediated through the activation of dopaminergic receptors

DA and DA agonist drugs produce a marked hyperactivity response after their bilateral administration into the nucleus accumbens of rats pretreated with a monoamine oxidase inhibitor [2, 5, 9] Since the sulfonium analog appears to exert DA agonist activity in the striatum, it was anticipated that this compound would exert a similar effect in the nucleus accumbens To test this possibility, we have compared the effects produced by the sulfonium analog with those produced by DA after intraaccumbens administration

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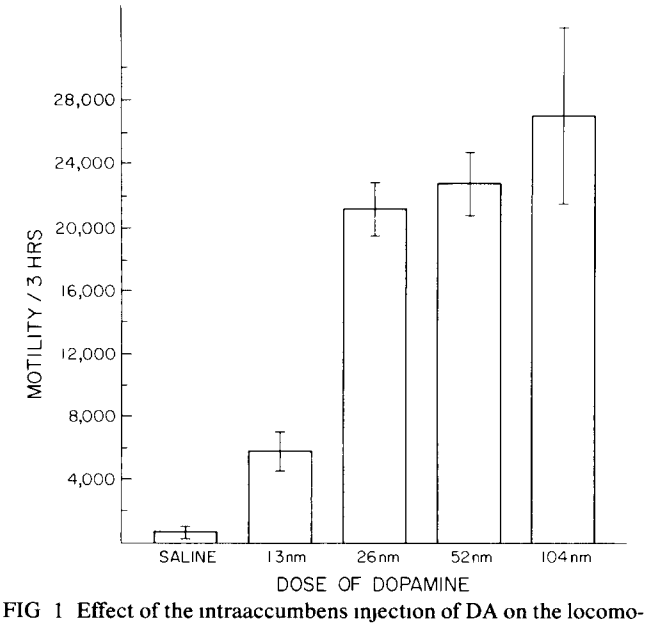

FIG 1 Effect of the intraaccumbens injection of DA on the locomotor activity of rats pretreated with nialamide Rats were injected with nialamide, 100 mg/kg, IP and 1 hour later with different doses of DA (expressed as nmoles) or vehicle directly into the nucleus accumbens Locomotor activity was recorded for 3 hours Each value represents the mean locomotor activity±S E M of 4 determinations

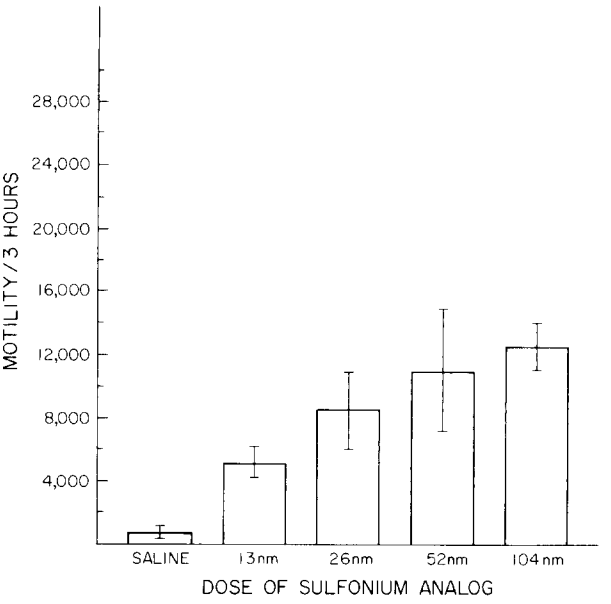

FIG 2 Effect of the intraaccumbens injection of the sulfonium analog of DA on the locomotor activity of rats pretreated with nialamide Rats were injected with nialamide, 100 mg/kg IP, and 1 hour later with different doses of the sulfonium analog (expressed as nmoles) or vehicle Locomotor activity was recorded for 3 hours Each value is the mean±S E M of 4 determinations

METHOD

Nucleus Accumbens Injections

Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 170–200 grams at the time of surgery were used throughout the experiments For the intraaccumbens injections rats were anesthetized with a halothane/oxygen mixture and placed in a stereotaxic frame (David Knopf Inst , Tujunga, CA) Holes were then drilled on each side of the skull at the following coordinates A 9 4, L±2 4 [7] for injection into the nucleus accumbens The needle of a 10 μl Hamilton Syringe (Hamilton Company, Reno, NV) was inserted at a 10 degree angle (to avoid puncturing the ventricles) into the holes to a depth of V −1 0, and 1 0 μl of drug or vehicle were injected bilaterally at a rate of 0 5 μl/min The micro-syringe was left in place for an additional minute to allow for diffusion of the solution away from the injection needle After the drug or vehicle injections, the skin incision was closed with wound clips and covered with lidocaine ointment to relieve any pain Rats recovered from anesthesia within 5–10 minutes after the removal of halothane and were placed in activity cages for measurement of locomotor activity Each rat was used only once for these studies

In the study using 6-hydroxydopamine, rats were injected bilaterally with 6-hydroxydopamine hydrobromide (8 μg of free base in 2 μl) or vehicle (0 1% ascorbic acid in saline) into the nucleus accumbens The rats were then returned to their home cage Ten days later, the rats were injected with amphetamine sulfate (1 5 mg/kg, IP) and their motor activity was measured In confirmation of previous reports, the stimulation of locomotor activity by amphetamine was lower in the 6-hydroxydopamine-treated rats compared to the vehicle-treated rats Three days later, all animals were injected with dopamine or the sulfonium analog directly into the nucleus accumbens using the procedure described above and then were placed in the cages for recording locomotor activity

Locomotor Activity

Rats were placed in locomotor activity cages for 10 minutes to allow them to adapt to the environment They were then removed from the cages, anesthetized with halothane/oxygen and injected with test drugs into the nucleus accumbens After drug administration, the rats were returned to the locomotor activity cages and activity was recorded as a function of time The locomotor activity cages (Opto-Varimex-minor, Columbus Instruments, Columbus OH) were designed to measure ambulatory movements, but not total horizontal or total vertical movements The cages contained 12 by 12 i r beams passing at a height of 5 cm from the bottom of the cage through a ventilated Plexiglas box measuring 42 cm by 42 cm and was 20 cm high Locomotor activity (i e , ambulatory movement) was recorded as the number of times two consecutive beams, 3 5 cm apart, were interrupted during the experimental interval The data were printed out on a digital counter All observations were made in an isolated environmental room, maintained at a constant temperature of 22±1°C

Medial Forebrain Bundle Injections

The effects of the sulfonium analogue on circling behavior were determined by the direct injection of compounds into the caudate nucleus on the same side of the brain as a unilateral 6-hydroxydopamine-induced lesion of the medial forebrain bundle [11] Rats were anesthetized with chloral hydrate 400 mg/kg IP, placed into the stereotaxic frame, and holes were drilled into the skull 6-Hydroxydopamine (8 μg) was injected through one of the holes in a volume of 4 μl into the right medial forebrain bundle using the coordinates A 3 4, V

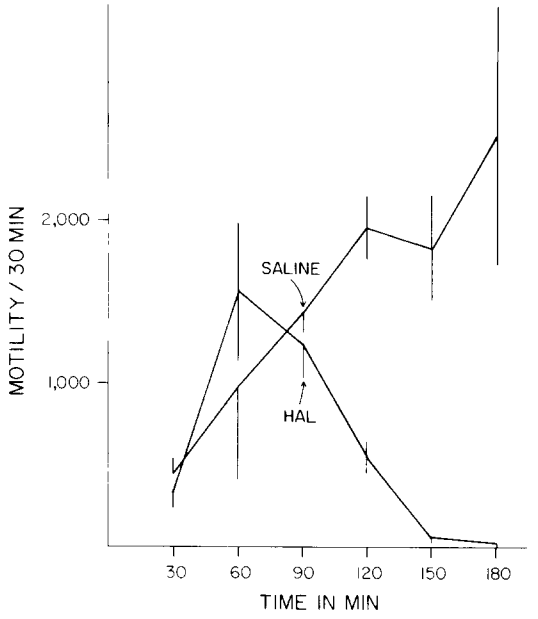

FIG 3 Effect of haloperidol on the locomotor activity induced by intraaccumbens administration of the sulfonium analog in nialamide-pretreated rats Rats were injected with nialamide, 100 mg/kg, IP, 1 hour before the injection of the sulfonium analog into the nucleus accumbens Locomotor activity was then recorded for 90 minutes at which time the rats were injected with either haloperidol, 0 2 mg/kg, IP, or saline, and the recording of locomotor activity was continued Each value is the mean±S E M of 4–5 observations The motor activity of the haloperidol-treated rats was significantly less than that of saline at 120 150 and 180 minutes after the sulfonium analog injection ($p<0$ 01)

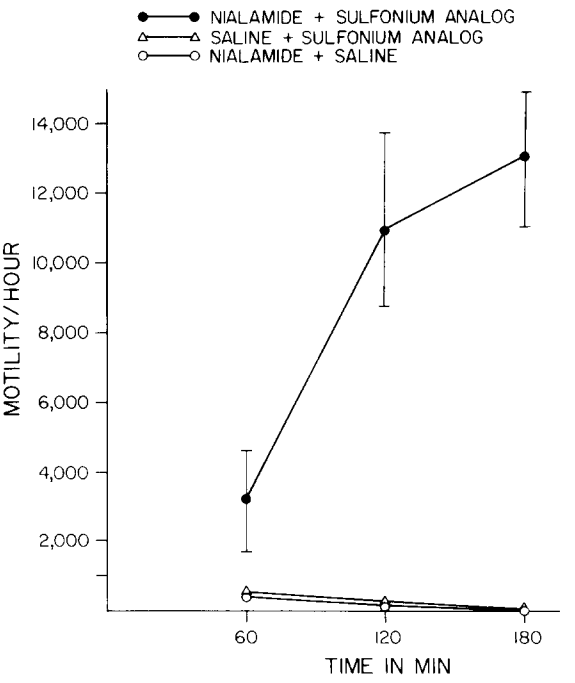

FIG 4 Effect of nialamide on the locomotor activity produced by the intraaccumbens administration of the sulfonium analog Rats were either injected with saline or nialamide, 100 mg/kg, IP Two hours later, the rats were injected into the nucleus accumbens with either vehicle or the sulfonium analog and locomotor activity determined Each value is the mean±S E M of 5 determinations The locomotor activity of the nialamide-sulfonium analog-treated group was significantly greater than that of the other groups ($p<0$ 01)

3 1, L 1 7 [7] A second hole was drilled into the skulls of these animals for later injection of drugs into the striatum at the coordinates A 8 2, V 0 0, and L 2 5 Twelve days after surgery the animals were tested for circling responses to apomorphine (1 mg/kg SC) Only those animals which responded to apomorphine with contralateral turning were selected for studying the effects of drugs injected intrastriatally

Fifteen days after 6-hydroxydopamine administration, rats were anesthetized with a halothane/oxygen mixture and placed in the stereotaxic frame The needle of a Hamilton syringe was inserted into the hole in the skull above the striatum to the appropriate depth, and solutions of the drugs were injected in a total volume of 2 0 μl at a rate of 1 0 μl/minute The rats recovered from anesthesia within 5 minutes of drug injection and were placed in a glass chamber for the monitoring of circling behavior

Circling Behavior

After the intrastriatal injections, the rats were placed into 22 liter hemispherical glass chambers The number of complete turns (360°) were counted for periods of 5 minutes at 15 minute intervals for one hour starting 15 minutes after drug injection

Drugs

The following compounds were purchased from Sigma Chemical Co (St Louis, MO) Nialamide, which was dissolved in a minimum amount of 0 1 N Hydrochloric acid and then diluted with distilled water, α-methyl-p-tyrosine (methyl ester), which was dissolved in distilled water The dimethylsulfonium analog of DA was synthesized as previously described [1] and was dissolved in a 0 2 mg/ml solution of ascorbic acid, the pH of the final solution was 5 0 Control animals were always injected with the appropriate vehicle Haloperidol (Haldol, McNeil Labs) was used as commercially prepared

Statistics

Data were expressed as the mean and the standard error of the mean (SEM) Significant differences were evaluated using the non-parametric two tailed Mann-Whitney U-test with a level of $p<0$ 05 being considered significant

RESULTS

Effect of the Intraaccumbens Administration of DA on the Locomotor Activity of Nialamide-Pretreated Rats

Rats were injected with nialamide (100 mg/kg IP), a monoamine oxidase (MAO) inhibitor One hour later, the rats were injected directly into the nucleus accumbens with different concentrations of DA and the motor activity was recorded for 3 hours As shown previously [2, 5, 9], DA produced a dose dependent stimulation of locomotor activity (Fig 1) Peak stimulation of activity occurred at approximately 2–4 hours after drug administration (data not shown)

Effect of the Intraaccumbens Administration of the Sulfonium Analog of DA on Locomotor Activity

After pretreatment with nialamide (100 mg/kg, IP), the

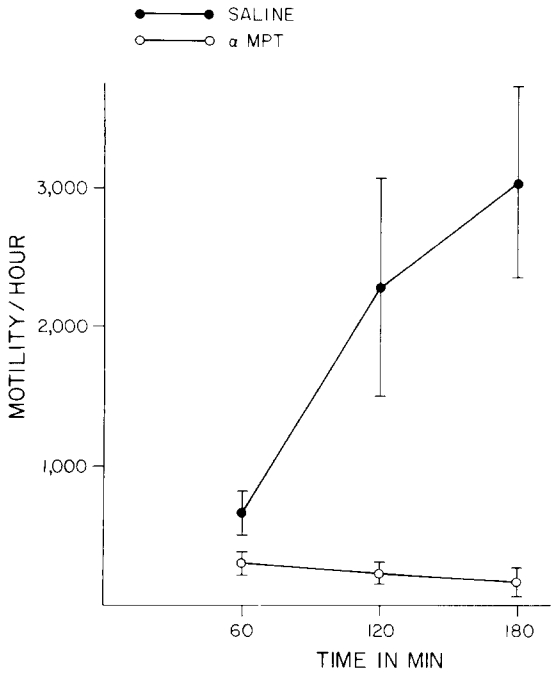

FIG 5 Effect of α-methyl-p-tyrosine pretreatment on the locomotor activity produced by the intraaccumbens administration of the sulfonium analog in nialamide pretreated rats Rats were injected with either saline or α-methyl-p-tyrosine, 250 mg/kg, IP Two hours later they were injected with nialamide 100 mg/kg, IP and one hour later with the sulfonium analog (52 nmoles) directly into the nucleus accumbens and locomotor activity was determined Each value is the mean±S E M of 4 observations The locomotor activity of the group pretreated with α-methyl-p-tyrosine was significantly less than that of the saline pretreated group at 60 min ($p<0$ 025) and at 120 and 180 min ($p<0$ 01)

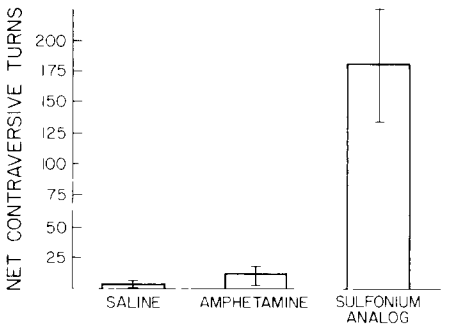

FIG 6 Effect of the direct injection of the sulfonium analog or amphetamine into the striatum on the circling behavior of rats previously injected with 6-hydroxydopamine Rats were injected with 6-hydroxydopamine into the medial forebrain bundle Three to five weeks after injection, the rats were injected with either vehicle, amphetamine sulfate (104 nmoles) or the sulfonium analog (104 nmoles) directly into the striatum on the 6-OHDA lesioned side The number of turns were determined at 5 minute intervals at 15, 30, 45 and 60 minutes For each rat the number of turns for each interval was added together Each value is the mean±S E M for 4 observations The turning of the sulfonium analog group is significantly greater than that of the saline group ($p<0$ 025) The turning of the amphetamine group is *not* significantly different from that of the saline group

sulfonium analog, like DA, also produced a dose dependent stimulation of locomotor activity (Fig 2) This hypermotility response produced by doses of 26 to 104 nmoles was smaller for the sulfonium analog than for DA (Figs 1 and 2) In order to determine whether the increase in locomotor activity induced by the sulfonium analog was mediated through the stimulation of DA receptors, the rats were injected with either haloperidol (0 2 mg/kg, IP) or saline 1 5 hours after the intraaccumbens injection of the sulfonium analog Haloperidol was found to produce a marked inhibition of the stimulation of locomotor activity induced by the sulfonium analog (Fig 3)

Effect of Nialamide on the Stimulation of Locomotor Activity Induced by the Sulfonium Analog of DA

In this study, rats were injected with either saline or nialamide (100 mg/kg, IP), a monoamine oxidase inhibitor One hour later, rats were injected into the nucleus accumbens with either saline or the sulfonium analog (104 nmoles), and their locomotor activity was determined (Fig 4) As shown previously, the sulfonium analog produced an intense stimulation of locomotor activity of animals pretreated with nialamide In contrast, the sulfonium analog was not able to stimulate locomotor activity in animals pretreated with saline instead of nialamide (Fig 4) In fact, the activity of these animals was not significantly different from that of rats pretreated with nialamide and injected with saline into the nucleus accumbens Higher doses of the sulfonium analog (up to 416 nmoles) also failed to stimulate locomotor activity in the absence of nialamide pretreatment

Effect of α-Methyl-p-Tyrosine on the Stimulation of Locomotor Activity Induced by the Intraaccumbens Injection of the Sulfonium Analog

Rats were injected with either saline or α-methyl-p-tyrosine, 250 mg/kg, IP Two hours later, they were injected with nialamide, and one hour later, with 52 nmoles of the sulfonium analog into the nucleus accumbens, and their locomotor activity recorded Figure 5 shows that α-methyl-p-tyrosine pretreatment completely inhibited the stimulation of locomotor activity induced by the sulfonium analog in nialamide-pretreated animals

Effect of the Intrastriatal Administration of the Sulfonium Analog on Circling Behavior in Rats Previously Lesioned With 6-Hydroxydopamine

Rats, previously injected into the right medial forebrain bundle with 6-hydroxydopamine, were injected into the right striatum with either vehicle, amphetamine sulfate (104 nmoles) or the sulfonium analog (104 nmoles) In contrast to our previous study [1], none of the animals were pretreated with nialamide The number of complete turns made by these animals were counted at 5 minute intervals at 15, 30, 45, and 60 minutes after injection The total number of turns for each animal was summed As shown in Fig 6, rats injected intrastriatally with vehicle turned a total of 3 5±0 65 (S E M) times Amphetamine produced a small increase in circling (11±6), which was not statistically significant In contrast to amphetamine, the sulfonium analog produced a marked stimulation of circling (181±42), which was statistically significant The direction of circling induced by the sulfonium analog was always to the side which was contralateral to the striatal injection

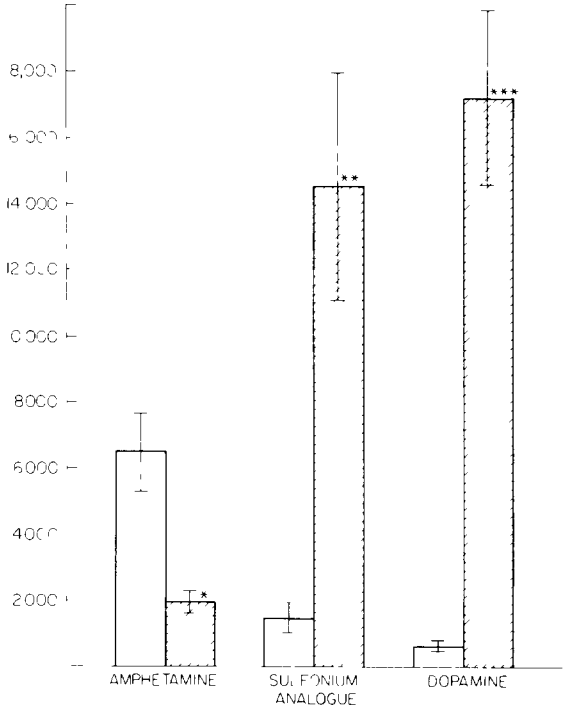

FIG 7 Effect of the intraaccumbens administration of the sulfonium analog and DA on the locomotor activity of rats previously lesioned in the nucleus accumbens with 6-hydroxydopamine Rats were injected bilaterally in the nucleus accumbens with either 6-hydroxydopamine (hatched bar) or vehicle Ten days after injection, the rats were injected with amphetamine sulfate (1 5 mg/kg IP) and locomotor activity recorded Three days later, all rats were injected into the nucleus accumbens with either DA (104 nmoles) or the sulfonium analog (104 nmoles) and locomotor activity was recorded for 3 hr Each bar is the mean ± S E M of 4–6 animals $^{*}p<0$ 05, $^{**}p<0$ 025 $^{***}p<0$ 005 when compared to the vehicle-treated group

Effect of the Intraaccumbens Administration of the Sulfonium Analog on the Locomotor Activity of Rats Previously Lesioned in the Nucleus Accumbens With 6-Hydroxydopamine

Rats, previously injected into the nucleus accumbens with 6-hydroxydopamine or vehicle, were injected with amphetamine sulfate (1 5 mg/kg, IP) and locomotor activity was measured for 2 hours Figure 7 shows that the amphetamine-induced stimulation of locomotor activity was reduced by over 50% in the 6-hydroxydopamine treated rats

Three days after the amphetamine injection, both 6-hydroxydopamine and vehicle-treated rats were injected into the nucleus accumbens with either dopamine (104 nmoles) or the sulfonium analog (104 nmoles) of dopamine and locomotor activity was recorded for 2 hours Figure 7 shows that both DA and the sulfonium analog produced a marked stimulation of locomotor activity in the 6-hydroxydopamine-treated rats compared to the vehicle-treated controls

DISCUSSION

In this study, a behavioral model was used to determine if the sulfonium analog of DA can activate DA receptors in the nucleus accumbens The bilateral administration of DA and DA agonists into the nucleus accumbens has been shown previously to stimulate locomotor activity in rats pretreated with a monoamine oxidase inhibitor [2, 5, 9] and this effect was blocked by DA receptor antagonists In the present study we have found that the intraaccumbens administration of the sulfonium analog of DA or DA into rats pretreated with the monoamine oxidase inhibitor, nialamide, produced an intense and prolonged stimulation of locomotor activity (Figs 1 and 2) The stimulation of locomotor activity produced by the sulfonium analog was inhibited by the DA receptor antagonist, haloperidol (Fig 3), suggesting that this effect is caused by the activation of DA receptors in the nucleus accumbens

Since the sulfonium analog is not an amine, it is unlikely to be metabolized by monoamine oxidase Consequently, we studied the effect of the sulfonium analog in animals that were not pretreated with nialamide Surprisingly, the sulfonium analog was unable to stimulate locomotor activity in these rats even when extremely high doses were administered This result is consistent with the concept that the stimulation of locomotor activity by the sulfonium analog is mediated indirectly through the release of endogenous DA, possibly from a vesicular store Alternatively, it is possible that the sulfonium analog binds to monoamine oxidase, decreasing its concentration at dopaminergic receptor sites [3]

To test the possibility that the hyperactivity produced by the sulfonium analog in nialamide-treated rats is mediated by endogenous DA, rats were pretreated with α-methyl-p-tyrosine, a DA synthesis inhibitor, before the administration of nialamide and the sulfonium analog It was found that α-methyl-p-tyrosine markedly reduced the hypermotility response to the sulfonium analog in nialamide-pretreated rats This observation provides further evidence that the hypermotility response produced by the sulfonium analog in the presence of a monoamine oxidase inhibitor is mediated by endogenous dopamine The sulfonium analog could release DA from nerve terminals which would then stimulate locomotor activity by activating DA receptors This concept is consistent with the recent observation that the sulfonium analog can enhance the release of exogenously taken up ^{3}H-DA from a striatal slice preparation [12]

In previous studies in which rats were pretreated with a monoamine oxidase inhibitor, it was shown that after intrastriatal injection, the sulfonium analog of DA, as well as DA, produced intense contraversive circling in rats previously lesioned unilaterally with 6-hydroxydopamine [1] This circling behavior was thought to be due to a direct action of both compounds on DA receptors that were made supersensitive by the destruction of DA neurons with 6-hydroxydopamine Since in these studies all rats were pretreated with a monoamine oxidase inhibitor before intrastriatal injection, the circling response produced by the sulfonium analog could have been mediated through the release of DA from surviving DA nerve terminals, the released DA being protected from metabolism by monoamine oxidase Therefore, in the present study, rats, previously lesioned unilaterally with 6-OHDA, were not pretreated with a monoamine oxidase inhibitor before the injection of drugs into the striatum In addition, the effects of the sulfonium analog were compared with equimolar doses of amphetamine, a prototype DA releasing agent Under these conditions, only the sulfonium analog produced significant contraversive circling (Fig 6), in fact, the circling produced by amphetamine was not significantly different from that produced by saline These results suggest that the intense

circling produced by the injection of the sulfonium analog into the striatum is not due to the release of endogenous DA but is caused by direct action of the sulfonium analog on striatal dopaminergic receptors that were made supersensitive by treatment with 6-hydroxydopamine

To determine whether the sulfonium analog of DA can activate supersensitive DA receptors in the nucleus accumbens, rats were injected into the nucleus accumbens with 6-hydroxydopamine or vehicle and the effects of drugs on locomotor activity were tested The response of the 6-hydroxydopamine-treated rats to amphetamine was reduced by over 50%, which is consistent with a reduction in the amount of released DA due to a loss of dopaminergic nerve terminals in the nucleus accumbens In contrast, the locomotor activity of the 6-hydroxydopamine-treated rats was markedly stimulated by DA and the sulfonium analog of DA These results suggest that the sulfonium analog of dopamine can directly activate dopaminergic receptors in the nucleus accumbens that have become supersensitive after 6-hydroxydopamine administration

One possible interpretation of these observations is that the sulfonium analog can only activate DA receptors that have become supersensitive as a result of denervation [4, 6, 8] However, our recent in-vitro studies on the effect of the sulfonium analog on the DA receptors in the striatum that regulate acetylcholine release do not support this concept [12] These studies show that the sulfonium analog can inhibit the depolarization induced release of ^{3}H-acetylcholine from striatal slices depleted of DA with both reserpine and α-methyl-p-tyrosine [12] In contrast, amphetamine was unable to inhibit ^{3}H-acetylcholine release under these conditions Therefore, it appears that at least in this preparation the analog can directly activate striatal DA receptors, which have not become supersensitive as a result of 6-hydroxydopamine pretreatment

The results of this study show that the permanently charged sulfonium analog of DA can exert both direct as well as indirect DA agonist activity in the nucleus accumbens

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