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RECEPTOR SUBTYPE-SPECIFIC DOPAMINERGIC AGENTS AND UNCONDITIONED BEHAVIOR

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Agonists and antagonists specific for the D1 or D2 dopamine (DA) receptor subtypes influence unconditioned behavior. D1 agonists given systemically increase locomotor activity and grooming; increased activity also follows central administration to structures including the nucleus accumbens. D2 agonists given systemically produce pronounced increases in locomotor activity and stereotypy; intra-accumbens injections also enhance activity. Doses of D1 and D2 agonists that are ineffective when given alone produce locomotor increases when given together showing a synergism of effect for the two receptor subtypes. D1 and D2 antagonists decrease locomotor activity, induce catalepsy and antagonize the stimulant effects of nonspecific DA agonists. D2 antagonists block the stimulant effects of D1 or D2 agonists and D2 antagonists block the stimulant effects of D2 or D1 agonists. In animals acutely depleted of DA, stimulation of both D1 and D2 receptors appears necessary to produce behavioral effects. In DA supersensitive rodents, either D1 or D2 agonists produce behavioral effects. In DA supersensitive primates, however, D2 but not D1 agonists reverse deficits in locomotor activity. It is concluded that stimulation of both D1 and D2 receptors is necessary to produce behavioral effects in normosensitive animals. In DA denervated, supersensitive animals, this DA receptor subtype interdependence appears to be lost.

The neurotransmitter dopamine (DA) has a widespread distribution within the mammalian central nervous system [19]. There are at least two subtypes of receptors for this transmitter and Kebabian and Calne [75] have categorized the receptors as D1 and D2; the D1 receptor stimulates the enzyme adenylate cyclase, whereas the D2 receptor is either unrelated to, or in some areas of the brain inhibits, this enzyme[1].

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Currently, DA neurotransmission is implicated in at least two behavioral functions: unconditioned motor activity and reward-related learning [13]. Numerous studies have demonstrated that enhanced dopaminergic transmission results in a general increase in locomotor activity and stereotypy, while a decrease in DA transmission results in hypomotility and catalepsy [33]. The integrity of DA neurotransmission also appears necessary for the acquisition and maintenance of learning that is governed by rewarding stimuli [13, 14, 159]. Over the past several years the introduction of pharmacological compounds that are relatively specific for DA receptor subtypes has led to the evaluation of the possible contribution of D1 and D2 receptors to behavioral phenomena previously found to involve DA neurotransmission (for reviews see Refs. 30, 71, 74, 111, 153, 154). In this paper, studies which examined the effects of D1 and D2 receptor subtype-specific pharmacological agents on unconditioned behaviors will be reviewed. Studies examining the role of DA receptor subtypes in reward-related learning have recently been reviewed in other papers [15, 18].

Drugs that preferentially stimulate either the D1 or D2 receptor have been found to influence unconditioned locomotor activity. A precise summary of these studies is difficult because of the wide variety of behavioral dependent measures employed. For example, some studies speak of agonist effects on locomotor activity as assessed with automated activity chambers while others report stereotypy ratings. The stereotypy ratings, however, frequently involve a range of activity including increased locomotion at the lower end and in-place activities such as sniffing and gnaving at the upper end. The degree to which automated measures of locomotor activity and various rating scales assess the same behaviors is difficult to determine [16, 92]. A similar problem exists for DA receptor antagonists wherein the amount of overlap between hypoactivity, as assessed by automated, measures, and catalepsy, as determined by experimenter observations, is again unclear. Finally, other unconditioned behaviors influenced by DA include yawning, repetitive opening and closing of the mouth and perioral movements. Again, the similarity among these dependent variables is not known and it is not known if they are the same or independent responses. Nevertheless, it is possible to summarize the effects of receptor-subtype specific DA drugs on unconditioned behavior if it is assumed that various dependent measures, for example catalepsy and reduced locomotion, are related.

D1 AND D2 AGONISTS

D1 Agonists: Unlike nonspecific DA agonists (e.g., amphetamine or apomorphine) which stimulate locomotor activity and induce stereotypy in rats [32, 143], the D1-specific agonist SKF 38393 has been reported to be without effect [128]. However, recent studies have shown that in well-habituated animals SKF 38393 did stimulate sniffing and locomotion, although the effect was smaller than that seen with amphetamine or apomorphine [16, 93, 96, 98, 100]. Furthermore, the stimulant effect was shown to be stereoselective, suggesting that the R-enantiomer was the active form of the drug [96, 98]. Recently we have carried out an extensive analysis of the effects of SKF 38393 on horizontal and vertical activity during 4 h sessions in photocell-equipped activity monitors and found dose-dependent stimulation of both activities (Fig. 1). SKF 38393 has also been

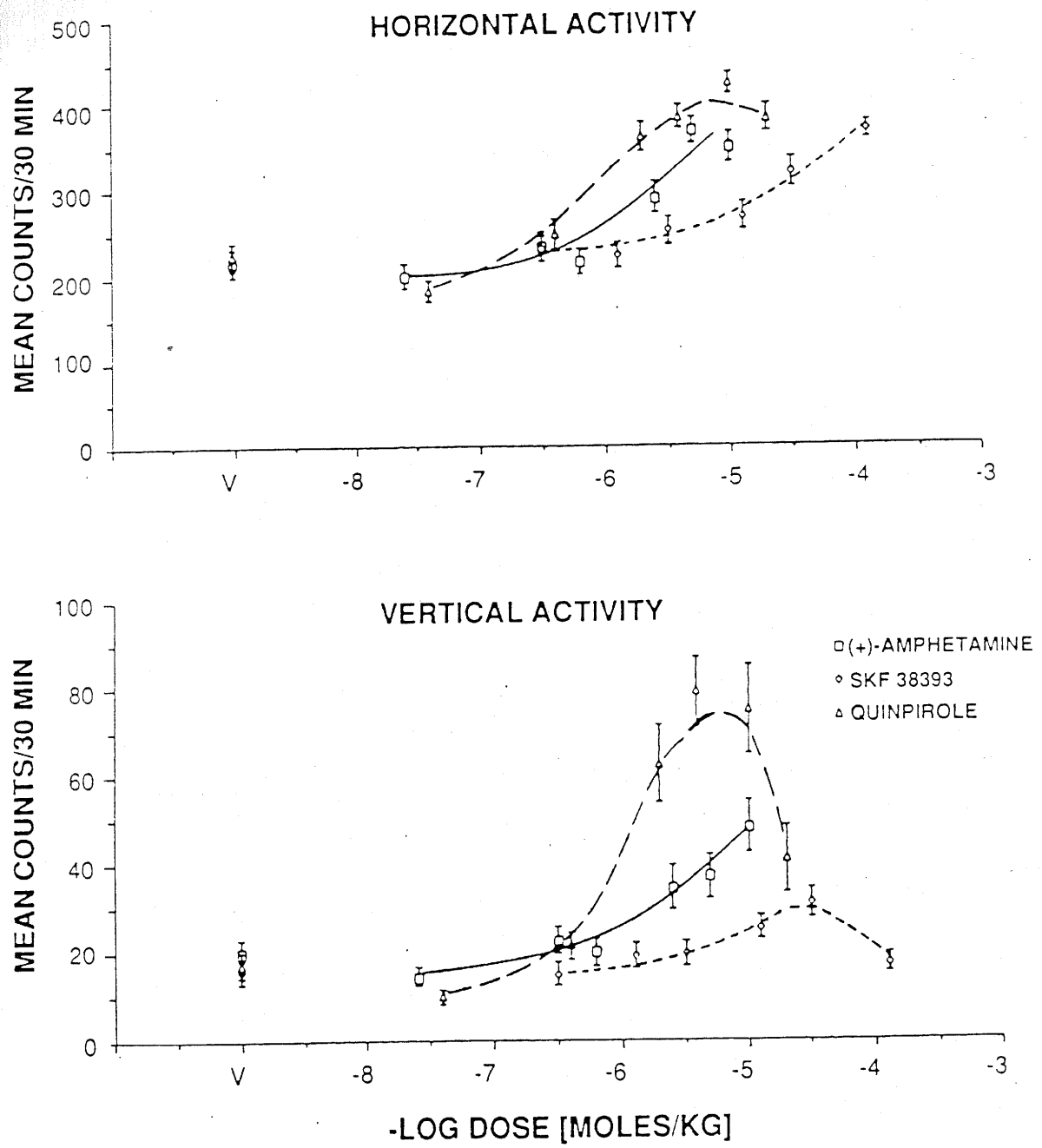

Fig. 1. Dose-response curves illustrating mean (± SEM) horizontal and vertical activity following administration of (+)-amphetamine, SKF 38393 or quinpirole. For each drug, 12 rats that had previously been habituated to the testing environment were treated (*ip*) with all doses in a random order. Sessions in automated chambers assessing horizontal and vertical activity were 4 h in duration and occurred 48 apart. (+)-Amphetamine (vehicle (V), 0.01, 0.1, 0.25, 1.0, 2.0 and 4.0 mg/kg), quinpirole (V, 0.01, 0.1, 0.5, 1.0, 2.5 and 5.0 mg/kg) and SKF 38393 (V, 0.1, 0.4, 1.0, 4.0, 10.0 and 40.0 mg/kg) doses have been transformed (log of moles/kg) to facilitate comparisons among drugs

reported to produce desynchronization of electroencephalographic (EEG) activity in rats and rabbits, a physiological measure of arousal similarly affected by nonspecific DA agonists [114, 116, 117]. It has been suggested that the desynchronized EEG is reflective of behavioral activation [95].

Many studies have reported that SKF 38393 stimulates grooming behavior

in rodents [9, 23, 46, 86, 93a, 100, 116, 134, 135, 136, 155]. Fletcher and Starr [46] reported decreased locomotion, rearing and head-dipping in a holeboard apparatus following SKF 38393 in brief (7.5 min) sessions; as they also noted increased grooming, it is possible that this behavior competed with the other activities during the brief test sessions. Perhaps grooming and locomotor responses follow a different time course, and had longer sessions been utilized, a stimulant effect may have emerged. Researchers have reported no effect of SKF 38393 on yawning behavior [85, 129a, 133, 160]; however, SKF 38393 did block yawning induced by low doses of apomorphine [161]. Finally, SKF 38393 has been found to produce increased opening and closing of the mouth or tremulous oral movements [69, 81, 127, 128].

Some studies have investigated the possible site of action of SKF 38393 by examining the behavioral effects of unilateral or bilateral microinjections into DA innervated structures. Contralateral rotation, an index of locomotor stimulation, was reported when SKF 38393 was injected unilaterally into the zona reticulata of the substantia nigra, an effect similar to that observed with amphetamine or DA [11, 66]. In the frontal cortex, however, amphetamine produced contralateral circling [139] whereas SKF 38393 was without significant effect [17]. Bilateral microinjections of SKF 38393 into the nucleus accumbens produced a dose-dependent and long-lasting increase in coordinated forward locomotion [38]. The D1 agonist CY 208 – 243 also enhanced locomotion when injected into the nucleus accumbens but the magnitude (and duration) of the effect was considerably less than that observed with SKF 38393 [38]. Thornton et al. [140] microinjected SKF 38393 into the habenula nucleus of rats and observed enhanced rearing and locomotion. Finally, bilateral ventral striatal injections of the D1 agonist fenoldopam produced a moderate increase in sniffing and only a small increase in locomotion and grooming [21].

In summary, it appears that pharmacological activation of the D1 receptor with systemic injections of D1 agonists leads to increased locomotor activity. The effect is not as strong as that seen following the nonspecific DA agonists, and is typically seen only in well-habituated animals. However, unlike systemic administration, intracranial microinjections of the D1 agonist SKF 38393, particularly into the nucleus accumbens, produced marked and prolonged increases in locomotor activity. The substantia nigra pars reticulata as well as the habenula nucleus may also be involved in the locomotor stimulant effects of D1 agonists. In addition to locomotor stimulation, grooming and small perioral movements are seen with systemic administration of D1 agonists. Stereotyped behaviors, like those observed following nonspecific DA agonists, have not been reported; however increased sniffing was observed following microinjection of SKF 38393 into the ventral striatum.

D2 Agonists: In general, systemically administered selective D2 agonists are more potent and efficacious in stimulating locomotor activity than D1 agonists. Increased locomotor activity has been reported following administration of the D2 agonist bromocriptine in mice [70] and rats [60, 93]. Similar effects have been seen with the D2 agonists, LY 141865 [16], its active isomer, quinpirole (previously LY 171555) [9, 23, 39, 40, 69, 86, 155], (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) [89, 90] or RU 24213 [91, 96, 123, 135, 136]. In agreement with these findings, we have found that quinpirole increased horizontal and

vertical activity in a dose-related manner (Fig. 1). Stereotypy also has been reported following administration of bromocriptine [67, 70, 93], quinpirole [93a, 114, 155, 156], (−)N-0437 [151] or RU 24213 [91, 93a, 96, 123, 155]. However, at least in the case of quinpirole, the stereotypy response was qualitatively dissimilar to that induced by nonselective DA agonists [39, 155].

Injection of the D2 agonists quinpirole, BHT 920, (+)3PPP, (−)N-0437 or bromocriptine produced yawning [85, 129a, 133, 141, 145, 146, 160]. Recently, Ushijima and colleagues [144] showed that the frequency of bromocriptine-induced yawning was lower in 12-month-old than in 2-month-old rats. The effects of D2 agonists on grooming, a prominent behavioral effect of D1 stimulation, are equivocal; it has been reported that quinpirole had little effect [23], RU 24213 decreased grooming [134] and quinpirole or RU 24926 increased grooming [155]. Like receptor-nonselective and D1 agonists, quinpirole produced EEG desynchronization in the rabbit [114, 117].

Researchers investigating the possible site of action of D2 agonists in mediating locomotion and stereotypy have microinjected them into DA innervated structures. It was found that unilateral injections of quinpirole into the pars reticulata of the substantia nigra induced ipsilateral rotation [11]. As SKF 38393, DA or amphetamine produced contralateral rotation when injected into this structure [11, 66] and DA into the striatum also produced contralateral rotation [72], it may be that ipsilateral rotation seen following intranigral quinpirole resulted from an inhibition of DA release on the injected side. In the frontal cortex, LY 141865 or quinpirole, like amphetamine, produced contralateral circling [17, 139]. Bilateral intraaccumbens injections of quinpirole produced a small enhancement of locomotor activity [38]; injections into the habenula nucleus produced a significant decrease in grooming and locomotion, but only at the middle dose [140]. Finally, ventral striatal injections of quinpirole increased sniffing and oral behaviors (licking, chewing and/or biting) [21].

In summary, systemic administration of D2 agonists seems to produce stimulant effects on behavior similar to, although possibly weaker than, those seen following treatment with nonselective DA agonists. D2 agonists also produce yawning but their effects on grooming are unclear. Intracranial microinjection studies have revealed that the motoric effects of D2 agonists may be at least partially due to D2 receptor stimulation in the frontal cortex and nucleus accumbens, although many sites still need to be investigated. Interestingly, the D2 agonist quinpirole produced only a small increase in locomotor activity when injected into the nucleus accumbens; this is somewhat surprising given the role of this structure in the locomotor stimulant effects of nonselective agonists. The increased sniffing produced by D2 agonists may be mediated, at least in part, by D2 receptor stimulation in the ventral striatum.

D1 and D2 Agonists in Combination: A number of researchers have reported synergistic behavioral effects of combined treatment with D1 and D2 agonists. Treatment with doses of each compound that failed to produce significant effects when given alone led to an effect when given together. Thus, co-injection of the D1 agonists SKF 38393, SKF 75670 or Lu 24−040 and the D2 agonists bromocriptine, quinpirole, RU 24213 or RU 24926 has been reported to produce oral stereotypies or stereotyped behavior in rats and locomotor activity or climbing in mice [9, 36, 62, 63, 65, 91, 93a, 101, 152, 155, 156]. It is interesting to

note that administration of a D1 and D2 agonist produced behavioral response almost indistinguishable from that of apomorphine [155].

Synergistic effects have also been observed when D1 and D2 agonists are injected intracerebrally. A synergistic effect on locomotor activity occurred when quinpirole and SKF 38393 were locally applied to the nucleus accumbens of rats [121]. Similarly, infusions of quinpirole and the D1 agonist fenoldopam into the ventral striatum of rats resulted in markedly enhanced sniffing and paw-nibbling [21]. Low doses of SKF 38393 also potentiated yawning produced by quinpirole or bromocriptine [133, 145]. Microinjections of a D1 or D2 agonist into the ventral striatum increased jaw movements in ketamine-anesthetized rats; a synergistic effect on jaw movements was observed when low doses of each agonist were injected concurrently [78].

In a recent study, Martin-Iverson et al. [89] found that animals receiving chronic infusions of the D2 agonist PHNO eventually showed tolerance to the stimulant effects during the daytime but not during the nighttime when they were normally more active. They further observed that injections of the D1 agonist SKF 38393 during the daytime reversed the apparent tolerance to the stimulant effects of PHNO. They suggested that daytime tolerance may have been related to the effects of PHNO on presynaptic D2 receptors leading to a decrease in the endogenous release of DA; as endogenous release is significantly higher during the night, this effect may not have occurred at that time. As stimulation of both D1 and D2 receptors may be necessary for the observation of DA-mediated behaviors in intact animals (see below), the large decrease in endogenous DA produced by PHNO during the daytime may have led to a loss of stimulation of D1 receptors and therefore apparent tolerance to the stimulant effects of PHNO at postsynaptic D2 receptors [89]. From this point of view the reversal of daytime tolerance to PHNO by SKF 38393 can be understood.

Further support for this hypothesis was recently provided [136]. These researchers found that low presumably presynaptic doses of apomorphine or the D2 agonist RU 24213 produced decreases in the locomotor activity of mice. This effect was reversed by SKF 38393 in a dose that was by itself ineffective. According to the reasoning of Martin-Iverson et al. [89], the decrease in endogenous DA release resulting the from stimulation of presynaptic D2 receptors may have led to a loss of stimulation of D1 receptors, having lower affinity than D2 receptors, and therefore a decrease in locomotor activity. Injection of the D1 agonist may have reinstated stimulation of these receptors and behavior returned to normal levels.

D1 AND D2 ANTAGONISTS

D1 Antagonists: These compounds, like nonselective DA receptor blockers, produced decreases in locomotor activity and induced catalepsy. Thus, decreased activity has been reported following administration of the D1 antagonist SCH 23390 [29, 34, 46, 57, 59, 134, 135]. Recently, we have observed similar effects of SCH 23390 on horizontal and vertical activity (Fig. 2).

SCH 23390 has been found to antagonize the stimulant effects of apomorphine or amphetamine on locomotor activity and stereotypy [3, 22, 29, 34, 50, 61,

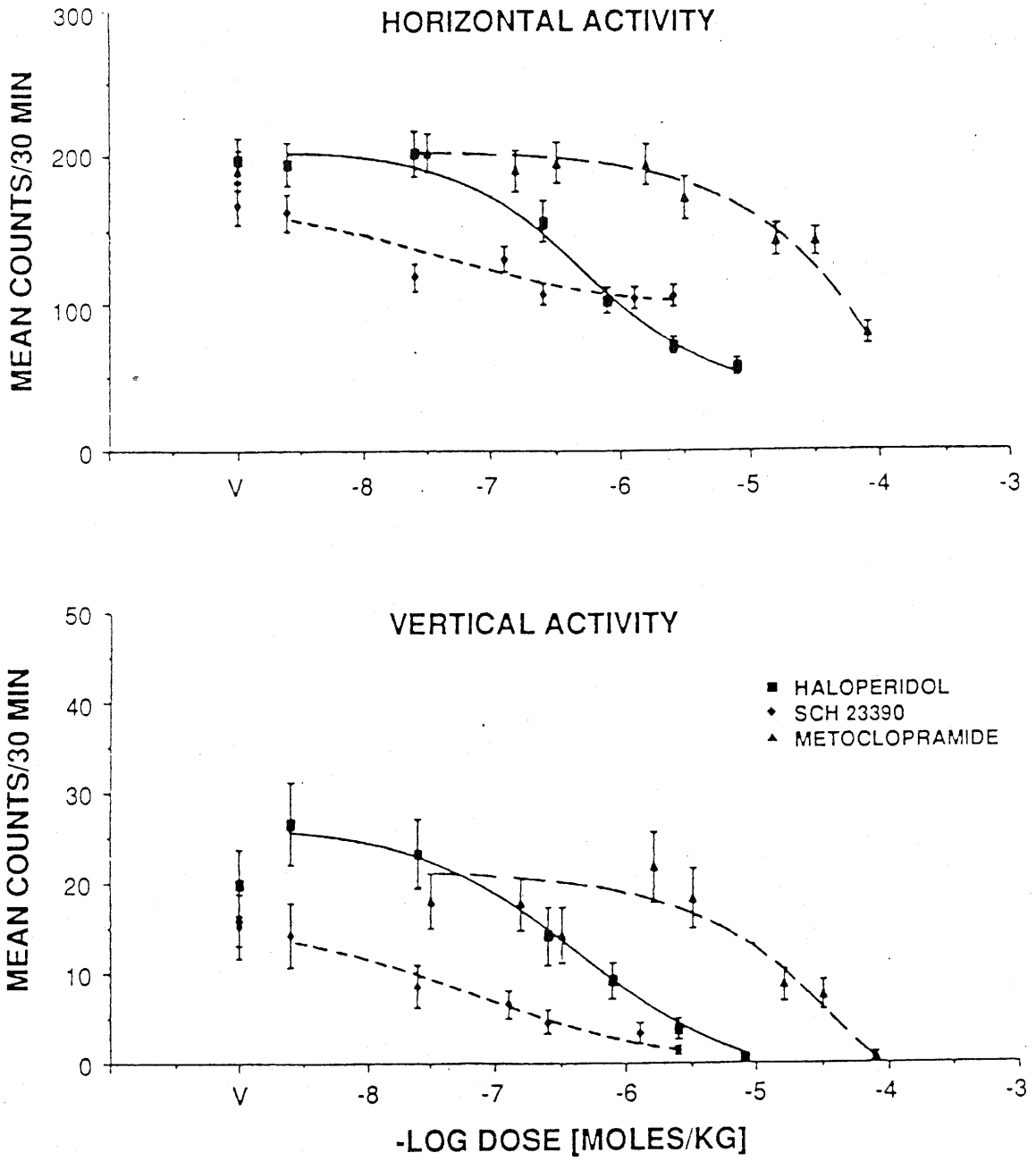

Fig. 2. Dose-reponse curves illustrating mean (± SEM) horizontal and vertical activity following administration of haloperidol, SCH 23390 or metoclopramide. Twelve rats were treated with each drug (see Figure 1 caption for procedure). Haloperidol (vehicle (V), 0.001, 0.01, 0.1, 0.3, 1.0 and 3.0 mg/kg, *ip*), SCH 23390 (0, 0.001, 0.01, 0.05, 0.1, 0.5 and 1.0 mg/kg, *sc*) and metoclopramide (0, 0.01, 0.05, 0.1, 0.5, 5.0, 10.0 and 25.0 mg/kg *ip*) doses have been transformed to facilitate comparisons among drugs

86, 88, 90, 148, 152]. SCH 23390 also antagonized the stimulant effect of the DA agonist DP-5,6-ADTN [58] and of the opiate agonist morphine [84]. The D1 antagonist SKF 83566 produced a similar effect on apomorphineinduced stereotypy [99]. Finally, SCH 23390 also decreased apomorphine-induced yawning [104, 129a] and blocked the EEG desynchronization produced by apomorphine or L-DOPA [114, 115].

D1 receptor antagonists have been shown to block the effects of D1 or D2 receptor-specific agonists. Thus, SCH 23390 antagonized sniffing and locomo-

tion [97, 98] and EEG desynchronization [114, 116, 117] produced by SKF 38393. SCH 23390 also antagonized SKF 38393-induced grooming [46, 97, 117]. Furthermore, the decreased activity reported by Fletcher and Starr [46] following SKF 38393 (see section on D1 Agonists) was reversed by D1 receptor blockade. Increases in locomotor activity, climbing or stereotypy following D2 agonists were also blocked by SCH 23390 [5, 26, 86, 90, 96, 114, 117, 123, 155, 162] or by the D1 antagonist, R-SKF 83566 [96, 99]. SCH 23390-induced catalepsy was reversed by a D2 agonist [99]. SCH 23390 also blocked yawning produced by D2 agonists [85, 129a, 146] and antagonized oral stereotypies or climbing behavior seen after the co-administration of a D1 and D2 agonist [9, 101]. SCH 23390 blocked the locomotor stimulant effects of bromocriptine plus SKF 38393 observed in mice acutely treated with the catecholamine synthesis inhibitor alpha-methyl-p-tyrosine (AMPT) [65]. However, SCH 23390 failed to block EEG desynchronization following quinpirole [114, 117].

Intracerebral microinjections have been utilized to localize brain regions involved in the behavioral effects of SCH 23390. Bilateral microinjections of SCH 23390 into the nucleus accumbens decreased spontaneous locomotor activity [121]; similar injections into either the ventral striatum or nucleus accumbens reduced the locomotor stimulant effect of apomorphine [3]. Consistent with these findings, it was shown that unilateral injections of SCH 23390 into the ventral striatum produced ipsilateral turning in rats following a systemic injection of apomorphine or methamphetamine [79]. Catelepsy was observed when SCH 23390 was injected into the striatum, nucleus accumbens or globus pallidus [49, 118] but not the ventromedial thalamus, cerebral cortex overlying the striatum, substantia nigra pars reticulata, ventral tegmental area, superior colliculus, periaqueductal gray or habenula [49]. Finally, intravenous apomorphine induced jaw movements in ketamine-anesthetized rats; these movements were reduced when SCH 23390 was locally applied to the ventral but not dorsal striatum [78, 80].

In summary, D1 antagonists appear to possess the same properties as nonselective DA receptor blockers. They decrease locomotor activity, induce catalepsy, and antagonize the stimulant effects of nonspecific DA agonists. As expected, they antagonize the behavioral effects of D1 agonists but, perhaps surprisingly, D1 antagonists also block most of the behavioral effects associated with D2 agonists. This latter finding suggests that stimulation of both D1 and D2 receptors is necessary for the observation of behavioral effects mediated by DA. Finally, preliminary evidence suggests that the nucleus accumbens and striatum as well as the globus pallidus may be important areas involved in the cataleptic and motor suppressant effects of SCH 23390.

D2 Antagonists: We have found that the D2 antagonist metoclopramide produced decreases in horizontal and vertical activity (Fig. 2), results in good agreement with those seen with other D2 antagonists [29, 147]. Several D2 antagonists induced catalepsy in rats or mice [1, 29, 42, 53, 76, 77, 112, 113, 147]. Furthermore, the stimulant effects of apomorphine or amphetamine were antagonized by the D2 antagonists metoclopramide, sulpiride, clebopride, raclopride, remoxipride, eticlopride, sultopride and YM 09151 – 2 [3, 37, 53, 68, 83, 87, 113, 122, 125, 126, 147, 148, 152]. Sulpiride inhibited behavioral activation but not EEG activation following L-DOPA in rabbits [115]. Sulpiride also antagonized apo-

morphine-induced yawning [129a]. Finally, Rosengarten et al. [127] found that sulpiride, like a D1 agonist, led to an increase in perioral movements.

As was the case for D1 antagonists, D2 antagonists block some of the behavioral effects of D1 or D2 agonists. Thus, the D2 antagonists Ro 22−2586, metoclopramide or sulpiride blocked increases in locomotor activity, climbing or stereotypy observed following D2 receptor stimulation [96, 115, 123, 162]. Sulpiride blocked yawnig following D2 receptor stimulation [85, 129a, 146, 160]. Similarly, locomotor activity and rearing following D1 receptor stimulation were also decreased by metoclopramide or Ro 22−2586 [96, 98] and the increase in activity following intra-accumbens injections of SKF 38393 was blocked by systemic treatment with spiperone [38]. However, D2 receptor blockade failed to antagonize D1 receptor-stimulated grooming [97]. Finally, the D2 receptor blockers YM 09151−2 or clebopride antagonized oral stereotypies or climbing behavior seen after the co-administration of a D1 and D2 agonist [9, 101].

Several investigators have been interested in localizing the site of action of D2 antagonists. Costall and Naylor [32] showed that the stimulant effects of DA applied bilaterally to the caudate-putamen, nucleus accumbens or olfactory tubercle were antagonized by sulpiride; metoclopramide produced similar effects but failed to block the nucleus accumbens effect. The latter finding is surprising considering that bilateral microinjections of metoclopramide into the nucleus accumbens of rats reduced spontaneous locomotion [121] and blocked locomotor hyperactivity induced by peripheral administration of apomorphine [107]. Arnt [3] showed that bilateral microinjection of (−)-sulpiride or YM 09151-2 into the ventral striatum or nucleus accumbens, but not into a number of other DA-innervated structures, reduced the locomotor stimulant effects of apomorphine. Intra-accumbens injections of raclopride also decreased exploratory activity as well as hyperactivity and rearing produced by intra-accumbens injections of amphetamine [149]. Looking at the effects of unilateral central injections of D2 antagonists in animals treated peripherally with amphetamine or apomorphine, it has been found that intrastriatal metoclopramide [120] or intrafrontocortical metoclopramide or sulpiride produced ipsilateral rotation in rats [105, 106, 139].

Similarly, ventral but not dorsal striatal injections of sulpiride or YM 09151−2 produced ispilateral circling in response to a systemic injection of apomorphine or methamphetamine [79]. Intrafrontocortical cocaine produced contralateral turning that was antagonized by co-administration of sulpiride [106]. Catalepsy has also been observed following microinjections of sulpridie into the ventro-rostral striatum and to a lesser extent the nucleus accumbens [118]. Finally, ventral striatal injections of sulpiride and YM 09151−2 blocked jaw movements induced by systemic apomorphine in ketamine-anesthetized rats [78, 79]. Together, these data point to the importance of the ventral striatum, nucleus accumbens and frontal cortex in mediating the motor suppressant and cataleptic effects of D2 antagonists.

In summary, D2 receptor blockade produces behavioral effects similar to those seen after treatment with nonselective DA antagonists. Thus, it decreases locomotor activity, induces catalepsy, and antagonizes the stimulant effects of DA agonists. As expected, it antagonizes the behavioral effects of D2 agonists;

D2 receptor blockade also blocks most of the behavioral effects of D1 agonists with the exception of grooming and, in the case of small perioral movements, D2 blockade appears to produce the same effects as a D1 agonist. Again, these data suggest that, with the exception of grooming and perioral movements, both D1 and D2 stimulation may be necessary to observe behavioral effects mediated by DA. Although the evidence is still preliminary, it appears that the nucleus accumbens, ventral striatum and frontal cortex are important target areas for the motor suppressant and cataleptic effects of D2 antagonists.

D1 and D2 Antagonists in Combination: A number of researchers have reported synergistic behavioral effects of combined treatment with D1 and D2 antagonists. Treatment with doses of each compound that failed to produce significant effects when given alone led to an effect when given together. Thus, the combined administration of a D1 antagonist with a D2 antagonist produced catalepsy [119, 142], suppressed locomotion and rearing [28, 35] and produced marked synchronized EEG activity [20]. Combined administration of selective antagonists also blocked apomorphine-induced stereotypy and quinpirole-induced hyperactivity [35].

D1 AND D2 AGONISTS IN ANIMALS ACUTELY DEPLETED OF DA

A number of studies have examined the possible consequences of acute treatments with DA depleting drugs on the behavioral effects of D1 or D2 agonists. Mice or rats treated with the catecholamine synthesis inhibitor AMPT or a combination of AMPT and the granule depletor reserpine did not exhibit the usual behavioral responses to SKF 38393 or the D2 agonists bromocriptine, quinpirole or B-HT920, presumably as a result of reduced endogenous DA levels stimulating the alternate receptor [23, 38, 55, 62, 63, 64, 65, 67, 70, 86, 137, 155, 156, 162]. Recently, Ushijima et al. [144] reported this effect of AMPT plus reserpine on bromocriptine-induced yawning in young (2 month-old), but not 12 month-old rats suggesting that it may be age-dependent. There was another exception; grooming produced by injection of the D1 agonist SKF 38393 was not antagonized by acute treatments with AMPT plus reserpine [65]. Co-treatment with a D1 and D2 agonist in catecholamine-depleted animals was seen to be effective in restoring locomotor activity and/or stereotypy [12, 23, 38, 58, 62, 63, 65, 86, 129, 137, 138, 155, 156] and this effect was blocked by either SCH 23390, sulpiride or spiperone [57, 129].

From these data it appears that stimulation of both DA receptor subtypes is necessary to produce behavioral effects. The one exception to this pattern is grooming stimulated by SKF 38393; apparently it did not require the stimulation of D2 receptors by endogenous DA as it was unaffected by combined injections of AMPT and reserpine. This is entirely consistent with the finding that a D2 antagonist failed to block SKF 38393-induced grooming (see section on D2 Antagonists).

D1 AND D2 COMPOUNDS IN DA SUPERSENSITIVE ANIMALS

Bilateral DA Denervation: It has been demonstrated that treatments which result in a chronic depletion of DA lead to a supersensitive response when DA receptors are subsequently stimulated. Thus, when treated with nonselective

DA agonists, behavioral responses were augmented, suggesting receptor supersensitivity. In contrast to animals undergoing acute depletions of DA, which failed to show locomotor responses to D1 or D2 agonists, rats and mice with DA receptor supersensitivity exhibited enhanced behavioral responses to D1 or D2 agonists. Furthermore, there was an unexpected change in the ability of DA receptor subtype antagonists to block agonist-induced effects. Following bilateral injections of the neurotoxin, 6-hydroxydopamine (6-OHDA) rats showed enhanced locomotor activity when injected with SKF 38393 or the D2 agonist pergolide; in addition, they responded at doses that were ineffective in intact animals. As expected, SCH 23390 antagonized the effect of SKF 38393, and clebopride antagonized the effect of pergolide. However, unlike results from intact rats, as reviewed above, SCH 23390 failed to antagonize the effects of pergolide, and clebopride failed to antagonize the effects of SKF 38393. Furthermore, neither antagonist blocked the effects of apomorphine but they did when co-administered [4]. Related findings have been reported by Breese and his coworkers [25, 26].

A similar pattern of results was seen in rats following chronic treatment with the catecholamine-depleting drug reserpine which presumably also produced receptor supersensitivity [5, 85]. However, some discrepancies exist in the literature. Rubinstein et al. [129] found that SKF 38393 or quinpirole alone stimulated activity in mice chronically treated with reserpine. Like Arnt [5], they found that sulpiride blocked the effect of quinpirole but not SKF 38393; unlike Arnt [5], they found that SCH 23390 blocked the effects of both SKF 38393 and quinpirole. Besides the species difference, the possible basis for these discrepant findings is unclear. It is noteworthy, however, that the effects of SCH 23390 on SKF 38393-induced activity were greater than those on quinpirole-induced activity in the Rubinstein et al. [129] study. In general, these findings suggest that the need to stimulate both D1 and D2 receptors for the observation of behavioral effects mediated by DA, as seen in intact rats and mice, may be lost in DA denervated animals.

A somewhat different picture has emerged from studies with primates. It has been found that the DA neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can produce parkinsonian symptoms, including decreased locomotor activity, in marmoset and Macacca fascicularis monkeys [31, 43, 109, 110]. These effects were associated with a loss of striatal DA, enhanced response to apomorphine and increased binding of [3H] spiperone to DA receptors demonstrating receptor supersensitivity [43]. It was found that the D2 agonists bromocriptine or LY 141865 (or its active isomer LY 171555), but not the D1 agonist SKF 38393, were effective in relieving the parkinsonian symptoms [12, 31, 43, 109, 110]. Co-administration of SKF 38393 with LY 171555 prevented in a dose-dependent manner the motor activation induced by LY 171555 [12, 110]. Thus, it appeared that D2 receptor activation was essential for motor activation in MPTP-induced parkinsonism in monkeys. Unlike the DA supersensitive rodent in which either D1 or D2 stimulation could produce locomotor effects, only D2 agonists appeared to be effective in the DA supersensitive monkey.

Human beings with Parkinson's disease appear to show a similar selectivity of responsiveness to D2 agonists but not D1 agonists. Thus, it has been reported that the D2 agonist bromocriptine is an effective treatment in Parkinson's

disease (for a review see Ref. 82). The D1 agonist SKF 38393, on the other hand, was shown to be ineffective in a double blind placebo-controlled study of Parkinson's patients [24]. These results are in good agreement with those from MPTP-treated monkeys and suggest that primates chronically depleted of DA require D2 receptor stimulation for the reinstatement of locomotor activity.

Unilateral DA Denervation: There have been many studies investigation the effects of selective DA receptor compounds on motor behavior in animals with unilateral nigrostriatal DA denervation. These animals, like those with bilateral denervation, developed DA supersensitivity on the denervated side. When treated peripherally with direct-acting DA agonists, contralateral rotation was seen. Thus, rotation was reported following systemic treatment with the D1 agonist SKF 38393 [6, 7, 8, 44, 51, 52, 73, 103, 131, 157, 158] and the D2 agonists LY 141865, quinpirole, RU 24213, (−) N-0437, bromocriptine or pergolide [6, 7, 8, 45, 51, 54, 55, 56, 70, 73, 124, 150, 151, 157, 158].

Contralateral rotation was also observed with direct application of SKF 38393 to the denervated striatum [47, 48, 52, 131], nucleus accumbens or frontal cortex [47]. In rats with unilateral lesions, similar effects were seen with the D2 agonist lisuride injected into these structures as well as the globus pallidus, ventral thalamus, substantia nigra or periaqueductal gray; SKF 38393, however was inactive in these latter structures [47, 48].

As expected, D1 antagonists blocked the effects of SKF 38393 on turning [6, 7, 8, 47, 48, 73, 103] and D2 antagonists blocked D2 agonist effects [6, 7, 8, 47, 48, 54, 73]. But, as was the case for bilaterally DA-denervated rats, D1 antagonists failed to block D2 agonist effects and vice versa [6, 7, 8, 47, 48, 54]. Karlsson et al. [73] actually reported an increase in CY 208−243- or bromocriptine-induced circling following sulpiride or SCH 23390, respectively. D1 antagonists or D2 antagonists alone, although decreasing apomorphine-induced circling, failed to block it, but when combined a blockade was observed [7, 29, 48, 53, 54, 56, 68]. Although these findings suggest that D1 and D2 receptors act independently in the rodent with a lesion, there is one report of a synergistic interaction; a low dose of SKF 38393, which by itself had no effect, potentiated quinpirole-induced contralateral turning in rats with unilateral 6-OHDA lesions of the substantia nigra [126].

Some studies employed unilateral lesion techniques that did not lead to a DA supersensitive response and investigated the effects of DA receptor subtype-specific compounds on rotation. As expected, they found results consistent with those of studies of intact animals rather than studies of animals with supersensitive DA receptors. Thus, Arnt and Perregaard [10] hemitransected the forebrain just caudal to the striatum and found that peripheral administration of apomorphine produced ipsilateral rotation. The effect would have resulted from the action of apomorphine on the intact side as striatal output on the transected side would have been lost. In this paradigm, D2 agonists produced ipsilateral rotation while D1 agonists were without effect. However, the effect of D2 stimulation was augmented by co-treatment with a D1 agonist. Either the D1 antagonist SCH 23390 or the D2 antagonists YM 09151−2 blocked the effect of the two agonists given together.

In a related study, Barone et al. [12a] made unilateral intrastriatal injections of the excitotoxin quinolinic acid; this compound leads to loss of cells but not

fibres of passage [41]. As a result, striatal output on the injected side was impaired. They found that SKF 38393 was without effect whereas quinpirole increased ipsilateral rotation. They also demonstrated that co-administration of an ineffective dose of quinpirole with SKF 38393 led to rotation. Finally, the D1 antagonist SCH 23390 blocked the effect of the D2 agonist quinpirole. The results of this study and that of Arnt and Perregaard [10] were consistent with results obtained in intact rats. Thus, D2 agonists were more effective than D1 agonists in stimulating activity and the effect could be blocked by either D1 or D2 antagonists. These data provide further support for the conclusion that stimulation of both D1 and D2 receptors is necessary for observation of behavioral effects of DA in normosensitive animals.

In a recent study, Calderon et al. [27] reported that SCH 23390 produced catalepsy in rats that was abolished by bilateral quinolinic acid lesions of the striatum. As was the case in the study of Barone et al. [12a], this lesion would eliminate striatal output cells normally influenced by DA. Thus, the motor inhibitory effects of the D1 receptor blocker were lost.

In summary, animals with unilateral or bilateral DA denervations producing supersensitivity show strong behavioral effects when treated with either D1 or D2 agonists. Unlike the intact animals where D1 or D2 antagonists can block the effects of DA receptor subtype-specific agonists or apomorphine, in the DA denervated animal, D1 agonist effects are only blocked by D1 antagonists and D2 agonist effects are only blocked by D2 antagonists. Furthermore, antagonism of the behavioral effects of apomorphine in the denervated animal requires blockade of both D1 and D2 receptors. In DA supersensitive monkeys or people with Parkinson's disease, on the other hand, simulation of D2 receptors reverses the deficits in locomotor activity whereas D1 agonists are ineffective. These findings suggest that rodents and primates differ in their response to DA devervation regarding the ability of agonists acting at either D1 or D2 receptors to produce locomotor activity.

SUMMARY AND CONCLUSIONS

When all of the data concerning the role of D1 and D2 receptors in the control of unconditioned behaviors are taken together a fairly consistent picture begins to emerge. Considering first the normosensitive animals, it appears that D1 and D2 receptors are interdependent in their involvement in the control of locomotor activity. Stimulation of either receptor subtype leads to increases in activity although D2 agonists generally have a larger effect on activity than D1 agonists. Subeffective doses of D1 and D2 agonists (or D1 and D2 antagonists) have a synergistic action when co-administered. Injections of antagonists specific for either receptor subtype leads to a decrease in unstimulated locomotor activity or a diminution in the effects of agonists stimulating either receptor subtype.

Besides locomotor activity, stimulation of D2 receptors produces yawning but a consistent effect on grooming has not been seen; D2 receptor stimulation also produces stereotyped behaviors. Again, there seems to be an interdependence between the two receptor subtypes; yawning or stereotypy produced by D2 receptor stimulation is blocked by either D2 or D1 antagonists.

Stimulation of D1 receptors produces grooming and small perioral movements but not stereotyped behaviors like those typically seen following large doses of D2 agonists or DA agonists not specific a receptor subtype. Unlike D1 receptor-stimulated locomotor activity which is antagonized by D2 receptor blockers, grooming and perioral movements are not (but see Ref. 81). Thus, D1 receptor-mediated grooming and perioral movements seem to be exceptions to the otherwise general finding that co-stimulation of the two receptor subtypes is needed for the expression of D1 or D2 agonist effects in normosensitive rats and mice.

The apparent need to stimulate both D1 and D2 receptors to produce locomotor and some other unconditioned behaviors in normosensitive animals is lost in chronically denervated animals that are supersensitive to the effects of DA or DA agonists. However, there appear to be important species differences. Generally, in rodents undergoing unilateral or bilateral 6-OHDA-induced destruction of the nigrostriatal DA system, the locomotor effects of D1 agonists are not blocked by D2 antagonists and those of D2 agonists are not blocked by D1 antagonists. Similar results have been reported following chronic treatments with catecholamine depleting drugs. Thus, stimulation of either D1 or D2 receptors alone in DA supersensitive rodents appears to be sufficient to produce locomotor activity. In primates made DA supersensitive either with MPTP or as a result of Parkinson's disease, on the other hand, D2 but not D1 agonists are effective in reversing locomotor deficits. Thus, in primates with DA receptor supersensitivity, stimulation of D2 receptors appears to be necessary for locomotor effects.

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Footnote. A third DA receptor subtype (D3) has recently been cloned [132]. The novel D3 receptor appears to be localized largely within the nucleus accumbens, olfactory tubercle and islands of Calleja and also on cell bodies and dendrites of DA neurons in the ventral tegmental area and substantia nigra. Behavioral characterization of this receptor awaits the development of compounds that possess selective affinity for this receptor.

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