ELSEVIER

European Journal of Pharmacology 322 (1997) 137–145

ejp

Tremulous jaw movements induced by the acetylcholinesterase inhibitor tacrine: effects of antiparkinsonian drugs

Michael S. Cousins, Debbie L. Carriero, John D. Salamone *

Department of Psychology, University of Connecticut, Storrs, CT 06269-1020 USA

Received 23 December 1996; accepted 24 December 1996

Abstract

Several experiments were conducted to study the effects of established or potential antiparkinsonian drugs on the tremulous jaw movements induced by the anticholinesterase tacrine (9-amino-1,2,3,4-tetrahydroaminoacridine hydrochloride). In the first group of four experiments, separate groups of animals that received 2.5 or 5.0 mg/kg tacrine showed a dose-dependent decrease in tremulous jaw movements following co-administration of the non-selective dopamine receptor agonist apomorphine, the full dopamine D_2 receptor agonist bromocriptine, and the full dopamine D_1 receptor agonist APB (*R*(+)-6-bromo-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine). Co-administration of the partial dopamine D_1 receptor agonist SKF 38393 (*R*(+)-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-benzazepine; 7.5–30.0 mg/kg) did not reduce tremulous jaw movements produced by 2.5 or 5.0 mg/kg tacrine. In animals treated with 2.5 mg/kg tacrine, co-administration of SKF 38393 resulted in a dose-related trend towards a potentiation of tremulous jaw movements. In the second group of experiments, all rats received 2.5 mg/kg tacrine. The dopamine precursor L-DOPA (L-3,4-dihydroxyphenylalanine), the dopamine and norepinephrine releasing agent amantadine, and the muscarinic receptor antagonist benztropine all reduced tremulous jaw movements induced by 2.5 mg/kg tacrine. Across all experiments, it was noted that apomorphine, bromocriptine and benztropine were more potent than amantadine and L-DOPA. These results are broadly consistent with the therapeutic doses of these agents noted in the clinical literature. The results of these experiments indicate that tremulous jaw movements in rats may be a useful model for evaluating potential antiparkinsonian agents.

Keywords: Tacrine; Cognex; Acetylcholine; Vacuous chew; Purposeless; Tremor; Parkinson's disease; Alzheimer's disease

1. Introduction

Considerable evidence indicates that cholinergic systems are involved in idiopathic and drug-induced parkinsonism (Duvoisin, 1967; Marsden et al., 1975; Acquilonius, 1980). Muscarinic receptor antagonists frequently are used as treatments for neuroleptic-induced parkinsonism (Marsden et al., 1975; McEvoy, 1983). Several studies have shown that cholinomimetic drugs can induce or exacerbate parkinsonian symptoms in humans. Muscarinic receptor agonists have been shown to enhance parkinsonism (Noring et al., 1984). The acetylcholinesterase inhibitor physostigmine was shown to worsen symptoms of idiopathic Parkinson's disease (Duvoisin, 1967). Physostigmine also has been shown to exacerbate 'rabbit syndrome', which is a neuroleptic-induced perioral tremor (Weiss et al., 1980). The anticholinesterase tacrine (Cognex), which is used to treat Alzheimer's disease, can lead to the production of parkinsonian side-effects such as bradykinesia, rigidity and tremor (Ott and Lannon, 1992; Keltner, 1994). Ott and Lannon (1992) demonstrated that tacrine-induced parkinsonism could be ameliorated by L-3,4-dihydroxyphenylalanine (L-DOPA).

One of the motor effects of cholinomimetics in rats is the induction of tremulous jaw movements (also known as 'vacuous jaw movements' or 'vacuous', or 'purposeless' chewing). Tremulous jaw movements are rapid vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular object; these movements are induced by centrally acting muscarinic receptor agonists and anticholinesterases (Rupniak et al., 1983; Salamone et al., 1986; Stewart et al., 1988; Levin et al., 1989; Salamone et al., 1990; Collins et al., 1991, 1993; Baskin et al., 1994; Carriero et al., 1996; Mayorga et al., 1996). More recently, the anticholinesterase tacrine has been shown to induce a dose-related increase in tremulous jaw move-

* Corresponding author. Tel.: (1-860) 486-4302; Fax: (1-860) 486-2760.

0014-2999/97/$17.00
PII S0014-2999(97)00008-3

ments in the range of 2.5–10.0 mg/kg (Mayorga et al., 1996). These movements were reduced by systemic or ventrolateral striatal microinjection of scopolamine (Mayorga et al., 1996). Slow motion videotape analysis showed that the local frequency of tacrine-induced jaw movements peaked in the range of 3–6.6 Hz (Mayorga et al., 1996), which is consistent with the tremor frequency that is observed in parkinsonian patients (Adams and Victor, 1981). Thus, it has been suggested that tacrine-induced tremulous jaw movements share some characteristics with human parkinsonian tremor (Carriero et al., 1996; Mayorga et al., 1996).

One of the ways in which tremulous jaw movements resemble human parkinsonism is that, in both cases, there is an interaction between dopamine and acetylcholine. Several lines of evidence indicate that dopamine and acetylcholine systems interact to affect motor control (Acquilonius, 1980; Duvoisin, 1967; Bartholini, 1987). As well as being produced by cholinomimetics, jaw movements that resemble chewing are induced by dopamine receptor antagonists, and by pharmacological and neurotoxic depletion of dopamine (Rupniak et al., 1983; Jicha and Salamone, 1991; Baskin and Salamone, 1993; Steinpreis et al., 1993; Steinpreis and Salamone, 1993; Finn et al., 1996). Haloperidol-induced jaw movements were enhanced by both pilocarpine and physostigmine (Rupniak et al., 1983). The chewing-like jaw movements produced by haloperidol were also decreased by scopolamine (Rupniak et al., 1983; Steinpreis et al., 1993). Reserpine plus a low, presynaptic dose of apomorphine led to tremulous jaw movements in the same frequency range as tacrine-induced movements; these movements were suppressed by co-administration of scopolamine (Salamone and Baskin, 1996). Conversely, the jaw movements produced by pilocarpine were reduced by the non-selective dopamine agonist apomorphine (Stewart et al., 1988).

It was of interest in the present study to determine if antiparkinsonian drugs would be effective at reducing tacrine-induced tremulous jaw movements. Two groups of experiments were conducted. In the first group of experiments, apomorphine (Lees, 1993), the full dopamine D_1 receptor agonist *R*(+)-6-bromo-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (APB; SKF 82958; O'Boyle et al., 1989), and the full dopamine D_2 receptor agonist bromocriptine were studied. Although the partial dopamine D_1 receptor agonist SKF 38393 (*R*(+)-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-benzazepine) has been reported to be ineffective at reducing parkinsonian symptoms in monkeys (Close et al., 1990) and humans (Braun et al., 1987) it was also evaluated to validate the present animal model. For the first group of experiments, two doses of tacrine (2.5 and 5.0 mg/kg) were used to induce tremulous jaw movements. Doses of apomorphine, APB, bromocriptine, or SKF 38393 were co-administered with the low or high dose of tacrine and the effects upon tremulous jaw movements were evaluated. Based upon the results of the first group of experiments, a single dose of tacrine (2.5 mg/kg) was used for the evaluation of additional drugs in the second group of experiments. The catecholamine releasing agent amantadine and the nonselective muscarinic receptor antagonist benztropine have antiparkinsonian effects in non-human primates and humans; these drugs were evaluated along with L-DOPA for their effects on tacrine-induced tremulous jaw movements.

2. Materials and methods

2.1. Subjects

A total of 164 male Sprague-Dawley rats (Harlan Sprague-Dawley) weighing between 300–400 g were used in the present study. These animals were group housed in a colony maintained at 23°C which was on a 12-h light/dark cycle (lights on 07:00 h). Water and food were available ad libitum. All rats were cared for according to University guidelines.

2.2. Drugs

Tacrine (9-amino-1,2,3,4-tetrahydroaminoacridine hydrochloride), apomorphine hydrochloride, and L-DOPA (L-3,4-dihydroxyphenylalanine) were obtained from Sigma (St. Louis, MO, USA). Amantadine hydrochloride, benztropine mesylate, bromocriptine ((+)-bromocriptine methanesulfonate), APB (SKF 82958 or (±)-chloro-APB HBr) and SKF 38393 ((±)-SKF 38393 hydrochloride) were obtained from Research Biochemicals International (Boston, MA, USA). All drugs were dissolved in 0.1% ascorbate obtained from Fisher (Fair Lawn, NJ, USA). Amantadine, apomorphine, and benztropine were injected in volumes of 1.0 ml/kg. APB was injected at 2.0 ml/kg. Bromocriptine, L-DOPA, and SKF 38393 were dissolved in volumes of 6.0 ml/kg. With the exception of the L-DOPA experiment, all drug treatments were given in a single injection that combined tacrine and one of the doses of other drugs. With L-DOPA, different doses of L-DOPA or injections of vehicle were made in a separate injection given 50 min before tacrine.

2.3. Behavioral procedures

Although a number of different drug treatments were studied, all rats received an i.p. injection that contained tacrine, either alone or in combination with another drug. Immediately after injection of tacrine, rats were placed in an elevated Plexiglas observation box (28 × 28 × 28 cm, with a wire mesh floor) for a 10 min habituation period. All rats were observed for a 5-min period, 10–15 min after tacrine injection. An observer blind to treatment recorded the number of tremulous jaw movements, yawns, and rears

with mechanical hand counters and noted the occurrence of stereotypy (e.g., repetitive tongue protrusions, licking or gnawing). Tremulous jaw movements were defined as rapid vertical deflections of the lower jaw that resembled chewing but were not directed at any apparent physical stimulus. Yawns were defined as a gradual opening of the mouth, with a brief pause in the fully open position, ending with a rapid closure that was more rapid than the initial opening. If an animal was observed to groom or exhibit directed chewing, there was a 5 s time-out period during which tremulous jaw movements or yawns were not counted. Rears were counted when both forepaws were vertical to the horizontal plane of the top of the rear paws.

2.4. Experiments

In the first four experiments, the effects of apomorphine, bromocriptine, SKF 38393 and APB on tacrine-induced jaw movements were assessed. Separate groups of rats were used for each of the four drug experiments, and within each experiment, separate groups of rats were assigned to receive either 2.5 or 5.0 mg/kg of tacrine in order to induce tremulous jaw movements. The numbers of rats assigned to each experiment were as follows: apomorphine ($n = 9$, $n = 10$, with low and high dose of tacrine, respectively), bromocriptine ($n = 18$, $n = 18$), SKF 38393 ($n = 18$, $n = 17$, respectively), or APB ($n = 18$, $n = 14$, respectively). In addition to receiving one dose of tacrine alone, each rat also received injections of tacrine plus the dopamine agonist being assessed. The following doses were used: apomorphine (0.25, 0.5, 1.0 mg/kg), bromocriptine (5.0, 10.0, 20.0 mg/kg), SKF 38393 (7.5, 15.0, 30.0 mg/kg), or APB (0.5, 1.0, 2.0 mg/kg). Within each of the four experiments, every rat received four drug treatments (i.e., one dose of tacrine alone, and the same dose of tacrine plus a low, middle, or high challenge dose of dopamine agonist), once a week for 4 weeks in a randomly varied order. Thus, each experiment in this first group of four had a 2×4 design (two tacrine doses with separate groups, and four different drug treatments within each group).

In the second phase of this investigation, three experiments were conducted to study the ability of amantadine, benztropine and L-DOPA to reverse the effects of 2.5 mg/kg tacrine on jaw movements. As in the first four experiments, separate groups of rats were used to assess each drug (amantadine, $n = 18$; benztropine, $n = 9$; L-DOPA, $n = 15$). In addition to receiving one dose of 2.5 mg/kg tacrine alone, each rat also received injections of tacrine plus three doses of either amantadine (15.0, 30.0, 60.0 mg/kg), benztropine (2.5, 5.0, 10.0 mg/kg), or L-DOPA (50.0, 100.0, 200.0 mg/kg). For all three experiments, each rat received one of the four drug treatments (i.e., tacrine alone, or tacrine plus a low, middle, or high challenge dose of the other drug) once a week for 4 weeks in a randomly varied order.

2.5. Data analysis

The seven experiments were analyzed separately. In the first four experiments, tremulous jaw movements were analyzed by a 2×4 (tacrine dose $\times$ dose of co-administered drug) factorial analysis of variance (ANOVA) with repeated measures on drug dose (Systat version 5.0, Evanston, IL, USA). For the last three experiments, tremulous jaw movements were analyzed by a repeated measures ANOVA with four levels (tacrine alone and tacrine plus three doses of the other drug). Planned comparisons (Keppel, 1982) were made between the tacrine-alone condition and each of the three drug conditions in which another drug was co-administered with tacrine. In the first four experiments, if there was no significant interaction then the 2.5 and 5.0 mg/kg tacrine groups were combined for the planned comparisons. Single degree of freedom linear contrasts were also conducted (Systat, version 5.0). Significance was determined at the 5% significance level. Because their was very little yawning or rearing behavior, these data were not analyzed.

3. Results

3.1. Experiments 1–4

The effect of apomorphine on tacrine-induced tremulous jaw movements is shown in Fig. 1. There was not a significant effect of dose of tacrine ($F(1,17) = 0.28$, ns) on tremulous jaw movements, but there was a significant

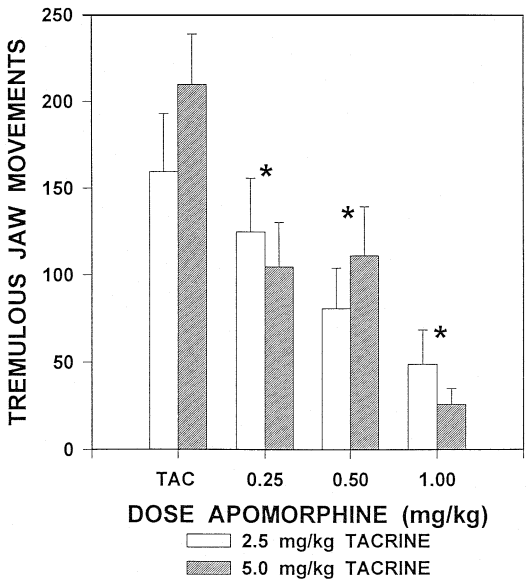


Fig. 1. Mean (±S.E.M.) number of tremulous jaw movements for each 5-min observation period. All rats received either 2.5 or 5.0 mg/kg tacrine alone (TAC), and also received injections tacrine plus 0.25, 0.5 and 1.0 mg/kg apomorphine. * Significant difference from tacrine alone, $P < 0.05$; collapsed across both the 2.5 and 5.0 mg/kg tacrine groups.

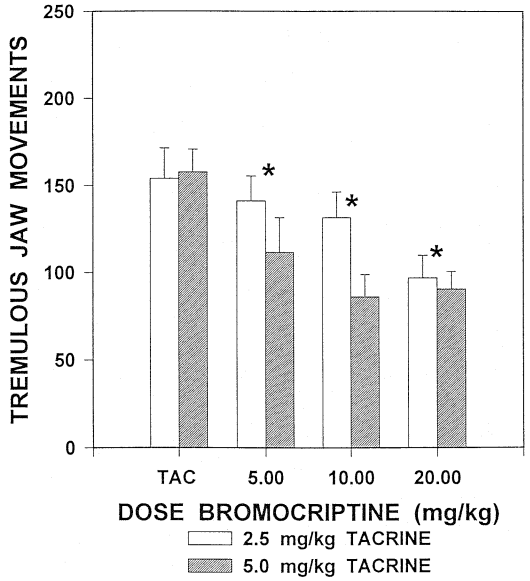


Fig. 2. Mean (±S.E.M.) number of tremulous jaw movements for each 5-min observation period. All rats received either 2.5 or 5.0 mg/kg tacrine (TAC), and also received injections tacrine plus 5.0, 10.0 and 20.0 mg/kg bromocriptine. * Significant difference from tacrine alone, $P < 0.05$; collapsed across both the 2.5 and 5.0 mg/kg tacrine groups.

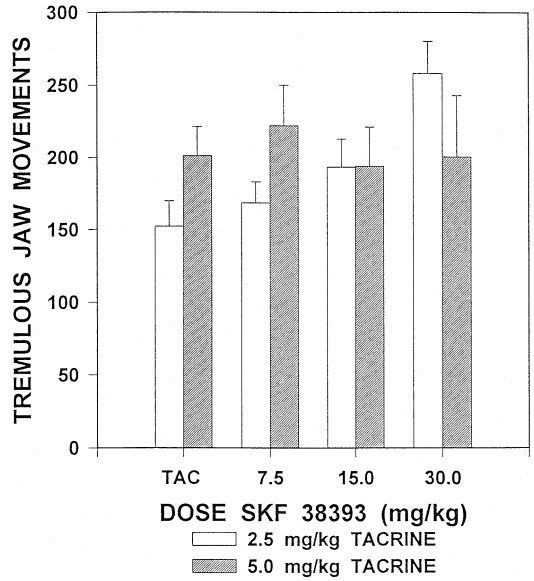


Fig. 3. Mean (±S.E.M.) number of tremulous jaw movements for each 5-min observation period. All rats received either 2.5 or 5.0 mg/kg tacrine (TAC), and also received injections tacrine plus 7.5, 15.0 and 30.0 mg/kg SKF 38393.

effect of apomorphine ($F(3,51) = 10.82$, $P < 0.001$). There was not a significant interaction between dose of tacrine and dose of apomorphine ($F(3,51) = 0.99$, ns). Planned comparisons collapsed across both the 2.5 and 5.0 mg/kg tacrine groups indicating that all three doses of apomorphine plus tacrine differed from tacrine alone. There was also a significant linear trend across doses of apomorphine ($F(1,17) = 29.46$, $P < 0.001$), but no interaction of the linear components at the different doses of tacrine ($F(1,17) = 0.99$, ns).

The effect of bromocriptine on tremulous jaw movements induced by tacrine is presented in Fig. 2. There was not a significant effect of dose of tacrine ($F(1,34) = 2.07$, ns). There was a significant effect of bromocriptine ($F(3,102) = 8.67$, $P < 0.001$), but no interaction ($F(3,102) = 1.50$, ns). Planned comparisons collapsed across both the 2.5 and 5.0 mg/kg tacrine groups indicating that all three doses of bromocriptine plus tacrine differed from tacrine alone. There was also a significant linear trend across doses of bromocriptine ($F(1,34) = 21.24$, $P < 0.001$), but no interaction of the linear components at different doses of tacrine ($F(1,34) = 0.28$, ns).

The effect of SKF 38393 on tacrine-induced tremulous jaw movements is shown in Fig. 3. There was no significant effect of tacrine ($F(1,33) = 0.33$, ns), no significant effect of SKF 38393 ($F(3,99) = 1.71$), and no interaction ($F(3,99) = 2.37$, ns). There was no significant linear trend across different doses of SKF 38393 ($F(1,33) = 3.19$, ns), but there was a significant interaction of the linear trends at different tacrine doses ($F(1,33) = 4.55$, $P < 0.05$), with SKF 38393 increasing the tremulous jaw movements induced by 2.5 mg/kg tacrine more than those induced by 5.0 mg/kg tacrine.

The effect of APB on tremulous jaw movements produced by tacrine is shown in Fig. 4. There was a significant effect of dose of tacrine ($F(1,30) = 6.84$, $P < 0.05$) and significant effect of dose of APB ($F(3,90) = 11.65$, $P < 0.001$), but there was no interaction ($F(3,90) = 1.08$, ns). Planned comparisons collapsed across both the 2.5 and

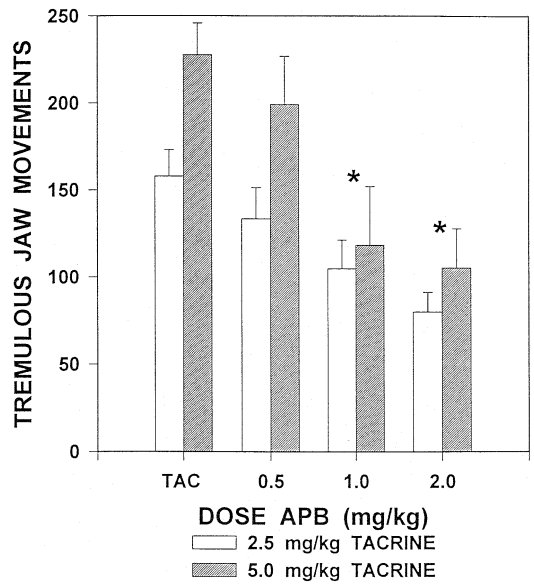


Fig. 4. Mean (±S.E.M.) number of tremulous jaw movements for each 5-min observation period. All rats received either 2.5 or 5.0 mg/kg tacrine (TAC), and also received injections tacrine plus 0.5, 1.0 and 2.0 mg/kg APB. * Significant difference from tacrine alone, $P < 0.05$; collapsed across both the 2.5 and 5.0 mg/kg tacrine groups.

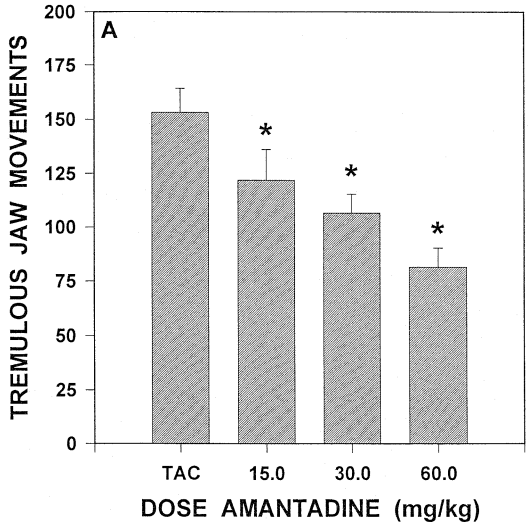
5.0 mg/kg tacrine groups indicating that 1.0 and 2.0 mg/kg APB plus tacrine differed from tacrine alone. There was a significant linear trend across different doses of APB ($F(1,30) = 43.58$, $P < 0.001$), but no significant interaction of the linear components at different doses of tacrine ($F(1,30) = 2.97$, ns).

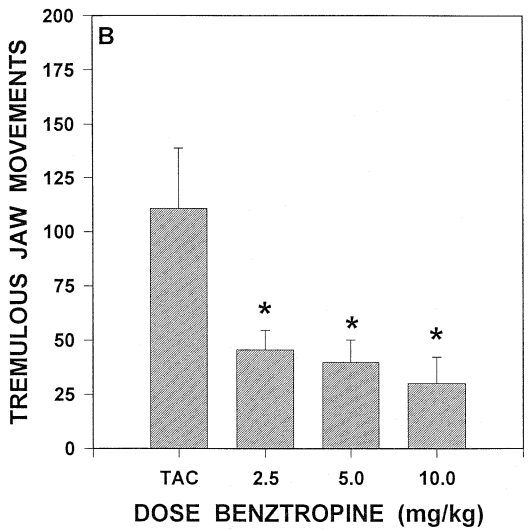
3.2. Experiments 5–7

The effect of amantadine on tremulous jaw movements produced by tacrine is shown in Fig. 5A. Amantadine significantly reduced jaw movements induced by tacrine ($F(3,51) = 9.19$, $P < 0.001$). Planned comparisons determined that all three doses of amantadine reduced tremulous jaw movements, and there was a significant linear trend to the reduction of jaw movements by amantadine ($F(1,17) = 33.39$, $P < 0.001$). The effect of benztropine on tacrine-induced tremulous jaw movements is shown in Fig. 5B. Benztropine produced a significant reduction of tacrine-induced jaw movements ($F(3,24) = 5.85$, $P < 0.01$). Planned comparisons indicated that all three doses of benztropine reduced tremulous jaw movements. There was also a significant linear trend to the reduction of tremulous jaw movements ($F(3,24) = 5.85$, $P < 0.01$). The effect of L-DOPA on tremulous jaw movements induced by tacrine is shown in Fig. 5C. L-DOPA produced a significant overall reduction of jaw movements ($F(3,42) = 4.65$, $P < 0.01$). Planned comparisons showed that all three doses of L-DOPA significantly reduced tremulous jaw movements. There was also a significant linear component to the reduction of tacrine-induced jaw movements ($F(1,14) = 4.66$, $P < 0.05$).

3.3. General observations

Although not statistically evaluated, stereotypy was observed in some animals following high doses of dopamine receptor agonists. Some stereotyped behavior was observed in 10 of the 19 rats that received 1.0 mg/kg apomorphine, and 7 of the 32 rats that received 2.0 mg/kg APB. Other observations included whole-body spasms that were seen in most animals at 60.0 mg/kg amantadine and piloerection that was observed in all rats at 100.0 and 200.0 mg/kg L-DOPA. An index of the magnitude of the suppression of tacrine-induced jaw movement activity across different experiments is the percentage of observations in which less than 20 tremulous jaw movements were counted over the 5-min observation period. Examined this way, 41% of the observations following benztropine and 33% of the observations following apomorphine treatment





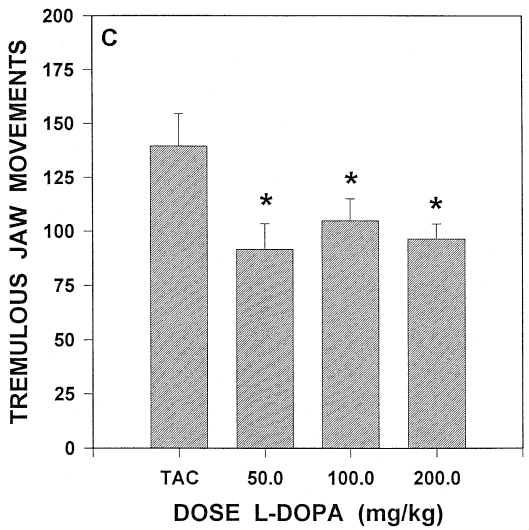


Fig. 5. Mean (±S.E.M.) number of tremulous jaw movements for each 5-min observation period. All rats received injections of 2.5 mg/kg tacrine (TAC). Effects are shown for amantadine (A), benztropine (B) and L-DOPA (C). * Significant difference from tacrine alone, $P < 0.05$.

had less than 20 tremulous jaw movements. In contrast, none of the other challenge drugs had greater than 10% of the observations with less than 20 tremulous jaw movements (10% of APB observations, 8% of SKF 38393, 7% of L-DOPA, 4% of amantadine and 4% of bromocriptine).

4. Discussion

Consistent with previous reports, the anticholinesterase tacrine produced high levels of jaw movement activity (Carriero et al., 1996; Mayorga et al., 1996). SKF 38393 was ineffective at reducing tremulous jaw movements, and instead produced a trend towards an increase in the tremulous jaw movements induced by the lower dose of tacrine. These results are consistent with previous work showing that SKF 38393 failed to suppress pilocarpine-induced vacuous chewing (Levin et al., 1989), and that SKF 38393 also is capable of producing low levels of jaw movement activity (Rosengarten et al., 1993; but see also Murray and Waddington, 1989). Apomorphine, APB, bromocriptine, amantadine, benztropine and L-DOPA all reduced tacrine-induced tremulous jaw movements in a dose-dependent manner. Apomorphine, benztropine and bromocriptine were much more potent than amantadine and L-DOPA for reducing tacrine-induced jaw movements. This pattern of relative potency is similar to the pattern shown in the clinical usage of these antiparkinsonian drugs (Oertel and Dodel, 1995). Therefore, several different antiparkinsonian drugs, with a variety of different pharmacological actions, all were effective at reducing tremulous jaw movements produced by tacrine.

The present data are consistent with previous work that examined cholinomimetic-induced tremulous jaw movements. In the present study, the centrally acting muscarinic receptor antagonist benztropine was shown to block tacrine-induced jaw movements. Several previous reports have demonstrated that the jaw movements induced by pilocarpine, physostigmine, or tacrine can be reduced by the centrally acting muscarinic antagonist scopolamine, but not by methyl scopolamine (Rupniak et al., 1983; Salamone et al., 1986; Stewart et al., 1989; Mayorga et al., 1996). Furthermore, local injections of either scopolamine, methyl scopolamine, or atropine into the ventrolateral neostriatum have been shown to block the tremulous jaw movements induced by tacrine, physostigmine, carbachol, or pilocarpine (Kelley et al., 1989; Salamone et al., 1990; Kikuchi de Beltran et al., 1992; Mayorga et al., 1996). Taken together, these data indicate that cholinomimetics produce tremulous jaw movements by stimulation of central muscarinic receptors, which are likely to be located in the ventrolateral portion of the neostriatum. Additionally, the present results provide further evidence of acetylcholine/dopamine interactions in the production of tremulous jaw movements. Using the cholinergic receptor agonist pilocarpine, Stewart et al. (1988) had determined that tremulous jaw movements can be reduced by apomorphine co-administration. The present study confirmed these findings with apomorphine, and extended them to include some additional dopamine receptor agonists.

In the parkinsonian drug literature, there has been debate for some time about the relative effectiveness of D_1 and D_2 stimulation for producing antiparkinsonian effects. It is well known that non-selective dopamine receptor agonists, such as apomorphine, can have antiparkinsonian effects (Lees, 1993). Moreover, drugs that are somewhat D_2 selective, such as bromocriptine, also are effective antiparkinsonian agents (Lang, 1987). The first widely studied dopamine D_1 receptor agonist, SKF 38393, was assessed in clinical studies and found to be ineffective for the treatment of Parkinson's disease (Braun et al., 1987). This pattern of results suggested that the critical pharmacological characteristic of an antiparkinsonian drug was dopamine D_2 receptor agonism. However, there are several problems with that conclusion. SKF 38393 is only a partial agonist, with moderate efficacy for stimulating cAMP production (Watts et al., 1993). More recently, a new generation of dopamine D_1 receptor agonists, such as dihydrexine, SKF 81297 and APB, have been tested in dopamine-depleted primate models of parkinsonism. These studies suggest that antiparkinsonian effects can be achieved by dopamine D_1 receptor agonists (Taylor et al., 1991; Blanchet et al., 1993; Vermulen et al., 1993, 1994), including APB (Akai et al., 1995; Gnanalingham et al., 1995). The present results confirm and extend these findings, in that SKF 38393 was shown to be ineffective at reversing tacrine-induced tremulous jaw movements, yet the full agonist APB significantly reduced these movements. Thus, evidence suggests that either dopamine D_1 or D_2 receptor agonists can have some antiparkinsonian activity. Because some anatomical evidence suggests that dopamine D_1 and D_2 receptors are localized on distinct populations of striatal cells, the present results suggest that dopaminergic modulation of either the 'direct' or the 'indirect' pathway can produce therapeutic effects in Parkinson's disease (see Young and Penney, 1993; Alexander et al., 1990; DiChiara et al., 1994). Additional work in both primates and rodents should focus on the ability of dopamine receptor agonists of various types to produce antiparkinsonian effects, so that the critical pharmacological characteristics of the therapeutic effects of these drugs can be determined.

The neurochemical basis of dopamine receptor agonist-induced reversal of tremulous jaw movements is uncertain. It has been suggested that dopamine receptor agonists that decrease the activity of adenylate cyclase would be effective at reducing tremulous jaw movements induced by cholinomimetics (Levin et al., 1989). According this view, the inability of SKF 38393 to antagonize tremulous jaw movements may be related to the D_1-mediated stimulation of cAMP production by this drug (Izenwasser and Katz, 1993). However, there does not appear to be a simple

relation between cAMP production and cholinomimetic-induced tremulous jaw movements. First of all, there is conflicting evidence about the effects of bromocriptine and apomorphine on cAMP production (Gumulka et al., 1976; Battaglia et al., 1985; Onali et al., 1985; Memo et al., 1986). In addition, although dopamine D_1 receptor stimulation is typically seen as activating postsynaptic cAMP activity (Kebabian and Calne, 1979; Izenwasser and Katz, 1993), dopamine D_1 receptor stimulation can also be uncoupled from cAMP production (Andersen and Nielsen, 1986; Mailman et al., 1986). Some evidence indicates that there may be two types of dopamine D_1 receptor, one that activates adenylate cyclase and one that acts through some other mechanism (Rosengarten et al., 1993; Deveney and Waddington, 1995). It is important to consider that the full dopamine D_1 receptor agonist APB is more efficacious than SKF 38393 at stimulating cAMP production (O'Boyle et al., 1989; Izenwasser and Katz, 1993), yet APB actually decreases tacrine-induced jaw movements. Muscarinic receptor agonists are highly effective at inducing tremulous jaw movements, despite the fact that they decrease cAMP production (McKinney et al., 1989). Thus, it remains unclear if the modulation of cholinomimetic-induced jaw movements is dependent upon cAMP mechanisms, or upon the action of some other second messenger system. The effect of dopamine receptor agonists on second messenger activity in the presence of muscarinic stimulation is not known, and future research should focus upon this type of neurochemical interaction between dopamine and acetylcholine systems.

When considering the reduction of tacrine-induced jaw movements by antiparkinsonian drugs, it may also be useful to consider the effects of dopamine D_1 and D_2 receptor agonists upon in vivo striatal acetylcholine function. Cholinergic stimulation is known to induce parkinsonian symptoms, and evidence indicates that dopamine antagonism or depletions can enhance striatal acetylcholine release (DeBoer et al., 1993). Thus, it is possible that parkinsonian symptoms are induced by enhanced cholinergic function, and that antiparkinsonian effects of dopamine receptor agonists could be occurring because these drugs reduce acetylcholine release. Consistent with the present data, systemic administration of apomorphine (Stadler et al., 1973; Guyenet et al., 1974), and bromocriptine (DeBoer et al., 1993), have been shown to decrease striatal extracellular acetylcholine levels. Also consistent with the present data is the finding that under physiological conditions, the partial dopamine D_1 receptor agonist SKF 38393 can increase striatal acetylcholine release, whereas the dopamine D_2 receptor agonist quinpirole decreases striatal acetylcholine release (DeBoer and Abercrombie, 1996). The effects of APB or amantadine upon striatal acetylcholine release have not been evaluated, and future research is needed to evaluate the effects of dopamine receptor agonists on extracellular acetylcholine in the presence of tacrine. Nevertheless, there are some problems in attempting to find a direct relation between striatal acetylcholine activity and tremulous jaw movements. There is conflicting evidence about the effects of apomorphine on striatal acetylcholine release (Bertorelli and Consolo, 1990). L-DOPA, which was effective at reducing tacrine-induced jaw movements, actually tends to increase striatal acetylcholine levels (DeBoer et al., 1993). Also, evidence indicates that reserpine, which can induce tremulous jaw movements, decreases rather than increases striatal acetylcholine release (Bertorelli et al., 1992; Imperato et al., 1994). Thus, as in the case of second messenger production, there is not a clear relation between striatal acetylcholine release and tremulous jaw movements. It is possible that there are several different neurochemical effects that lead to tremulous jaw movements, and not all of them are directly dependent upon acetylcholine release. Moreover, it is possible that some antiparkinsonian treatments act to modulate cholinergic transmission, whereas other treatments have their therapeutic effects via different actions.

In summary, tacrine-induced tremulous jaw movements can be suppressed by antiparkinsonian agents. L-DOPA, apomorphine, amantadine, bromocriptine, APB, and benztropine were effective at reducing tremulous jaw movements produced by tacrine. SKF 38393, which is not an effective treatment for Parkinson's disease, did not reduce tacrine-induced jaw movements. Although L-DOPA is the most widely used therapy and has been used against parkinsonian tremor in Alzheimer's patients (Ott and Lannon, 1992), it is not without its disadvantages. Future research involving tacrine-induced tremulous jaw movements in rats can be used to investigate additional antiparkinsonian treatments such as other dopamine receptor agonists, as well as antagonists at acetylcholine, serotonin, and excitatory amino acid receptors (Klockgether et al., 1991; Lees, 1993; DiChiara et al., 1994; Lange and Riederer, 1994).

Acknowledgements

This paper is dedicated to the memory of William F. Lexton. The work was supported by a grant from the National Institutes of Health (NINDS).

References

Acquilonius, S.M., 1980, Cholinergic mechanisms in the CNS related to Parkinson's disease, in: Parkinson's Disease – Current Progress (Elsevier/North Holland, Amsterdam) p. 17.

Adams, R.D. and M. Victor, 1981, Tremor, myoclonus, spasms and tics, in: Principles of Neurology (McGraw-Hill, New York, NY) p. 69.

Akai, T., M. Ozawa, M. Yamaguchi, E. Mizuta and S. Kuno, 1995, Combination treatment of the partial D_2 agonist terguride with the D_1 agonist SKF 82958 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys, J. Pharmacol. Exp. Ther. 273, 309.

Alexander, G.E., M.D. Crutcher and M.R. DeLong, 1990, Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions, Prog. Brain Res. 85, 119.

Andersen, P.H. and E.B. Nielsen, 1986, The dopamine D_1 receptor: biochemical and behavioral aspects, in: Neurobiology of Central D_1 Dopamine Receptors, eds. G.R. Creese and I. Creese (Plenum Press, New York, NY).

Bartholini, G., 1987, Functional neuronal relations in the basal ganglia and their clinical relevances, in: Neurotransmitter Interactions in the Basal Ganglia, ed. M. Sandler (Raven Press, New York, NY) p. 1.

Baskin, P. and J.D. Salamone, 1993, Vacuous jaw movements in rats induced by acute reserpine administration: interactions with different doses of apomorphine, Pharmacol. Biochem. Behav. 46, 793.

Baskin, P., G. Gianutsos and J.D. Salamone, 1994, Repeated scopolamine injections sensitize rats to pilocarpine-induced vacuous jaw movements and enhance striatal muscarinic receptor binding, Pharmacol. Biochem. Behav. 49, 437.

Battaglia, G., A.B. Norman, E.J. Hess and I. Creese, 1985, D_2 dopamine receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in rat striatum, Neurosci. Lett. 59, 177.

Bertorelli, R. and S. Consolo, 1990, D_1 and D_2 dopaminergic regulation of acetylcholine release from striata of freely moving rats, J. Neurochem. 54, 2145.

Bertorelli, R., M. Zambelli, G. Di Chiara and S. Consolo, 1992, Dopamine depletion preferentially impairs D_1- over D_2-receptor regulation of striatal in vivo acetylcholine release, J. Neurochem. 59, 353.

Blanchet, P., P.J. Bedard, D.R. Britton and J.W. Kebabian, 1993, Differential effects of selective D-1 and D-2 dopamine receptor agonists on levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-exposed monkeys, J. Pharmacol. Exp. Ther. 267, 275.

Braun, A., G. Fabbrini, M.M. Mouradian, C. Serrati, P. Barone and T. Chase, 1987, Selective D-1 dopamine receptor agonist treatment of Parkinson's disease, J. Neural Transm. 68, 41.

Carriero, D.L., G. Oustlay, A.J. Mayorga, G. Gianutsos and J.D. Salamone, 1996, Motor effects of tacrine administration in rats, Pharmacol. Biochem. Behav. (in press).

Close, S.P., P.J. Elliott, A.G. Hayes and A.S. Marriott, 1990, Effects of classical and novel agents in a MPTP-induced reversible model of Parkinson's disease, Psychopharmacology 102, 295.

Collins, P., C.L.E. Broekkamp, P. Jenner and C.D. Marsden, 1991, Drugs acting at D-1 and D-2 dopamine receptors induce identical purposeless chewing in rats which can be differentiated by cholinergic manipulation, Psychopharmacology 103, 503.

Collins, P., C.L.E. Broekkamp, P. Jenner and C.D. Marsden, 1993, Effect of chronic trifluoperazine administration and subsequent withdrawal on the production and persistence of perioral behaviors in two rat strains, Psychopharmacology 112, 437.

DeBoer, P. and E.D. Abercrombie, 1996, Physiological release of striatal acetylcholine in vivo: modulation by D_1 and D_2 dopamine receptor subtypes, J. Pharmacol. Exp. Ther. 277, 775.

DeBoer, P., E.D. Abercrombie, M. Heeringa and B.H.C. Westerink, 1993, Differential effect of systemic administration of bromocriptine and L-DOPA on the release of acetylcholine from striatum of intact and 6-OHDA-treated rats, Brain Res. 608, 198.

Deveney, A.M. and J.L. Waddington, 1995, Pharmacological characterization of behavioral response to SK&F 83959 in relation to 'D_1-like' dopamine receptors not linked to adenyl cyclase, Br. J. Pharmacol. 116, 2120.

DiChiara, G., M. Morelli and S. Consolo, 1994, Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions, Trends Neurosci. 17, 228.

Duvoisin, R.C., 1967, Cholinergic-anticholinergic antagonism in parkinsonism, Arch. Neurol. 17, 124.

Finn, M., A. Jassen, P. Baskin and J.D. Salamone, 1996, Tremulous characteristics of jaw movements, Pharmacol. Biochem. Behav. (in press).

Gnanalingham, K.K., D.D. Erol, A.J. Hunter, L.A. Smith, P. Jenner and C.D. Marsden, 1995, Differential anti-parkinsonian effects of benzazepine D_1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset, Psychopharmacology 117, 275.

Gumulka, S.W., V. Dinnendahl, H.D. Peters and P.S. Schonhofer, 1976, Effects of dopaminergic stimulants on cyclic nucleotide levels in mouse brain in vivo, Naunyn-Schmiedeberg's Arch. Pharmacol. 293, 75.

Guyenet, P., Y. Agid, F. Javoy, J.C. Beaujouan and J. Glowinski, 1974, Selective action of neuroleptics on the cholinergic neurons of the neostriatum in the rat: antagonism to apomorphine, C.R. Acad. Sci. Hebd. Seances Acad. Sci. D. 278, 2679.

Imperato, A., M.C. Obinu, L. Dazzi and G.L. Gessa, 1994, Does dopamine exert a tonic inhibitory control on the release of striatal acetylcholine in vivo? Eur. J. Pharmacol. 251, 271.

Izenwasser, S. and J.L. Katz, 1993, Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat, Eur. J. Pharmacol. 246, 39.

Jicha, G. and J.D. Salamone, 1991, Vacuous jaw movements and feeding deficits in rats with ventrolateral striatal dopamine depletions: possible model of parkinsonian symptoms, J. Neurosci. 11, 3822.

Kebabian, J.W. and D.B. Calne, 1979, Multiple receptors for dopamine, Nature 277, 93.

Kelley, A.E., V.P. Bakshi, J.M. Delfs and C.G. Lang, 1989, Cholinergic stimulation of the ventrolateral striatum elicits mouth movements in rats: pharmacological and regional specificity, Psychopharmacology 99, 542.

Keltner, N.L., 1994, Tacrine: a pharmacological approach to Alzheimer's disease, J. Psychosoc. Nurs. Ment. Health Serv. 32, 37.

Keppel, G., 1982, Design and Analysis: A Researchers Handbook (Prentice Hall, Englewood Cliffs, NJ).

Kikuchi de Beltran, K., N. Koshidawa, T. Saigusa, K. Watanabe, Y. Koshida and M. Kobayashi, 1992, Cholinergic/dopaminergic interaction in the rat striatum assessed from drug-induced repetitive oral movements, Eur. J. Pharmacol. 214, 181.

Klockgether, T., L. Turski, T. Honore, Z. Zhang, D. Gash, R. Kurlan and J.T. Greenamyre, 1991, The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys, Ann. Neurol. 30, 717.

Lang, A.E., 1987, Update on dopamine agonists in Parkinson's disease: 'beyond bromocriptine', Can. J. Neurol. Sci. 14 (Suppl. 3), 474.

Lange, K.W. and P. Riederer, 1994, Glutamatergic drugs in Parkinson's disease, Life Sci. 55, 2067.

Lees, A.J., 1993, Dopamine agonists in Parkinson's disease: a look at apomorphine, Fund. Clin. Pharmacol. 7, 121.

Levin, E.D., G.D. Ellison, R.E. See, D. South and E. Young, 1989, D_1 and D_2 dopamine receptor interactions with pilocarpine-induced oral activity in rats, Pharmacol. Biochem. Behav. 33, 501.

Mailman, R.B., D.W. Schulz, C.D. Kilts, M.H. Lewis, H. Rollema and S. Wyrick, 1986, Multiple forms of the D_1 dopamine receptor: its linkage to adenylate cyclase and psychopharmacological effects, Psychopharmacol. Bull. 22, 593.

Marsden, C.D., D. Tarsy and R.J. Baldessarini, 1975, Spontaneous and drug-induced movement disorders in psychotic patients, in: Psychiatric Aspects of Neurological Disease, eds. D.F. Bendon and D. Blumer (Grune and Stratten, New York, NY) p. 219.

Mayorga, A.J., D.L. Carriero, M.S. Cousins, G. Gianutsos and J.D. Salamone, 1996, Tremulous jaw movements produced by acute tacrine administration: possible relation to parkinsonian side effects, Pharmacol. Biochem. Behav. (in press).

McEvoy, J.P., 1983, The clinical use of anticholinergic drugs as treatment for extrapyramidal side effects of neuroleptic drugs, J. Clin. Psychopharmacol. 3, 288.

McKinney, M., D. Anderson, C. Forray and E.E. El-Fakahany, 1989, Characterization of the striatal M_2 muscarinic receptor mediating inhibition of cyclic AMP using selective antagonists: a comparison with brainstem M_2 receptor, J. Pharmacol. Exp. Ther. 250, 565.

Memo, M., C. Missale, M.O. Carruba and P.F. Spano, 1986, D_2 dopamine

receptors associated with inhibition of dopamine release from rat neostriatum are independent of cyclic AMP, Neurosci. Lett. 71, 192.
Murray, A.M. and J.L. Waddington, 1989, The induction of grooming and vacuous chewing by a series of selective D-1 dopamine receptor agonists: two directions of D-1:D-2 interaction, Eur. J. Pharmacol. 160, 377.
Noring, U., U.J. Povlesen, D.E. Casey and J. Gerlach, 1984, Effect of a cholinomimetic drug (RS 86) in tardive dyskinesia and drug-related parkinsonism, Psychopharmacology 84, 569.
O'Boyle, K.M., D.E. Gaitanopoulos, M. Brenner and J.L. Waddington, 1989, Agonist and antagonist properties of benzazepine and thienopyridine derivatives at the D_1 dopamine receptor, Neuropharmacology 28, 401.
Oertel, W.H. and R.C. Dodel, 1995, International guide to drugs for Parkinson's disease, Mov. Dis. 10, 121.
Onali, P., M.C. Olianas and G.L. Gessa, 1985, Characterization of dopamine receptors mediating inhibition of adenylate cyclase activity in rat striatum, Mol. Pharmacol. 28, 138.
Ott, B.R. and M.C. Lannon, 1992, Exacerbation of parkinsonism by tacrine, Clin. Neuropharmacol. 15, 322.
Rosengarten, H., J.W. Schweitzer and A.J. Friedhoff, 1993, A subpopulation of dopamine D_1 receptors mediate repetitive jaw movements in rats, Pharmacol. Biochem. Behav. 45, 921.
Rupniak, N.M.J., P. Jenner and C.D. Marsden, 1983, Cholinergic modulation of perioral behavior induced by chronic neuroleptic administration to rats, Psychopharmacology 79, 226.
Salamone, J.D. and P.B. Baskin, 1996, Vacuous jaw movements induced by reserpine and low-dose apomorphine: possible model of parkinsonian tremor, Pharmacol. Biochem. Behav. 53, 179.
Salamone, J.D., M.D. Lalies, S.L. Channell and S.D. Iversen, 1986, Behavioral and pharmacological characterization of the mouth movements induced by muscarinic agonists in the rat, Psychopharmacology 88, 467.
Salamone, J.D., C.J. Johnson, L.D. McCullough and R.E. Steinpreis, 1990, Lateral striatal cholinergic mechanisms involved in oral motor activities in the rat, Psychopharmacology 102, 529.
Stadler, H., K.G. Lloyd, M. Gadea-Ciria and G. Bartholini, 1973, Enhanced striatal acetylcholine release by chlorpromazine and its reversal by apomorphine, Brain Res. 55, 476.
Steinpreis, R.E. and J.D. Salamone, 1993, The effects of acute haloperidol and reserpine administration on vacuous jaw movements in three different age groups of rats, Pharmacol. Biochem. Behav. 46, 405.
Steinpreis, R.E., P. Baskin and J.D. Salamone, 1993, Vacuous jaw movements induced by sub-chronic administration of haloperidol: interactions with scopolamine, Psychopharmacology 111, 99.
Stewart, B.R., P. Jenner and C.D. Marsden, 1988, The pharmacological characterization of pilocarpine-induced chewing in the rat, Psychopharmacology 96, 55.
Stewart, B.R., P. Jenner and C.D. Marsden, 1989, Assessment of the muscarinic receptor subtype involved in the mediation of pilocarpine-induced purposeless chewing behavior, Psychopharmacology 97, 228.
Taylor, J.R., D.E. Lawrence, J.D. Redmond, J.D. Elsworth, R.H. Roth, D.E. Nocols and R.B. Mailman, 1991, Dihydrexidine, a full dopamine D_1 agonist, reduces MPTP-induced parkinsonism in monkeys, Eur. J. Pharmacol. 199, 389.
Vermulen, R.J., B. Drukarch, M.C.R. Sahadat, C. Goosen, E.C. Wolters and J.C. Stoof, 1993, The selective dopamine D_1 receptor agonist, SKF 81297, stimulates motor behavior of MPTP-lesioned monkeys, Eur. J. Pharmacol. 235, 143.
Vermulen, R.J., B. Drukarch, M.C.R. Sahadat, C. Goosen, E.C. Wolters and J.C. Stoof, 1994, The selective D_1 agonist SKF 81297 and the dopamine D_2 agonist LY 171555 act synergistically to stimulate motor behavior of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian monkeys, Mov. Dis. 6, 664.
Watts, V.J., C.P. Lawler, J.H. Gilmore, S.B. Southerland, D.E. Nichols and R.B. Mailman, 1993, Dopamine D_1 receptors: efficacy of full (dihydrexine) vs. partial (SKF38393) agonists in primates vs. rodents, Eur. J. Pharmacol. 242, 165.
Weiss, K.J., D.A. Ciraulo and R.I. Shader, 1980, Physostigmine test in the rabbit syndrome and tardive dyskinesia, Am. J. Psychiatry 137, 627.
Young, A.B. and J.B. Penney, 1993, Biochemical and functional organization of the basal ganglia, in: Parkinson's Disease and Movement Disorders, eds. J. Jankovic and E. Tolosa (Williams&Wilkins, Baltimore, MD) p. 1.