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Lack of synergism between caffeine and SKF 38393 on rotational behavior in 6-hydroxydopamine-denervated rats

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Abstract

We have recently shown a synergistic effect between caffeine and the dopamine D_2 receptor agonist, bromocriptine, on contralateral rotational behavior in unilaterally 6-hydroxydopamine-denervated rats. In addition, we found that bromocriptine prevented caffeine-induced tolerance to this behavior following repeated treatment. In the present study, we investigated whether or not the dopamine D_1 receptor agonist, (±)-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SKF 38393), presented similar characteristics. Different groups of rats received simultaneous injections of either vehicle plus vehicle, caffeine (40 mg/kg) plus vehicle, SKF 38393 (0.5, 1, 2, and 4 mg/kg) plus vehicle, or caffeine plus SKF 38393 (0.5, 1, 2, and 4 mg/kg) for 5 consecutive days, and both ipsilateral and contralateral rotational behavior was measured. Results showed that, on the first day of treatment, caffeine produced significantly more rotational behavior than did a low dose of SKF 38393 (0.5 mg/kg), and significantly less turning than at higher doses (2 and 4 mg/kg). Combined treatment with caffeine and a high dose of SKF 38393 (4 mg/kg) produced significantly more rotational behavior than did caffeine plus vehicle. With repeated administration, caffeine produced sustained tolerance to its effects on rotational behavior, whereas SKF 38393 did not. In the groups treated with low doses of SKF 38393 (0.5, and 1 mg/kg) plus caffeine, tolerance was observed while in the groups that received high doses of SKF 38393 (2 and 4 mg/kg) plus caffeine, no tolerance was observed to rotational behavior. These results suggest that maximal stimulation of dopamine D_1 receptors may be needed to prevent the tolerance effects of caffeine in this animal model. This finding may have clinical relevance to the therapeutic treatment of Parkinson's disease.

Keywords: Dopamine D_1 receptor; 6-Hydroxydopamine; Turning behavior; Behavioral tolerance

1. Introduction

Methylxanthines such as caffeine, theophylline and theobromine show psychostimulant properties in both humans and animals (see Garrett and Griffiths, 1997 for a review). In animals, these properties are evidenced by their ability to increase locomotor activity (Nehlig et al., 1992), to produce reinforcing effects (Dworkin et al., 1993; Griffiths and Mumford, 1995), and to potentiate the reinforcing and locomotor stimulant properties of dopamine receptor agonists (Schenk et al., 1994; Misra et al., 1986). Several mechanisms of action have been proposed to explain the psychostimulant effects of caffeine and other methylxanthines (for a review see Garrett and Griffiths, 1997). These include phosphodiesterase inhibition (Fuxe et al., 1978; Cardinali, 1980), catecholamine release (Berkowitz et al., 1970), direct action on dopamine receptors (Ungerstedt et al., 1981; Casas et al., 1988, 1989a,b; Ferré et al., 1990; Garrett and Holtzman, 1994a, 1995), intracellular mobilization of Ca^{2+} (Daly, 1993), direct antagonism on adenosine A_1 and A_2 receptors (Daly et al., 1981; Snyder et al., 1981; Fredholm et al., 1983; Nehlig et al., 1992; Fredholm, 1995), and indirect modulation of dopamine receptors through blockade of adenosine receptors (Ferré et al., 1991; Fredholm, 1995).

There is a vast amount of data emphasising the role of the dopaminergic system in the psychostimulant properties of methylxanthines. For instance, in humans it has been

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shown that methylxanthines decrease the levels of prolactin in healthy non-pregnant women (Casas et al., 1989a), as well as the undesirable extrapyramidal side-effects of neuroleptics in the treatment of schizophrenia (Casas et al., 1989b). In animals, biochemical studies have shown that caffeine modifies dopamine release in various brain regions (Govoni et al., 1984; Morgan and Vestal, 1989; Okada et al., 1996), and paraxanthine, a major metabolite of caffeine in humans, displaces the binding of [^{3}H]SCH 23390 (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) from rat membrane slices (Ferré et al., 1990). Behavioral data from animals with unilateral nigrostriatal 6-hydroxydopamine lesions demonstrate that methylxanthines, similarly to direct dopamine receptor agonists, induce long-lasting contralateral rotational behavior (Ungerstedt et al., 1981; Herrera-Marschitz et al., 1988; Casas et al., 1989c,d; Garrett and Holtzman, 1995). Selective dopamine D_2 receptor antagonists block this behavior, while selective dopamine D_1 receptor antagonists do not (Garrett and Holtzman, 1995), or only partially block rotational behavior in denervated rats (Ferré et al., 1992). These findings argue for a specific role for dopamine D_2 receptors in caffeine-induced rotational behavior.

Caffeine can also produce its acute effects through adenosine–dopamine receptor interactions. Adenosine A_1 and A_{2A} receptors are co-localized in the striatum with dopamine D_1 and D_2 receptors, respectively (Schiffmann et al., 1991; Fink et al., 1992; Ferré et al., 1996), where they interact in an opposing manner (Ferré et al., 1997). Indeed, functional postsynaptic interactions on striatal efferent neurons have been evidenced for both adenosine A_2/dopamine D_2 receptors (Ferré et al., 1991), and adenosine A_1/dopamine D_1 receptors (Abbracchio et al., 1987; Ferré et al., 1994). Hence, caffeine, by blocking adenosine receptors in the striatum, is able to increase dopaminergic function. All these data suggest that methylxanthines may be effective in the treatment of Parkinson's disease. However, one of the limitations for their introduction in the clinic is the rapid development of tolerance to their psychostimulant effects (Evans and Griffiths, 1992).

In rodents, repeated administration of caffeine has been shown to produce tolerance to its locomotor activating effects (Finn and Holtzman, 1987), and to the development of contralateral rotational behavior in unilateral 6-hydroxydopamine-denervated rats (Watanabe et al., 1982). The exact mechanisms through which tolerance to caffeine is produced, however, have yet to be established. Since the acute psychostimulant effects of caffeine may be mediated through adenosine/dopamine receptor interactions, it may be possible that the tolerance effects of caffeine on contralateral rotational behavior in denervated rats may also involve adaptive changes in these receptors during repeated caffeine administration. Thus, it has been shown that adenosine receptor supersensitivity may underlie caffeine tolerance effects (Fredholm, 1982; Hawkins et al., 1988; Kaplan et al., 1993), although other evidence argues against this hypothesis (Holtzman et al., 1991). Interestingly, changes in dopamine receptors following chronic treatment with caffeine have not yet been directly established, while behavioral and biochemical data point to the involvement of the γ-aminobutyric acid (GABA) neurotransmitter system in caffeine tolerance (Mukhopadhyay and Poddar, 1998), as well as of the cholinergic system (Casas et al., 1999a).

We have recently provided evidence showing that tolerance to caffeine-induced contralateral rotational behavior in denervated rats can be prevented by continuous co-administration of caffeine with the dopamine D_2 receptor agonist, bromocriptine (Casas et al., 1999b). This finding supports the involvement of dopamine D_2 receptors in the development of tolerance to caffeine, and suggests that caffeine may be very effective in the treatment of Parkinson's disease if it is co-administered with a dopamine D_2 receptor agonist. The aim of the present study was to further investigate the mechanisms by which tolerance to caffeine occurs after repeated treatment. For that purpose, we studied whether or not the dopamine D_1 receptor agonist, (±)-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SKF 38393), would prevent the tolerance to caffeine-induced contralateral rotational behavior in 6-hydroxydopamine-denervated rats when administered subchronically.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats were used in all groups. Initially, the rats (150 ± 10 g) were housed eight to a cage (59 × 38 × 20 cm), with free access to rat chow and water. They were kept in a temperature-controlled environment (21 ± 1°C) on a 12-h light/dark cycle (lights on at 8 a.m.) when they were not in experimental sessions. This experiment was carried out in compliance with the European Communities Council Directive of November 24, 1986 (86/609/EEC) for care and use of laboratory animals.

2.2. Surgical procedure

Rats weighing 150 ± 10 g were anaesthetized with a sodium pentobarbital solution (40 mg/kg i.p.) and placed in a David Kopf stereotaxic frame with the incisor bar set at 2.4 mm (König and Klippel, 1963). The animals were injected unilaterally into the left hemisphere with 8 μg of 6-hydroxydopamine HCl (calculated as free base, Sigma, USA) in 4 μl of physiological saline with 0.2% ascorbic acid using a Hamilton syringe with a conically shaped needle with maximum diameter 0.4 mm. The rate of

infusion was 1 μl/min. The infusions were aimed at the medial forebrain bundle (A: −4.4, L: −1.2, V: −7.8 mm, calculated from bregma and dura). This lesion has been shown to produce extensive unilateral denervation of the dopaminergic nigrostriatal system (Ungerstedt, 1971; Herrera-Marschitz and Ungerstedt, 1984). After surgery, rats were housed four to a cage for the remainder of the experiment.

2.3. Animal selection

In order to select the successfully denervated animals, thirty days post-surgery all rats were challenged with a low dose of apomorphine (0.05 mg/kg s.c.) four times at a 1-week interval between treatments (Casas et al., 1999c). Rats showing fewer than 500 half-turns (180°) in 1 h during the last two tests with apomorphine were not included in the study. Several authors have demonstrated that at least 90% dopamine depletion is needed for this dose of apomorphine to induce contralateral rotational behavior (Hefti et al., 1980; Ungerstedt and Herrera-Marschitz, 1981; Hudson et al., 1993).

2.4. Drugs

SKF 38393 HCl (RBI, Natick, USA), apomorphine HCl, and caffeine anhydrous (Sigma, Spain) were diluted in physiological saline. All doses were calculated as free base and injected subcutaneously (s.c.) in a volume of 1 ml/kg of body weight.

2.5. General procedure

Seventy-nine rats were randomly divided into 10 groups and received the following substances. Group 1: SKF 38393 (0.5 mg/kg) plus vehicle ($n = 7$); Group 2: SKF 38393 (0.5 mg/kg) plus caffeine (40 mg/kg) ($n = 9$); Group 3: SKF 38393 (1 mg/kg) plus vehicle ($n = 8$); Group 4: SKF 38393 (1 mg/kg) plus caffeine ($n = 6$); Group 5: SKF 38393 (2 mg/kg) plus vehicle ($n = 8$); Group 6: SKF 38393 (2 mg/kg) plus caffeine ($n = 8$); Group 7: SKF 38393 (4 mg/kg) plus vehicle ($n = 7$); Group 8: SKF 38393 (4 mg/kg) plus caffeine ($n = 8$); Group 9: caffeine plus vehicle ($n = 10$); Group 10: vehicle plus vehicle ($n = 8$). Each day, the animals were placed individually into plastic hemispheric bowls (40 cm in diameter), attached to a harness and connected to photoelectric detectors. Following a 20-min habituation period, the rats were given simultaneous injections of either SKF 38393 or vehicle plus caffeine or vehicle, and rotational behavior was measured. Both contralateral and ipsilateral half-turns (180°) were recorded for 12 h using a computerized system (Panlab, Spain). Treatments were given once daily for five consecutive days. Twelve-hour sessions were carried out in order to ensure that the entire period of caffeine action was measured.

2.6. Data analysis

Statistical comparisons were made using the SPSS/PC + computer program (SPSS, USA). Significance of differences between groups for contralateral and ipsilateral rotational behavior for the 5 days of treatment was evaluated using the multivariate analyses of variance (MANOVA). Post-hoc comparisons following significant interactions were made using the Contrast options of MANOVA in all cases.

3. Results

3.1. Contralateral rotational behavior

Fig. 1 shows the contralateral rotational behavior following administration of caffeine (40 mg/kg) plus vehicle, different doses of SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus vehicle, caffeine plus different doses of SKF 38393, or vehicle plus vehicle. Overall statistical analysis for the five days of treatment revealed a significant main effect of dose of SKF 38393: DOSE $F(4,69) = 65.39$, $P < 0.001$, a significant main effect of days of treatment: DAYS $F(4,276) = 28.84$, $P < 0.001$, no significant effect of caffeine treatment, and a significant interaction between these three factors: DOSE × CAFFEINE × DAYS $F(16,276) = 2.63$, $P < 0.002$.

Post-hoc analysis for each day of treatment showed that, on the first day, caffeine plus vehicle produced significantly more contralateral rotational behavior than did vehicle plus vehicle ($P < 0.003$). SKF 38393 produced contralateral rotational behavior in a dose-dependent manner where high doses (1, 2, 4 mg/kg) induced significantly more turning than did vehicle–vehicle ($P < 0.003$). As compared to caffeine plus vehicle, SKF 38393 plus vehicle produced significantly more rotational behavior at the dose of 2 and 4 mg/kg ($P < 0.001$), and less rotational behavior at the dose of 0.5 mg/kg ($P < 0.001$). Combination treatment with caffeine plus SKF 38393 produced significantly more rotational behavior than did caffeine plus vehicle only at the dose of 4 mg/kg of SKF 38393 ($P < 0.001$), but no significant differences were observed with respect to SKF 38393 plus vehicle, revealing the lack of synergism between these two substances at the doses tested under acute conditions.

On the second day of treatment, the group treated with caffeine plus vehicle produced significantly less rotational behavior with respect to the first day of treatment ($P < 0.009$), revealing the development of behavioral tolerance. SKF 38393, on the other hand, produced a transitory

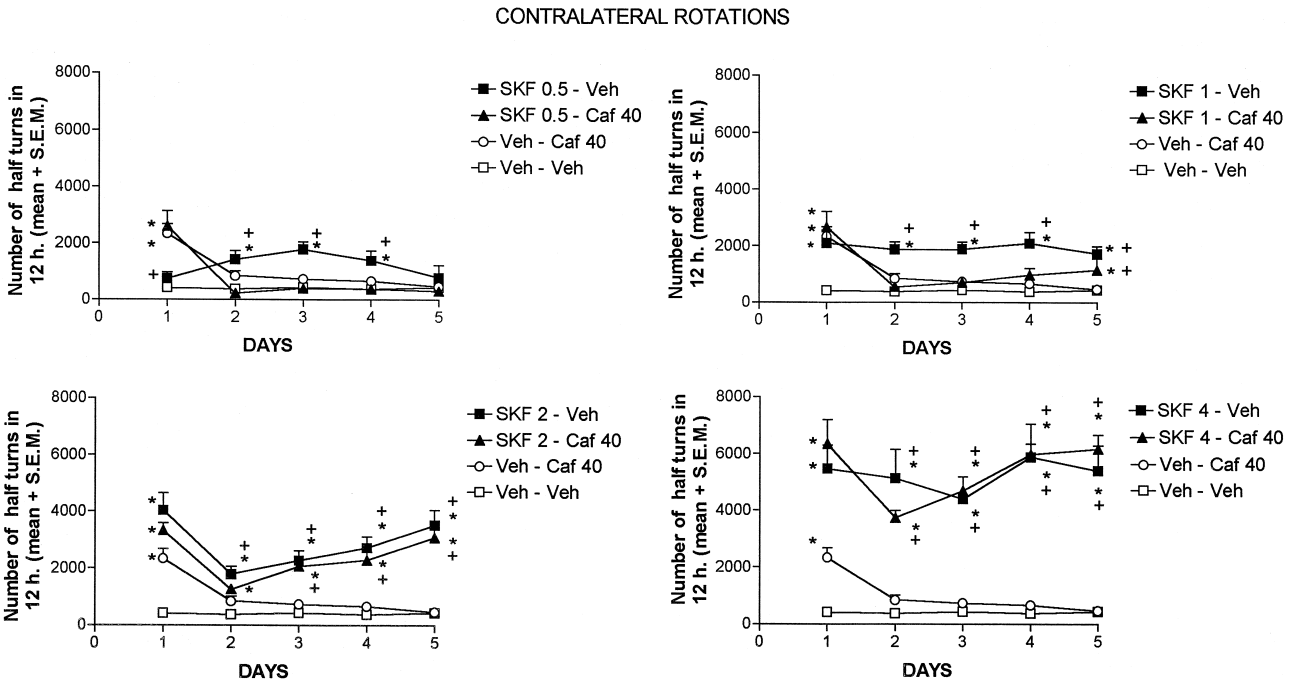

Fig. 1. Effects of repeated treatment with SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus vehicle, caffeine (40 mg/kg) plus vehicle or SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus caffeine (40 mg/kg) on contralateral rotational behavior in unilateral 6-hydroxydopamine-denervated rats. The asterisks (*) denote significant differences ($P < 0.05$) from the vehicle plus vehicle-treated controls, and the plus (+) signs denote significant differences ($P < 0.05$) from the vehicle plus caffeine-treated group.

decrease in rotational behavior as compared to that on the first day of treatment, but only at the dose of 2 mg/kg ($P < 0.007$). However, this level of rotational behavior was still superior to that observed with vehicle–vehicle ($P < 0.006$). SKF 38393 plus vehicle produced significantly more turning behavior than did caffeine plus vehicle

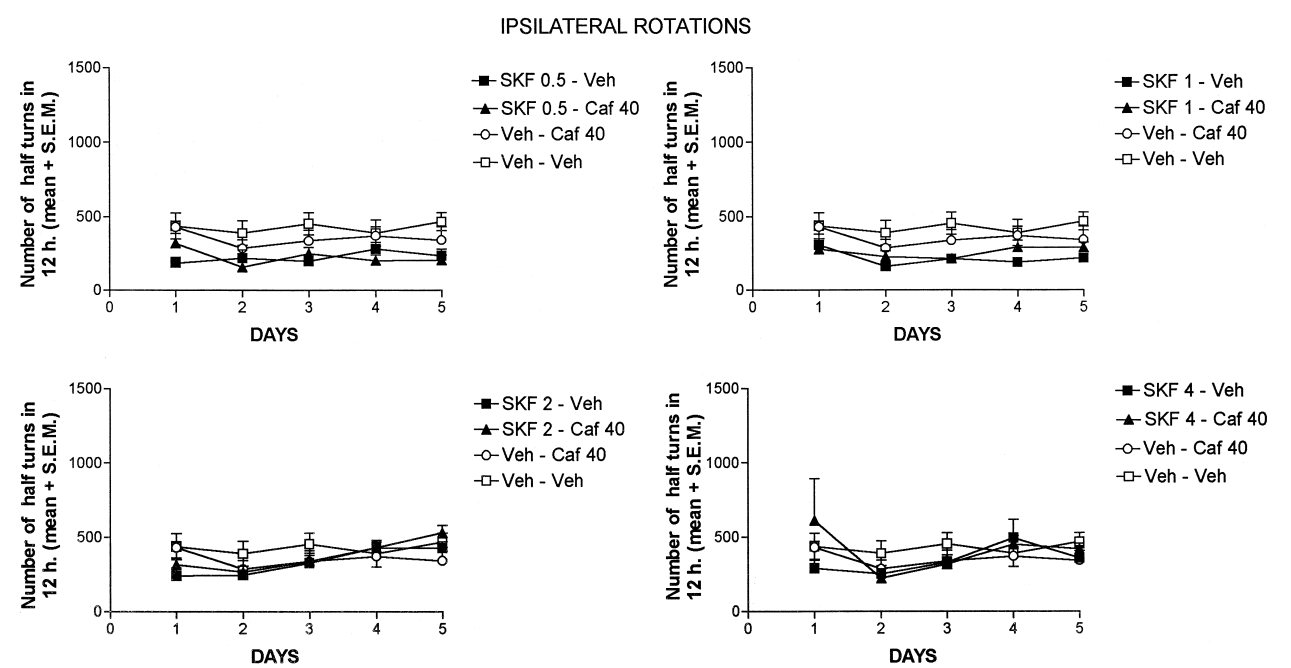

Fig. 2. Effects of repeated treatment with SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus vehicle, caffeine (40 mg/kg) plus vehicle or SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus caffeine (40 mg/kg) on ipsilateral rotational behavior in unilateral 6-hydroxydopamine-denervated rats.

at all the doses tested ($P < 0.05$). Combined treatment with caffeine and SKF 38393 produced significantly more rotational behavior than did caffeine plus vehicle only at the dose of 4 mg/kg ($P < 0.001$), and significantly less rotational behavior than SKF 38393 plus vehicle at the doses of 0.5, 1, and 4 mg/kg ($P < 0.05$).

On days three to five, caffeine still produced tolerance to its effects on rotational behavior. Significantly more rotational behavior was induced by SKF 38393 plus vehicle than by vehicle–vehicle ($P < 0.008$), or by caffeine plus vehicle ($P < 0.02$) at all the doses tested. Lower doses of SKF 38393 (0.5 and 1 mg/kg) in combination with caffeine produced less rotational behavior than did SKF 38393 (0.5 and 1 mg/kg) plus vehicle, whereas higher doses of SKF 38393 (2 and 4 mg/kg) produced similar levels of turning behavior relative to SKF 38393 (2 and 4 mg/kg) plus vehicle, and significantly more turning than did caffeine plus vehicle ($P < 0.002$).

3.2. Ipsilateral rotational behavior

Fig. 2 shows the ipsilateral rotational behavior following administration of caffeine (40 mg/kg) plus vehicle, different doses of SKF 38393 (0.5, 1, 2 and 4 mg/kg) plus vehicle, caffeine plus different doses of SKF 38393, and vehicle plus vehicle. A very small amount of ipsilateral rotational behavior was observed in the different groups of rats. Overall statistical analysis for the 5 days of treatment revealed a significant main effect of dose of SKF 38393: DOSE $F(4,69) = 6.05$, $P < 0.001$. Post-hoc analysis revealed that low doses of SKF 38393 (0.5 and 1 mg/kg) produced less turning behavior than did higher doses of SKF 38393 (2 and 4 mg/kg) ($P < 0.04$). No significant main effects for caffeine, days of treatment, nor significant interactions between factors were found.

4. Discussion

The present results are consistent with previous data (Herrera-Marschitz et al., 1988: Casas et al., 1989c,d; Garrett and Holtzman, 1995) showing that a single administration of caffeine produces more contralateral than ipsilateral rotational behavior in 6-hydroxydopamine denervated rats. Similarly, in the present study we confirmed previous observations that the dopamine D_1 receptor agonist, SKF 38393, produces dose-dependent contralateral rotational behavior (Paul et al., 1992; Jiang et al., 1993; Morelli et al., 1994), and very little ipsilateral turning.

The results obtained after acute combined treatment with SKF 38393 and caffeine indicate that these two substances show some interactive effects since caffeine potentiates the effects of low doses of SKF 38393, and high doses of SKF 38393 potentiate the effects of caffeine. However, no clear synergistic action was observed since caffeine did not potentiate the effects of high doses of SKF 38393. This lack of synergism was surprising considering the evidence showing that selective adenosine A_1 and A_{2A} antagonists potentiate the rotational behavior produced by dopamine D_1 receptor agonists in denervated rats (Pinna et al., 1996; Popoli et al., 1996). Thus, our results are in line with previous conclusions that caffeine-induced rotational behavior in denervated rats may not be mediated only by blockade of adenosine receptors in the striatum (Garrett and Holtzman, 1995). Furthermore, they suggest that, under certain conditions, caffeine-induced turning behavior may be mediated by other mechanisms of action not related to postsynaptic adenosine—dopamine receptor interactions. In this regard, there are biochemical data confirming this possibility for adenosine A_2/dopamine D_2 interactions by showing a lack of synergism between caffeine and dopamine D_2 receptor agonists (Svenningsson et al., 1995; Svenningsson and Fredholm, 1997).

When caffeine was repeatedly co-administered with SKF 38393, it appeared to inhibit the rotational behavior induced by low doses of (±)-SKF 38393 (0.5 and 1 mg/kg). These results were confirmed in a separate experiment showing that caffeine also inhibited the rotational behavior produced by a low dose (0.4 mg/kg) of the active enantiomer of (+) SKF 38393 (unpublished observations). Taken together, these results suggest strongly that the caffeine-induced inhibition of the effect of low doses of SKF 38393 on contralateral rotational behavior in this animal model is due to a specific interaction between these two substances.

One possible explanation for this effect is that overstimulation of dopamine D_1 receptors following combined treatment with caffeine and SKF 38393 produces rapid desensitization of these receptors. In line with this idea are the data showing that repeated treatment with dopamine D_1 agonists in this animal model results in receptor desensitization of D_1 responses, which correspond to changes in dopamine D_1 receptor levels in the striatum and substantia nigra pars reticulata (Engber et al., 1993). However, our results show that this receptor desensitization can be counteracted with repeated co-administration of high doses of SKF 38393 and caffeine.

The results showing that only high doses of SKF 38393 prevent the observed tolerance to the effects of caffeine on rotational behavior suggest that maximal stimulation of dopamine D_1 receptors may be needed for this effect to occur in this animal model. The results also imply that dopamine D_1 receptors may play a role in the behavioral tolerance to caffeine-induced effects following repeated treatment. In this respect, it has been shown that tolerance to the locomotor stimulant effects of caffeine is mediated by both dopamine D_1 and D_2 receptor sub-types (Garrett and Holtzman, 1994b). In our study, however, we did not find a clear dose–response effect of SKF 38393 with respect to the prevention of tolerance. In addition, since both caffeine and SKF 38393 were administered systemi-

cally, we cannot rule out completely the possibility that metabolic interactions may have contributed to the effects observed in this study. Therefore, further studies must be undertaken in order to confirm the participation of the dopamine D_1 receptor sub-type in caffeine-induced tolerance to rotational behavior in denervated rats.

These results, together with our previous data showing that the selective dopamine D_2 receptor agonist, bromocriptine, prevents tolerance to caffeine-induced rotational behavior (Casas et al., 1999b), are relevant to the introduction of methylxanthines in the treatment of Parkinson's disease since they suggest that one of the major limitations for their clinical use namely, tolerance to their psychostimulant effects, can be counteracted. In general, our results suggest that this may be achieved preferentially with dopamine D_2 rather than D_1 receptor agonists. Finally, our data agree with one clinical study demonstrating the relative efficacy of theophylline as an adjuvant of levodopa in parkinsonian patients (Mally and Stone, 1994).

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References

Abbracchio, M.P., Colombo, F., Di Luca, M., Zaratin, O., Cattabeni, F., 1987. Adenosine modulates the dopaminergic function in the nigrostriatal system by interacting with striatal dopamine dependent adenylate cyclase. Pharmacol. Res. Commun. 19, 275–286.

Berkowitz, B.A., Tarver, J.H., Spector, S., 1970. Release of norepinephrine in the central nervous system by theophylline and caffeine. Eur. J. Pharmacol. 10, 64–71.

Cardinali, D.P., 1980. Methylxanthines: possible mechanisms of action in the brain. Trends Pharmacol. Sci. 1, 405–407.

Casas, M., Ferré, S., Guix, T., Jané, F., 1988. Theophylline reverses haloperidol-induced catalepsy in the rat. Possible relevance to the pharmacological treatment of psychosis. Biol. Psychiatry 24, 642–648.

Casas, M., Ferré, S., Rodriguez, J., Jané, F., 1989a. Methylxanthines cause a decrease of prolactin plasma levels in healthy non-pregnant women. Hum. Psychopharmacol. 4, 33–39.

Casas, M., Torrens, M., Duro, P., Pinet, C., Alvarez, E., Udina, C., 1989b. Utilization des méthylxanthines, caféine et théophylline dans le traitement des troubles extrapyramidaux secondaires aux traitements par les neuroleptiques. L'Encéphale XV, 177–180.

Casas, M., Ferré, S., Cadafalch, J., Grau, J.M., Jané, F., 1989c. Rotational behavior induced by theophylline in 6-OHDA nigrostriatal denervated rats is dependent on the supersensitivity of striatal dopamine receptors. Pharmacol. Biochem. Behav. 29, 609–613.

Casas, M., Ferré, S., Cobos, A., Grau, J.M., Jané, F., 1989d. Relationship between rotational behavior induced by apomorphine and caffeine in rats with unilateral lesion of the nigrostriatal pathway. Neuropharmacology 28, 407–409.

Casas, M., Prat, G., Robledo, P., Barbanoj, M., Kulisevsky, J., Jané, F., 1999a. Scopolamine prevents tolerance to the effects of caffeine on rotational behavior in 6-hydroxydopamine-denervated rats. Eur. J. Pharmacol. 366, 1–11.

Casas, M., Prat, G., Robledo, P., Barbanoj, M., Kulisevsky, J., Jané, F., 1999b. Repeated co-administration of caffeine and bromocriptine prevents tolerance to the effects of caffeine in the turning behavior animal model. Eur. Neuropsychopharmacol. 9, 515–521.

Casas, M., Prat, G., Robledo, P., Jané, F., 1999c. Rotational behavior in dopamine nigrostriatal denervated rats: effects of a wide range of time intervals between apomorphine administrations. Pharmacol. Biochem. Behav. 62, 481–485.

Daly, J.W., 1993. Mechanisms of action of caffeine. In: Garattini, S. (Ed.), Caffeine, Coffee and Health. New York, Raven Press, pp. 97–150.

Daly, J.W., Burns, R.F., Snyder, S.H., 1981. Adenosine receptors in central nervous system: relationship to the central actions of methylxanthines. Life Sci. 28, 2083–2097.

Dworkin, S.I., Vrana, S.L., Broadbent, J., Pobinson, J.H., 1993. Comparing the reinforcing effect of nicotine, caffeine, methylphenidate and caffeine. Med. Chem. Res. 2, 593–602.

Engber, T.M., Marin, C., Susel, Z., Chase, T.N., 1993. Differential effects of chronic dopamine D_1 and D_2 receptor agonists on rotational behavior and dopamine receptor binding. Eur. J. Pharmacol. 236, 385–393.

Evans, S.M., Griffiths, R.R., 1992. Caffeine tolerance and choice in humans. Psychopharmacology 108, 51–59.

Ferré, S., Guix, T., Sallés, J., Badia, A., Parra, P., Jané, F., Herrera-Marschitz, M., Ungerstedt, U., Casas, M., 1990. Paraxanthine displaces the binding of [^{3}H]SCH 23390 from rat striatal membranes. Eur. J. Pharmacol. 179, 295–299.

Ferré, S., Herrera-Marschitz, M., Grabowska-Andén, M., Casas, M., Ungerstedt, U., Andén, N.-E., 1991. Postsynaptic dopamine/adenosine interactions: II. Postsynaptic dopamine agonism and adenosine antagonism of methylxanthines in short-term reserpinized mice. Eur. J. Pharmacol. 192, 31–37.

Ferré, S., Fuxe, K., von Euler, G., Johansson, B., Fredholm, B.B., 1992. Adenosine–dopamine interactions in the brain. Neuroscience 51, 501–512.

Ferré, S., Popoli, P., Giménez-Llort, L., Finnman, U.-B., Martínez, E., Scotti de Carolis, A., Fuxe, K., 1994. Postsynaptic antagonistic interaction between A1 and D1 receptors. NeuroReport 6, 73–76.

Ferré, S., O'Connor, W.T., Svenningsson, P., Björklund, L., Lindberg, J., Tinner, B., Strömberg, Y., Goldstein, M., Ögren, S.O., Ungerstedt, U., Fredholm, B.B., Fuxe, K., 1996. Dopamine D1 receptor-mediated facilitation of GABAergic neurotransmission in the rat striato-entopeduncular pathway and its modulation by adenosine A1 receptor-mediated mechanisms. Eur. J. Neurosci. 8, 1545–1553.

Ferré, S., Fredholm, B.B., Morelli, M., Popoli, P., Fuxe, K., 1997. Adenosine–dopamine receptor–receptor interactions as an integrative mechanism in the basal ganglia. TINS 20, 482–487.

Fink, J.S., Weaver, D.R., Rivkees, S.A., Peterfreund, R.A., Pollack, A., Addler, E.M., Reppert, S.M., 1992. Molecular cloning of the rat A2 adenosine receptor: selective co-expression with D_2 dopamine receptors in rat striatum. Mol. Brain Res. 14, 186–195.

Finn, I.B., Holtzman, S.G., 1987. Pharmacological specificity of tolerance to caffeine-induced stimulation of locomotor activity. Psychopharmacology 93, 428–434.

Fredholm, B.B., 1982. Adenosine actions and adenosine receptors after 1 week treatment with caffeine. Acta Physiol. Scand. 115, 283–286.

Fredholm, B.B., 1995. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol. Toxicol. 76, 93–101.

Fredholm, B.B., Herrera-Marschitz, M., Jonzon, B., Lindström, K., Ungerstedt, U., 1983. On the mechanisms by which methylxanthines enhance apomorphine-induced rotation behaviour in the rat. Pharmacol. Biochem. Behav. 19, 535–541.

Fuxe, K., Fredholm, B.B., Ögren, S.O., Agnati, L.F., Hökfelt, T., Gustafsson, J.A., 1978. Pharmacological and biochemical evidence for the dopamine agonistic effect of bromocriptine. In: Hökfelt, B.,

Nillius, S.J. (Eds.), The Dopamine Agonist Bromocriptine. Sandoz, Stockholm, pp. 27–56.
Garrett, B.E., Griffiths, R.R., 1997. The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol. Biochem. Behav. 57, 533–541.
Garrett, B.E., Holtzman, S.G., 1994a. D1 and D2 dopamine receptor antagonists block caffeine-induced stimulation of locomotor activity in rats. Pharmacol. Biochem. Behav. 47, 89–94.
Garrett, B.E., Holtzman, S.G., 1994b. Caffeine cross-tolerance to selective dopamine D1 and D2 receptor agonists but not to their synergistic interaction. Eur. J. Pharmacol. 262, 65–75.
Garrett, B.E., Holtzman, S.G., 1995. Does adenosine receptor blockade mediate caffeine-induced rotational behavior? J. Pharmacol. Exp. Ther. 274, 207–214.
Griffiths, R.R., Mumford, G.K., 1995. Caffeine — a drug of abuse? In: Bloom, F.E., Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. Raven Press, New York, pp. 1699–1713.
Govoni, S., Petkov, V.V., Montefusco, C., Missale, C., Battatini, F., Spano, P.F., Trabucchi, M., 1984. Differential effects of caffeine on dihydroxyphenylacetic acid concentration in various rat brain dopaminergic structures. J. Pharm. Pharmacol. 36, 458–460.
Hawkins, M., Dugish, M., Porter, N., Urbanic, M., Radulovacki, M., 1988. Effects of chronic administration of caffeine on adenosine A1 and A2 receptors in rat brain. Brain Res. Bull. 21, 479–482.
Hefti, F., Melamed, E., Wurtman, R.J., 1980. Partial lesions of the dopaminergic nigrostriatal system in rat brain: biochemical characterization. Brain Res. 195, 123–137.
Herrera-Marschitz, M., Ungerstedt, U., 1984. Evidence that striatal efferents relate to different dopamine receptors. Brain Res. 323, 269–278.
Herrera-Marschitz, M., Casas, M., Ungerstedt, U., 1988. Caffeine produces contralateral rotation in rats with unilateral dopamine denervation: comparisons with apomorphine-induced responses. Psychopharmacology 94, 38–45.
Holtzman, S.G., Mante, S., Minneman, K.P., 1991. Role of adenosine receptors in caffeine tolerance. J. Pharmacol. Exp. Ther. 256, 62–68.
Hudson, J.L., van Horne, C.G., Strömberg, Y., Brock, S., Clyton, J., Masserano, J., Hofferm, B.J., Gerhardt, G.A., 1993. Correlation of apomorphine- and amphetamine-induced turning with nigrostriatal dopamine content in unilateral 6-hydroxydopamine lesioned rats. Brain Res. 626, 167–174.
Jiang, H., Jackson-Lewis, V., Muthane, U., Dollison, A., Ferreira, M., Espinosa, A., Parsons, B., Przedborski, S., 1993. Adenosine receptor antagonists potentiate dopamine receptor agonist-induced rotational behavior in 6-hydroxydopamine-lesioned rats. Brain Res. 613, 347–351.
Kaplan, G.B., Greenblatt, D.J., Kent, M.A., Cotreau-Bibbo, M.M., 1993. Caffeine treatment and withdrawal in mice: relationships between dosage, concentrations, locomotor activity and A1 adenosine receptor binding. J. Pharmacol. Exp. Ther. 266, 1563–1572.
König, J.F.R., Klippel, R.A., 1963. The Rat Brain: A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem. Williams and Wilkins, Baltimore.
Mally, J., Stone, T.W., 1994. The effect of theophylline on parkinsonian symptoms. J. Pharm. Pharmacol. 46, 515–517.
Misra, A., Vadlamani, N., Pontani, R.B., 1986. Effect of caffeine on cocaine locomotor stimulant activity in rats. Pharmacol. Biochem. Behav. 24, 761–764.
Morelli, M., Fenu, S., Pinna, A., Di Chiara, G., 1994. Adenosine A2 receptors interact negatively with dopamine D1 and D2 receptors in unilaterally 6-hydroxydopamine-lesioned rats. Eur. J. Pharmacol. 251, 21–25.
Morgan, M.E., Vestal, R.E., 1989. Methylxanthines effects on caudate dopamine release as measured by in vivo electrochemistry. Life Sci. 45, 2025–2039.
Mukhopadhyay, S., Poddar, M.K., 1998. Is GABA involved in the development of caffeine tolerance. Neurochem. Res. 23, 63–68.
Nehlig, A., Daval, J.-L., Debry, G., 1992. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res. Rev. 17, 139–170.
Okada, M., Mizuno, K., Kaneko, S., 1996. Adenosine A1 and A2 receptors modulate extracellular dopamine levels in rat striatum. Neurosci. Lett. 212, 53–56.
Paul, M.L., Graybiel, A.M., David, J.-C., Robertson, H.A., 1992. D1-like and D2-like dopamine receptors synergistically activate rotation and c-*fos* expression in the dopamine depleted striatum in a rat model of Parkinson's disease. J. Neuroscience 12, 3729–3742.
Pinna, A., Di Chiara, G., Wardas, J., Morelli, M., 1996. Blockade of A2a adenosine receptors positively modulates turning behavior and c-Fos expression induced by D1 agonists in dopamine-denervated rats. Eur. J. Neurosci. 8, 1176–1181.
Popoli, P., Giménez-Llort, L., Pezzola, A., Reggio, R., Martínez, E., Fuxe, K., Ferré, S., 1996. Adenosine A1 receptor blockade selectively potentiates the motor effects induced by dopamine D1 receptor stimulation in rodents. Neurosci. Lett. 218, 209–213.
Schenk, S., Valadez, A., Horger, B.A., Snow, S., Wellman, P.J., 1994. Interactions between caffeine and cocaine in tests of self-administration. Behav. Pharmacol. 5, 153–158.
Schiffmann, S.N., Jacobs, O.P., Vanderhaeghen, J.-J., 1991. Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not substance P neurons: and in situ hybridization histochemistry study. J. Neurochem. 57, 1062–1067.
Snyder, S.H., Katims, J.J., Annau, A., Bruns, R.F., Daly, J.W., 1981. Adenosine receptors and the behavioral actions of methylxanthines. Proc. Natl. Acad. Sci. U. S. A. 78, 3260–3265.
Svenningsson, P., Fredholm, B.B., 1997. Caffeine mimics the effect of a dopamine D2/3 receptor agonist on the expression of immediate early genes in globus pallidus. Neuropharmacology 36, 1309–1317.
Svenningsson, P., Nomikos, G.G., Fredholm, B.B., 1995. Biphasic changes in locomotor behavior and in expression of mRNA for NGFI-A and NGFI-B in rat striatum following acute caffeine administration. J. Neurosci. 15, 7612–7624.
Ungerstedt, U., 1971. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. Acta Physiol. Scand. 367, 69–93.
Ungerstedt, U., Herrera-Marschitz, M., 1981. Behavioural pharmacology of dopamine receptors mechanisms. In: Stjärne, L., Hedqvist, P., Lagerkrantz, H., Wenmalm, A. (Eds.), Chemical Neurotransmission. Academic Press, New York, pp. 481–494.
Ungerstedt, U., Herrera-Marschitz, M., Casas, M., 1981. Are apomorphine, bromocriptine, and the methylxanthines agonists at the same dopamine receptor? In: Gessa, G.L., Corsini, G.U. (Eds.), Apomorphine and Other Dopaminomimetics. Raven Press, New York, p. 85.
Watanabe, H., Ikeda, M., Watanabe, K., 1982. Development of tolerance to dopaminergic stimulating effect of theophylline in mice with unilateral striatal 6-hydroxydopamine lesions. Eur. J. Pharmacol. 79, 125–128.