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Dopamine D_1 receptor desensitization profile in MPTP-lesioned primates

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Abstract

The motor effects of dopamine D_1 receptor activation and the optimal way to stimulate these receptors were studied in a primate model of parkinsonism induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), using 2 selective full dopamine D_1 receptor agonists: A-77636 ([1*R*,3*S*] 3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride), and SKF 82958 (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide). A-77636 was administered to one group of primed monkeys ($N = 4$) previously treated with levodopa and other dopamine receptor agonists, while SKF 82958 was given to another group of drug-naive monkeys ($N = 3$). These drugs have different durations of efficacy, lasting > 20 h and approximately 1 h, respectively, and were administered once daily (A-77636) or thrice daily (SKF 82958) for 7 days. Both drugs demonstrated excellent antiparkinsonian efficacy and locomotor stimulation. However, a rapid, functionally important, homologous (selective for D_1 receptor agonists) desensitization process took place as early as on the second day with the longer-acting drug and a dose escalation of A-77636 failed to restore the initial benefit. Thrice daily dosing at a 4-h interval with the short-acting agent SKF 82958 maintained the maximal antiparkinsonian response but some shortening in the duration of response was observed after several days. These behavioral results show that dopamine D_1 receptors are susceptible to desensitization after prolonged occupancy and can be desensitized profoundly and independently of dopamine D_2 receptors in vivo in this model. Potent dopamine D_1 receptor agonists with an intermediate half-life may prove to be better adjuncts in the treatment of Parkinson's disease. Clinical entities with pathologically enhanced dopamine D_1 receptor-linked neural transmission might eventually also benefit from such desensitization.

Keywords: Dopamine D_1 receptor agonist; Desensitization; MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); Parkinson's disease

1. Introduction

For more than 25 years, levodopa has been the mainstay of therapy for Parkinson's disease patients. It is the most efficacious agent and its use has improved longevity (Diamond et al., 1987; Marttila et al., 1993). However, long-term management with levodopa is marred by predictable ('wearing-off') and later unpredictable ('on-off') response fluctuations in a majority of patients, often associated with various dyskinesias (Barbeau et al., 1971; Marsden and Parkes, 1977). These problems have prompted the development of direct dopamine agonists with different durations of efficacy, potency and selectivity for either the dopamine D_1 or D_2 receptors, the main subtypes present in the striatum. While the contribution of dopamine D_1 receptors to levodopa effects remains uncertain due to a lack of potent and selective agonists, dopamine D_2 receptor activation was thought to be essential for antiparkinsonian activity based on the poor results obtained, both in parkinsonian patients and in primates exposed to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), with the partial dopamine D_1 receptor agonist SKF 38393 (Close et al., 1985; Nomoto et al., 1985; Braun et al., 1987). Nonetheless, dopamine D_1 receptors are likely to play a determinant role in motor control (Clark and White, 1987).

Recent data now support the study of novel selective dopamine D_1 receptor agonists as potential therapeutic tools in Parkinson's disease. The dopamine D_1 receptor binding sites are not appreciably lost with the progression of the disease process since no significant downregulation of striatal dopamine D_1 receptors was demonstrated in treated parkinsonian patients in vitro (Raisman et al., 1985;

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Rinne et al., 1991) or in vivo using the technique of positron emission tomography (Shinotoh et al., 1993). The striatal levels of DARRP-32 (dopamine and cAMP-regulated phosphoprotein), a protein phosphorylated by stimulation of cAMP and linked to dopamine D_1 receptor function, remain normal in parkinsonian patients and MPTP-lesioned primates (Raisman-Vozari et al., 1990). Furthermore, the improvement contributed by dopamine D_1 receptor stimulation was illustrated by the ability of the dopamine D_1 receptor antagonist SCH 23390 ((*R*)-(+)-8 chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-*d*-hemimaleate, Shering, USA), to reduce the effects of levodopa in MPTP-lesioned marmosets (Elliott et al., 1992). Several other preclinical studies have also suggested that co-activation of both dopamine D_1 and D_2 receptors may be required to achieve optimal motor performance following dopamine denervation (Walters et al., 1987; Robertson et al., 1992; Gomez-Mancilla and Bédard, 1991; Gomez-Mancilla et al., 1993). Recently, direct evidence of definite antiparkinsonian activity provided by dopamine D_1 receptor agonism has been obtained in MPTP-lesioned primates challenged with several selective dopamine D_1 receptor agonists (Temlett et al., 1988; Taylor et al., 1991; Kebabian et al., 1992; Blanchet et al., 1993; Vermeulen et al., 1993). The partial functional dopamine D_1 receptor agonist CY 208-243 also showed some efficacy in parkinsonian patients (Temlett et al., 1989; Emre et al., 1992), but further studies with this drug were stopped due to toxicity. This shift in therapeutic focus beyond levodopa has also been characterized by interesting experimental attempts to better delineate the intrinsic regulatory mechanisms of the various dopamine receptor subtypes and the optimal way to stimulate them. Continuous dopamine stimulation is currently regarded to better regulate basal ganglia circuits and improve motor functioning in parkinsonian patients with response fluctuations to standard intermittent oral levodopa treatment (Sage et al., 1988; Cedarbaum et al., 1990; Mouradian et al., 1990) and rats bearing a unilateral chronic nigrostriatal dopamine deafferentation upon exposure to 6-hydroxydopamine (Juncos et al., 1989).

The optimal way to stimulate dopamine D_1 receptors in order to achieve long-term improvement in motor performance in animal models of Parkinson's disease has not been determined. Therefore, we elected to treat stable, MPTP-lesioned primates with selective dopamine D_1 receptor agonists of differing half-lives to determine the best approach to maintain antiparkinsonian activity over time. We herein report on our behavioral observations with two dopamine D_1 receptor agonists: A-77636 and SKF 82958. A-77636 ([1*R*,3*S*] 3-(1'-adamantyl)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-1*H*-2-benzopyran hydrochloride) (Kebabian et al., 1992) is a long-acting agonist that can produce prolonged behavioral activity (> 20 h) in both 6-hydroxydopamine rats and MPTP-lesioned primates. In vitro, A-77636 functions as a full agonist at the dopamine D_1 receptor and is 32-fold more selective at dopamine D_1 versus D_2 receptors (K_i of 39.8 and 1159 nM, respectively), with a lower affinity for β-adrenoceptors, α-adrenoceptors and 5-HT receptors. SKF 82958 (6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide) is a short-acting full dopamine D_1 receptor agonist (O'Boyle et al., 1989) that produces less than 2 h of antiparkinsonian efficacy in MPTP-lesioned primates (Blanchet et al., 1996). Binding studies on SKF 82958 (Andersen and Jansen, 1990) have revealed a 176-fold selectivity for dopamine D_1 versus D_2 receptors in vitro (K_i of 0.5 and 88 nM, respectively). Although the acute behavioral profile of these two agonists at their maximal effect appeared identical, repeated administration revealed profound differences upon activating dopamine D_1 receptors via intermittent versus continuous stimulation.

2. Materials and methods

2.1. Animals

A total of 7 ovariectomized, female cynomolgous monkeys (*Macaca fascicularis*) weighing 2.6–3.7 kg were used and divided in 2 groups. All animals were housed separately and exposed to a 12-h light/dark cycle. They were fed one large meal every day a few hours after drug administration and had free access to water. They had been all previously exposed to the neurotoxin MPTP hydrochloride, administered initially as a standard 2-mg bolus subcutaneously (s.c.) and followed by weekly 1-mg injections as necessary until an enduring and satisfactory parkinsonian syndrome developed. This requires a disability score on our scale of at least 4 points (see below). All parkinsonian animals were then allowed to recover for 2 months following the last MPTP injection before any drug treatment was attempted.

2.2. Drug treatment

The first group of 4 MPTP-lesioned animals had been part of other drug protocols and received various dopaminergic drugs, including levodopa, previous to this experiment. They were kept drug-free for 1 week before they were challenged once daily with a 2 mg/kg s.c. dose of A-77636 (Abbott Laboratories, Abbott Park, IL, USA) for 7 consecutive days. On the fourth day of A-77636 dosing, all monkeys were challenged with a single dose (1 mg/kg) of SKF 82958 (Research Biochemicals Int., Natick, MA, USA) and the following day, with a subthreshold dose (0.01 mg/kg) of the D_2-like dopamine receptor agonist quinpirole ((4a*R-trans*)-4,4a,5,6,7,8,8a,9-*o*-dihydro-5*n*-propyl-2*H*-pyrazolo-3-4-quinoline hydrochloride) (Eli Lilly and Co., Indianapolis, IN, USA). A saline injection was also given on the eighth day. Eight weeks later, the same monkeys received another 7-day course of A-77636

administered once daily according to the following dose-escalating treatment schedule: 0.5 (day 1–2), 1 (day 3), 2 (day 4), 4 (day 5), 6 (day 6) and 10 mg/kg (day 7). On the eighth day, they received a single high dose of SKF 82958 (4 mg/kg) followed 4 h later by a suprathreshold dose of quinpirole (0.1 mg/kg).

The second group of MPTP-lesioned animals ($N = 3$) was drug-naive when scheduled to receive SKF 82958 at the dose of 1 mg/kg thrice daily (4 h apart) for 7 days. All drugs were dissolved in normal saline and administered s.c.

2.3. Drug response monitoring

The locomotor response of each animal was recorded continuously (day and night) by photoelectric cells mounted on each home cage. Signals generated by light beam interruptions triggered by animal movements are cumulated by a computer program that provides a mobility count every 15 min.

The monkeys were also observed directly through a one-way screen and scored every 30 min up to 8 h to evaluate the extent and duration of the antiparkinsonian response as well as the presence of adverse effects including dyskinesia and stereotypy. Animals were rated in their regular home cages using a modified disability scale for MPTP monkeys that includes the following quantified motor and behavioral parameters: (a) posture: normal = 0 point, flexed = 1 point, crouched = 2 points; (b) mobility: active = 0 point, passive = 1 point; (c) climbing: present = 0 point, absent = 1 point; (d) gait: normal = 0 point, abnormal = 1 point; (e) tremor: absent = 0 point, present = 1 point; (f) eating: present = 0 point, absent = 1 point; (g) grooming: present = 0 point, absent = 1 point; (h) vocalization: present = 0 point, absent = 1 point; (i) social interaction: present = 0 point, absent = 1 point. A score from 0 to 3 points is considered to be normal and maximal disability is 10 points. Antiparkinsonian efficacy is considered present as long as the baseline score is improved by at least 2 points. Mean baseline disability scores for the 2 groups were 5.4 ± 0.6 (standard error of the mean) for the group previously treated with dopamine agonists, and 5.0 ± 0.6 for the drug-naive group.

Results pertaining to locomotor activity obtained from the various agonists were compared when appropriate by performing a one-way analysis of variance (ANOVA) followed by Dunnett's a posteriori test. Improvement in disability scores were compared with Friedman's test.

3. Results

Following injection of the first dose of A-77636, all animals showed significant improvement (by at least 3 points) on disability scores within 10 min and the maximal response persisted for 4 h in one subject and throughout the 8-h observation period in the others. Mobility counts (Fig. 1) provided evidence of significant locomotor hyperactivity ($P < 0.01$ on day 1) and nocturnal stimulation in all subjects. Some dyskinesia were also seen, but less than with levodopa as reported elsewhere (Blanchet et al., 1993). The second dose of A-77636 failed to reproduce the response elicited following the first injection. Only one subject showed a significant antiparkinsonian response and a less robust locomotor stimulation, present also into the dark cycle, was documented in 2 subjects. The continued dosing of A-77636 failed to stimulate motor behavior in any animal beyond that observed with the second dose

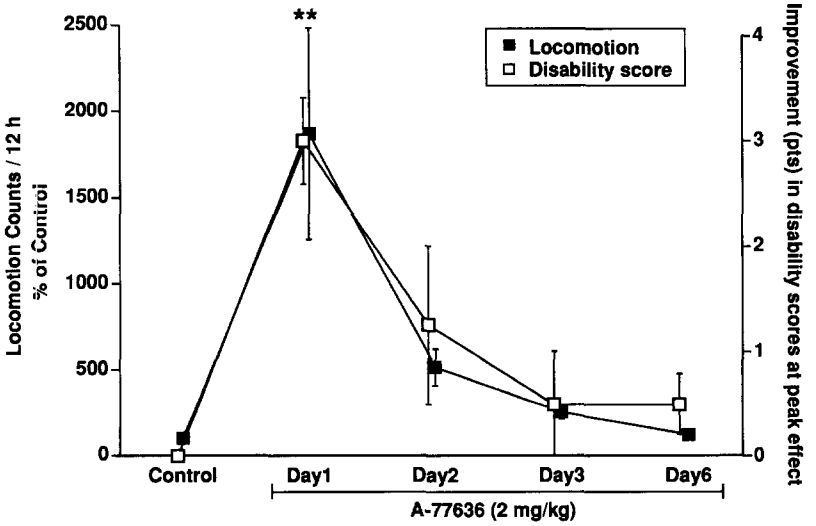

Fig. 1. Daytime (8AM-8PM) locomotor activity (■) and maximal improvement in parkinsonian disability scores (□) resulting from the daily administration of A-77636 (2 mg/kg s.c.) for 7 consecutive days. The mobility counts expressed each day represent the mean increase over control values expressed in % for all monkeys. Mean ± S.E.M. for 4 animals. ** $P < .01$ vs. control day for locomotion.

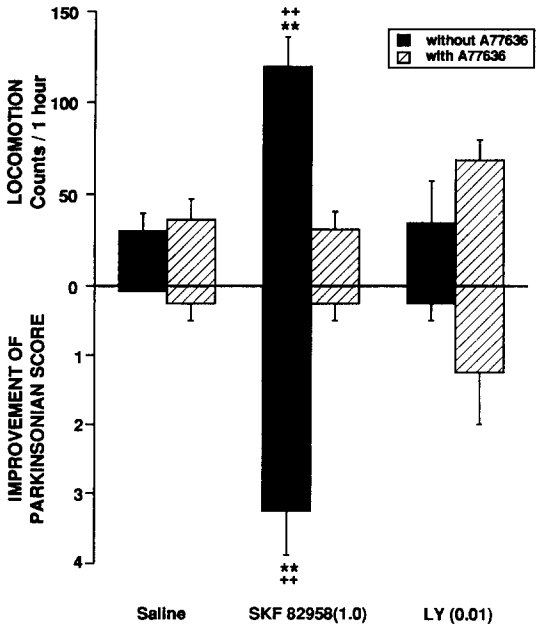

Fig. 2. Cumulative mobility counts recorded over 1 h (top histogram) and maximal improvement in parkinsonian score (bottom histogram) after a single dose of saline, SKF 82958 (1 mg/kg) and quinpirole (LY, 0.01 mg/kg), administered at baseline (black bars) and during (grey bars) continued daily dosing with A-77636 (2 mg/kg s.c.). Drug injections during the 7-day schedule of A-77636 treatment were given on day 4 (SKF 82958), day 5 (quinpirole) and day 8 (saline). Mean ± S.E.M. for 4 animals. $^{++}$ $P < 0.01$ vs. baseline results with saline. ** $P < 0.01$ vs. results obtained during A-77636 treatment.

(Fig. 1). In this context of altered responsivity, the administration of a suprathreshold dose of SKF 82958, the other dopamine D_1 receptor agonist, failed to stimulate locomotor activity or to improve the parkinsonian features in all subjects (Fig. 2). However, a subthreshold dose of quinpirole, a D_2-like dopamine receptor agonist, tended to increase locomotor activity and produced an antiparkinsonian response in 3 subjects, but failed to reach statistical significance (Fig. 2).

Similar observations resulted from the dose-escalating schedule of A-77636: the animals showed definite locomotor stimulation after the initial dose ($P < 0.01$), but failed to respond beyond the third dose despite increasing doses 20-fold relative to the effective initial injection (Fig. 3). Only one of the 4 subjects significantly improved its behavioral score after the administration of a dose of 4 mg/kg on day 5. Higher doses of A-77636 in the last 2 days of treatment were ineffective in all animals. Following the A-77636 treatments, SKF 82958 (4 mg/kg) on the subsequent day produced no antiparkinsonian effects, but quinpirole (0.1 mg/kg), injected 4 h following SKF 82958, produced a definite antiparkinsonian response with behavioral excitation lasting 4–5 h, an unusually long duration for this dose of quinpirole that usually lasts 2–3 h (data not shown).

The locomotor stimulation and degree of improvement in parkinsonian scores resulting from daily administration of SKF 82958 over 7 days are illustrated in Fig. 4. All drug-naive monkeys showed an excellent initial response to SKF 82958 averaging 47 min (35–60 min). Toward the end of the 7-day schedule, the maximal antiparkinsonian response was achieved but lasted for a shorter period of time, averaging 30 min. The latter observation has been reported in detail elsewhere (Blanchet et al., 1996). Furthermore, the increase in locomotor counts recorded over

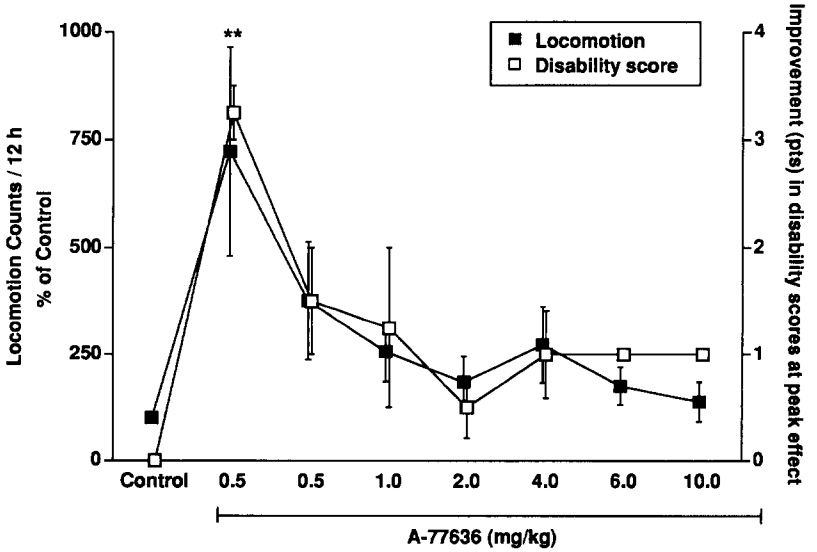

Fig. 3. Daytime (8AM-8PM) locomotor activity (■) and maximal improvement in parkinsonian disability scores (□) resulting from the administration of escalating (0.5–10 mg/kg s.c.) doses of A-77636 given once daily for 7 consecutive days. The mobility counts expressed each day represent the mean increase over control values expressed in % for all monkeys. Mean ± S.E.M. for 4 animals. ** $P < 0.01$ vs. control day for locomotion.

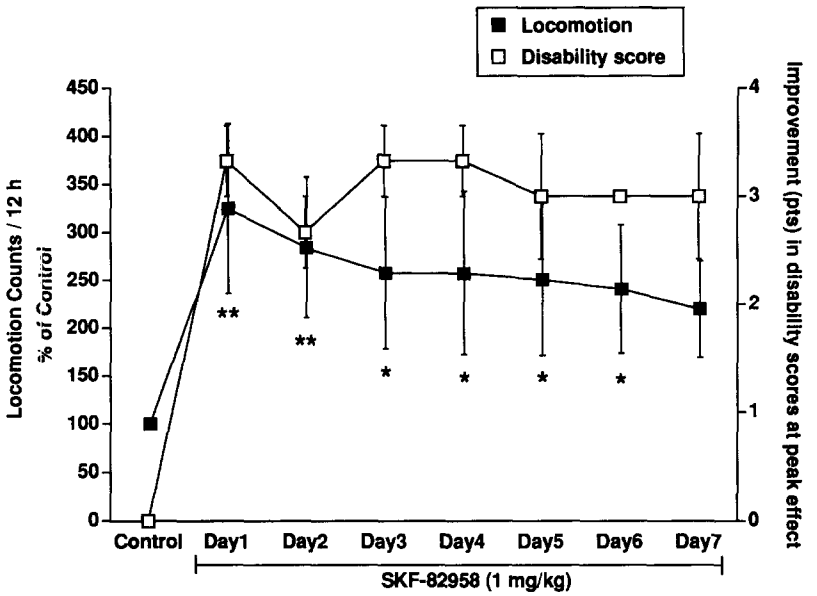

Fig. 4. Daytime (8:00 a.m. to 8:00 p.m.) locomotor activity (■) and maximal improvement in parkinsonian disability scores (□) resulting from the thrice daily dosing with SKF 82958. Mobility counts expressed each day represent the mean increase over control values expressed in percentages for all monkeys. Mean ± S.E.M. for 3 animals. ** $P < 0.01$ vs. control day for locomotion. * $P < 0.05$ vs. control day for locomotion.

12 h was maximal during the first 2 days and dropped slightly thereafter (Fig. 4).

4. Discussion

The foregoing observations confirm the acute antiparkinsonian efficacy of 2 structurally distinct D_1-selective dopamine receptor agonists (A-77636 and SKF 82958) in a primate model of Parkinson's disease. The maximal antiparkinsonian response following acute administration was similar whereas the duration of action clearly differentiated the 2 drugs. The behavioral effects of A-77636 outlasted the 8-h observation period and persisted through the dark cycle, as indicated by the locomotion counts and improved behavioral scores recorded the following morning (data not shown). In contrast, a clear return of parkinsonian symptomatology was observed within 60 min following injection of SKF 82958. Thus, these drugs exhibited definite differences in the temporal profile of central dopamine D_1 receptor occupancy upon acute administration.

Both the antiparkinsonian and locomotor responses were altered upon repeated administration of either drug over a time course as short as 1 week. A significant reduction in maximal locomotor activity and antiparkinsonian efficacy occurred as early as the second day of A-77636 treatment and affected all animals, eventually producing a complete loss of responsivity despite dose increases. This is in agreement with the literature on synthetic, postsynaptic receptor agonists that rapid development of tolerance is produced by continuous stimulation of the receptor. Continuous infusion of dopamine D_1 receptor agonists in 6-hydroxydopamine-treated mice (Winkler and Weiss, 1989) or administration of a long-acting dopamine D_1 receptor agonist to 6-hydroxydopamine-treated rats (Britton et al., 1991) also produced behavioral subsensitivity to subsequent dosing similar to our results.

Agonist-induced behavioral desensitization is not restricted to dopamine D_1 receptors, but is reportedly more rapid and complete compared to that observed for the dopamine D_2 receptor subsystem (Winkler and Weiss, 1989). Our experience supports this contention since loss of behavioral response following continuous dopamine D_1 receptor stimulation using the long-acting A-77636 exceeded in magnitude that resulting from continuous dopamine D_2 receptor stimulation in the same model (Blanchet et al., 1995). Similarly, complete loss of response was not observed following a 30- and 40-day continuous treatment in MPTP-lesioned monkeys using another dopamine D_2 reeptor agonist, (+)-4-propyl-9-hydroxynaphthoxazine, that produced a progressive decline in responsitivity to repeated dosing but global clinical scores remained better than before treatment initiation (Alexander et al., 1991). The mechanisms underlying the differences in the pharmacological responses remain poorly understood. The agonist A-77636 has a long behavioral half-life since there is no endogenous mechanism to rapidly eliminate a synthetic ligand compared to levodopa and its ability to concentrate in the brain may results in prolonged receptor occupancy that is nonphysiological (or toxic). Continuous stimulation with exogenous levodopa is reportedly less detrimental on D_1 receptor responsivity in 6-hydroxydopamine rats (Weick et al., 1990). Central dopamine D_1 receptors appear to be particularly susceptible to desensitization in vitro (Memo et al., 1982; Balmforth et al.,

1990; Barton and Sibley, 1990) and in vivo (Winkler and Weiss, 1989). In vitro, dopamine-induced desensitization of dopamine D_1 receptors is a well-documented phenomenon that occurs rapidly based on significant reduction in cAMP production following short preincubation with dopamine (Barton and Sibley, 1990; Landau et al., 1993; Jarvie et al., 1993). Both receptor downregulation and activation of a cAMP-dependent kinase are thought to contribute to the desensitization.

Our data provide another example that dopamine D_1 receptors can be desensitized independently of dopamine D_2 receptors in vivo (Winkler and Weiss, 1989). The rapid pharmacological desensitization process obtained with A-77636 was homologous to dopamine D_1 receptors as suggested by the absence of response to another dopamine D_1 receptor agonist SKF 82958. This lack of response likely reflects more than a mere rightward shift of the dose-response curve since the dose of SKF 82958 acutely administered was 20-fold higher than the minimal effective dose previously established in cynomolgous monkeys. Receptor downregulation is a more likely explanation for this lack of response. In contrast, a synergistic response to a challenge with a D_2-like dopamine receptor agonist (quinpirole) was observed in both chronic protocols with A-77636. Thus, some degree of dopamine D_1 receptor activation appears to be occurring to enhance the effects of a dopamine D_2 receptor agonist, although this level of stimulation is not sufficient to produce behavioral effects. A similar synergy has been reported in dopamine-depleted mice in which a 3-fold increase in the duration of locomotor response to a dopamine D_1 receptor agonist was produced upon co-treatment with a dopamine D_2 receptor agonist (Robertson et al., 1992). Co-administration of selective dopamine D_1 and D_2 receptor agonists to MPTP-lesioned primates also yielded additional therapeutic benefit (Gomez-Mancilla et al., 1993; Vermeulen et al., 1994) and prevented the tachyphylaxis observed following chronic treatment with bromocriptine, a dopamine D_2 receptor agonist (Rouillard et al., 1990). These data constitute evidence that behavioral responsivity can be influenced by a balance of functional activity between dopamine D_1 and D_2 receptors, and support the concept that co-activation of both subtypes is required for optimal, long-term efficacy (Walters et al., 1987).

The chronic administration of a short-acting dopamine D_1 receptor agonist (SKF 82958) produced a more favorable outcome since the maximal antiparkinsonian response obtained with each of 3 daily injections (given 4 h apart) was maintained. Nonetheless, such repeated, pulsatile stimulation brought about a shortening of the duration of response to a given injection after 1 week (Blanchet et al., 1996), which was partly responsible for the slight reduction in the total daily locomotor counts (Fig. 4). This 'wearing-off' phenomenon is reminiscent of that experienced by a majority of parkinsonian patients under chronic levodopa treatment. Obeso et al. (1992) have also observed that repeated administration of the partial dopamine D_1 receptor agonist CY 208-243 to MPTP primates during the course of a single day led to a significant reduction in behavioral response duration beyond the first bolus. A relative drop in locomotor response was also obtained in MPTP-lesioned primates after a 7-day treatment using CY 208-243 (Gomez-Mancilla et al., 1993). Similarly, a reduced response to closely spaced, repeated administration of the short-acting, mixed dopamine D_1 and D_2 receptor agonist apomorphine has been observed as early as with the second injection in both normal and dopamine-denervated rats (Castro et al., 1985) as well as in MPTP monkeys (Luquin et al., 1993). The same phenomenon is reportedly seen with apomorphine in parkinsonian patients (Grandas and Obeso, 1989) (see contradictory view by Hughes et al., 1991), and was found to be critically dependent on the time interval between doses. The fixed, 4-h dosing interval used in this experiment may have prevented a more pronounced tachyphylaxis in our monkeys although a shortening in response duration still occurred progressively following several days of treatment. In the absence of proper pharmacokinetic data, we cannot firmly conclude that the wearing-off phenomenon observed with SKF 82958 is due entirely to central pharmacodynamic alterations and not to alterations in absorption, metabolism or excretion. We can only suggest that postsynaptic receptor changes could perhaps promote 'wearing-off' complications, as proposed recently in Parkinson's disease (Bravi et al., 1994).

Our findings may be relevant to the design of therapeutic strategies in Parkinson's disease. Although substantial experimental evidence suggests that continuous levodopa replacement is more physiological and better regulates basal ganglia function (see Obeso et al., 1994, for review), studies using synthetic, direct-acting ligands raise the possibility that continuous stimulation of central dopamine receptors may not be universally beneficial for all dopamine receptor subtypes. In fact, intermittent but not continuous treatment with a selective dopamine D_1 receptor agonist was able to reverse the decreases in striatal mRNA expression of substance P and dopamine D_1 receptors resulting from chronic dopamine depletion following exposure to 6-hydroxydopamine in rats (Gerfen et al., 1990). The observations reported herein also support the idea that dopamine D_1 receptors are better regulated when not stimulated constantly. Although constant dopamine D_1 receptor occupancy is not likely to become a successful therapeutic strategy in PD, neuropsychiatric conditions characterized by overactive dopamine D_1 receptor transmission could eventually benefit from such strategic desensitization.

In conclusion, selective dopamine D_1 receptor agonists showed definite antiparkinsonian efficacy and locomotor hyperactivity when administered alone to MPTP-lesioned primates. However, a profound behavioral desensitization rapidly occurred with the longer-acting compound (A-77636), which was homologous to dopamine D_1 receptors

and refractory to significant dose escalations. A much shorter-acting drug (SKF 82958) maintained full antiparkinsonian efficacy but the response duration shortened and locomotor activation declined somewhat over 1 week. Thus, dopamine D_1 receptors appear particularly susceptible to desensitization and may require agonists with an intermediate half-life for optimal regulation and to avoid cumulative drug concentration in the brain. Potent dopamine D_1 receptor agonists with an intermediate duration of action may be good adjuncts in the treatment of Parkinson's disease and merit further attention. Further studies must be carried out to better understand dopamine receptor desensitization mechanisms.

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