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Muscarinic receptor agonists decrease cocaine self-administration rates in drug-naive mice

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Abstract

(5*R*,6*R*)-6-(3-Propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (PTAC) is a selective muscarinic receptor ligand. The compound exhibits high affinity for central muscarinic receptors with partial agonist mode of action at muscarinic M_2 and M_4 and antagonist mode of action at muscarinic M_1, M_3 and M_5 receptor subtypes. The compound was earlier reported to exhibit functional dopamine receptor antagonism in rodents despite its lack of affinity for dopamine receptors. In the present study, we report that PTAC, as well as the muscarinic receptor agonists pilocarpine and oxotremorine, dose-dependently decreased rates of intravenous self-administration (fixed ratio 1) of the indirect dopamine receptor agonist cocaine in drug naive mice. Similar decreases in cocaine self-administration rates were obtained with the dopamine receptor antagonists olanzapine, clozapine, risperidone, fluphenazine and haloperidol. These findings suggest that compounds with partial muscarinic receptor agonist mode of action may be used in the medical treatment of cocaine abuse.

Keywords: Muscarinic receptor agonist; Cocaine; Self-administration; Drug-naive; (Mouse)

1. Introduction

We have earlier reported that the selective muscarinic receptor ligand (5*R*,6*R*)-6-(3-Propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (PTAC) exhibits functional dopamine receptor antagonism in rodents despite its lack of affinity for dopamine receptors (Bymaster et al., 1998, 1999; Fink-Jensen et al., 1998; Sauerberg et al., 1998). PTAC exhibits high affinity for central muscarinic receptors with partial agonist mode of action at muscarinic M_2 and M_4 and antagonist mode of action at muscarinic M_1, M_3 and M_5 receptor subtypes (Bymaster et al., 1998). Importantly, PTAC does not induce parasympathomimetic side effects at pharmacologically relevant doses (Bymaster et al., 1998) in contrast to the traditional acetylcholine receptor agonists. Combination studies have shown that the acetylcholine receptor antagonist scopolamine is able to antagonize the effects of PTAC, indicating that the pharmacological effects of PTAC are mediated through an agonist mode of action at muscarinic receptors (Bymaster et al., 1998). In accordance with these data, we have also shown that the acetylcholine receptor agonists pilocarpine, oxotremorine and RS 86 inhibit dopamine receptor agonist-induced behaviours (Fink-Jensen et al., 1998).

Consequently, the use of muscarinic receptor partial agonists with affinity for M_2 and M_4 receptors, not endowed with parasympathomimetic side effects, have been suggested as a new approach to the medical treatment of schizophrenia (Bymaster et al., 1998, 1999; Sauerberg et al., 1998; Shannon et al., 1999).

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In the present study we wanted to test the effects of PTAC as well as the acetylcholine receptor agonists pilocarpine and oxotremorine on intravenous self-administration in drug-naive mice of the indirect dopamine receptor agonist cocaine. In addition, the dopamine receptor antagonists olanzapine, clozapine, risperidone, fluphenazine and haloperidol were tested.

2. Materials and methods

2.1. Animals

Male Bom:NMRI (Bomholtegaard, Ry, Denmark), weighing 20–22 g were used. Upon arrival, the mice were housed 20 per cage for 2–3 days in a 12 L: 12 D cycle with lights on at 6 A.M., 40–70% relative humidity, and free access to food (Altromin® 1324, Brogården, Copenhagen, Denmark) and water (1% citric acid, pH 2–3). Twenty-four hours prior to use, the mice were grouped 4 per cage. The mice were habituated to the experimental room 1–2 h before use. Experiments were performed between 9 A.M and 3 P.M. The studies were conducted in accordance with the Danish law on the care and use of laboratory animals and approved by the Danish Committee for Animal Research.

2.2. Drugs

Drugs were obtained from the following sources: Cocaine HCl, pilocarpine HCl, oxotremorine sesquifumerate, fluphenazine 2 HCl (Sigma); haloperidol (RBI); risperidone (Janssen); clozapine (Novartis); olanzapine (Lilly Research Laboratories, Indianapolis, IN, USA) and PTAC (Novo Nordisk, Måløv, Denmark). Risperidone was dissolved in a small amount of 80% ethanol and brought to volume with 0.9% saline solution. PTAC, Cocaine, pilocarpine, oxotremorine and fluphenazine were dissolved in 0.9% saline solution. Haloperidol and olanzapine were added to small amounts of 0.1 M HCl, brought to volume with 0.9% saline solution and NaOH was added to final pHs of 7. Clozapine was added to a small amount of 0.1 M HCl, sonicated, heated to about 60°C and brought to volume with 0.9% saline solution. The pH of the final solution was 4.5. All solutions were prepared immediately before use. Doses refer to the forms indicated.

2.3. Drug administration and self-administration procedure

The experimental procedure of Rasmussen and Swedberg (1998) was followed. Briefly, the mice were fitted with an intravenous catheter in the tail and tested in pairs such that both a contingent and a yoked control mouse received an intravenous infusion (1.4 μl) of cocaine or vehicle upon nose poking of the contingent mouse. A fixed ratio 1 (FR1) schedule with no time out between infusions was used. Nose poking of the yoked control mouse was recorded but produced no infusions. The yoked control mouse was used to assess if nose poking was dependent on non-specific drug-induced side effects. An unlimited number of infusions were available during the session (30 min) after a preceding habituation period (10 min) with no infusions. The purpose of conducting a unit dose–response study with cocaine was to identify the unit dose maintaining the highest rate of self-administration in contingent mice. This unit dose was used as the fixed self-administration unit dose in the experiments with administration of test compounds prior to cocaine self-administration. In these experiments, the mice were injected s.c. with saline or the test compound (injection volumes 0.2 ml) 30 min (including the 10 min habituation period) before the onset of self-administration.

2.4. Data analysis

Groups of mice (contingent and yoked control) were excluded from data analysis according to the criteria as previously published (Rasmussen and Swedberg, 1998). This resulted in groups of mice of $n = 10–15$ for inhibition studies and $n = 16–22$ for the unit dose–response study with cocaine. Two-way ANOVA was used to evaluate the effects of group (contingent versus yoked control), dose (including vehicle), and interaction between group and dose. For post hoc testing, Dunnett's test was used to evaluate single comparisons between groups of contingent drug mice and respective vehicle control, and Tukey's test was used to evaluate single comparisons between groups of contingent mice and respective yoked control mice. Statistical tests were performed using SigmaStat® 2.01. ED_{50}s and 95% confidence intervals (c.i.) for nose poking of contingent mice were calculated using non-sigmoidal regression analysis (GraphPad Prism® 2.0). Significance levels of $P < 0.05$ were used for statistical tests.

3. Results

Cocaine (Fig. 1) maintained self-administration in contingent mice, yielding an inverted U-shaped dose–response. There were significant main effects on nose poking of group ($P < 0.001$), unit dose ($P < 0.05$), and a significant group by unit dose interaction ($P < 0.01$). The unit dose at which nose poking in contingent mice peaked (mean 112) was 0.1 mg/kg/infusion ($P < 0.05$ relative to vehicle control). This cocaine unit dose was used as the fixed self-administered unit dose in the experiments with administration of test compounds prior to self-administration.

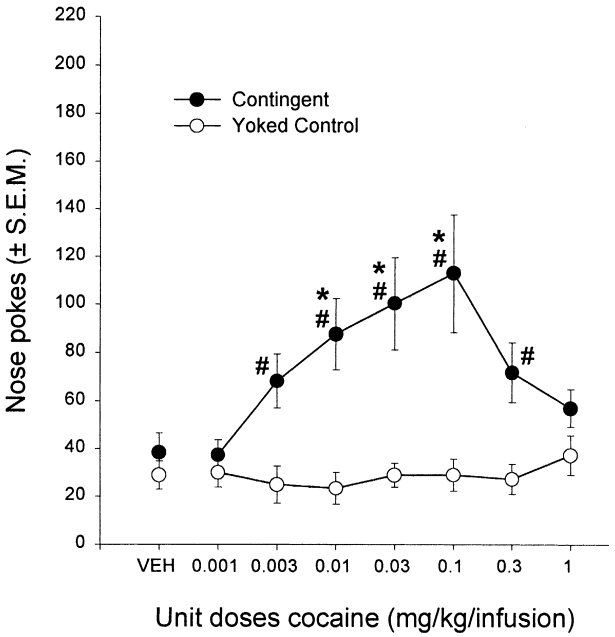

Fig. 1. Cocaine HCl self-administration in drug-naive mice. Shown are mean numbers of nose pokes (±S.E.M.) in contingent mice and yoked control mice (pairs of mice = 16–22). $^{*}P < 0.05$ compared to vehicle control, $\#P < 0.05$ compared to yoked control.

PTAC (Fig. 2) decreased rates of cocaine self-administration in contingent mice dose-dependently with significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.01$), and a significant group by dose interaction ($P < 0.01$). The ED_{50} was 0.003 mg/kg (c.i. 0.0003 to 0.03 mg/kg). There were no significant effects on nose poking of yoked control mice up to the dose of 0.003 mg/kg.

Pilocarpine (Fig. 3) decreased rates of cocaine self-administration with significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.01$), and a significant group by dose interaction ($P < 0.01$). The ED_{50} was 0.41 mg/kg (c.i. 0.12 to 1.47 mg/kg). There were no significant effects on nose poking of yoked control mice up to the dose of 3 mg/kg. Similarly, oxotremorine (Fig. 4) decreased rates of cocaine self-administration with significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.01$), and a significant group by dose interaction ($P < 0.05$). The ED_{50} was 0.01 mg/kg (c.i. 0.001 to 0.19 mg/kg). There were no significant effects on nose poking of yoked control mice up to the dose of 0.03 mg/kg.

All antipsychotic agents significantly decreased rates of cocaine self-administration without significant effects on nose poking of yoked control mice (graphs not shown). Haloperidol displayed significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.01$), and a significant group by dose interaction ($P < 0.05$). The ED_{50} was 0.003 mg/kg (c.i. 0.001 to 0.009 mg/kg). Similarly, fluphenazine displayed significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.05$), and a significant group by dose interaction ($P < 0.01$). The ED_{50}

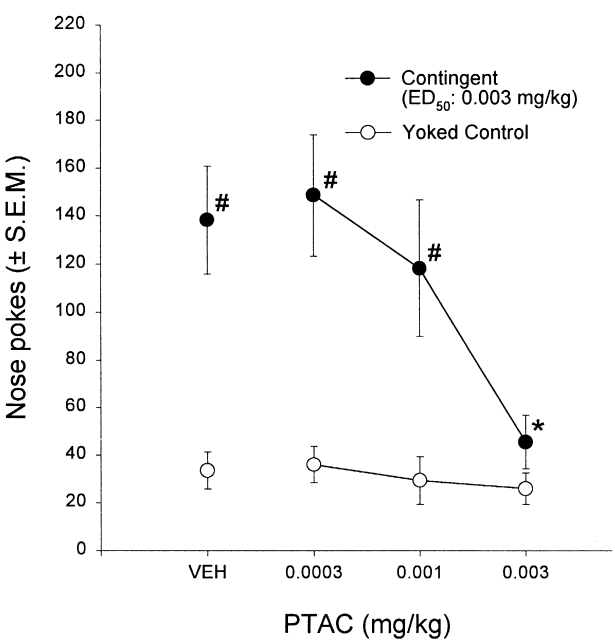

Fig. 2. PTAC induced inhibition of cocaine (0.1 mg/kg/infusion) self-administration. Shown are mean numbers of nose pokes (±S.E.M.) in contingent mice and yoked control mice (pairs of mice = 11–12), including the ED_{50} (mg/kg) for decrease in nose pokes of contingent mice. $^{*}P < 0.05$ compared to vehicle control, $\#P < 0.05$ compared to yoked control.

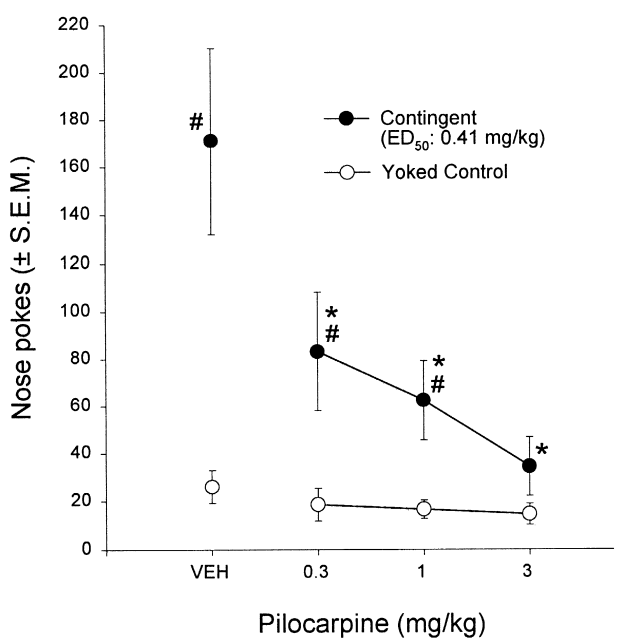

Fig. 3. Pilocarpine induced inhibition of cocaine (0.1 mg/kg/infusion) self-administration. Shown are mean numbers of nose pokes (±S.E.M.) in contingent mice and yoked control mice (pairs of mice = 10–14), including the ED_{50} for decrease in nose pokes of contingent mice. $^{*}P < 0.05$ compared to vehicle control, $\#P < 0.05$ compared to yoked control.

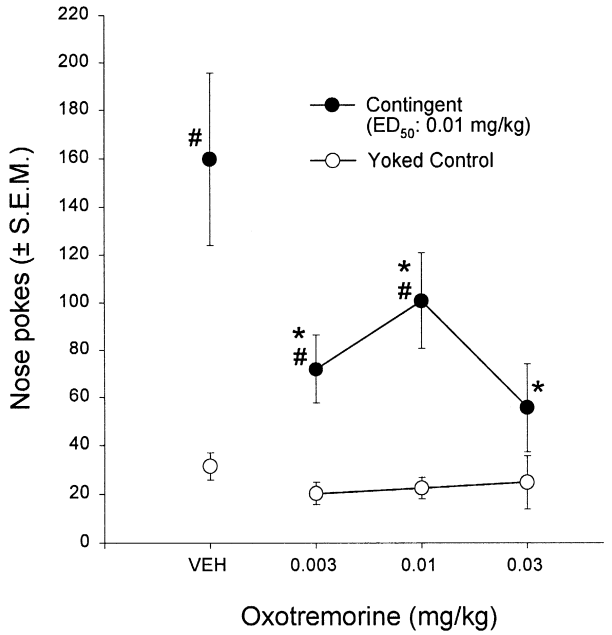

Fig. 4. Oxotremorine induced inhibition of cocaine (0.1 mg/kg/infusion) self-administration. Shown are mean numbers of nose pokes (±S.E.M.) in contingent mice and yoked control mice (pairs of mice = 10–14), including the ED_{50} for decrease in nose pokes of contingent mice. $^{*}P < 0.05$ compared to vehicle control, $\#P < 0.05$ compared to yoked control.

was 0.06 mg/kg (c.i. 0.03 to 0.13 mg/kg). Risperidone displayed significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.05$), and a significant group by dose interaction ($P < 0.05$). The ED_{50} was 0.08 mg/kg (c.i. 0.02 to 0.32 mg/kg). Clozapine displayed significant main effects on nose poking of group ($P < 0.001$), dose ($P < 0.001$), and a significant group by dose interaction ($P < 0.05$). The ED_{50} was 2.89 mg/kg (c.i. 0.9 to 9.3 mg/kg). Finally, olanzapine displayed significant main effects on nose poking of group, ($P < 0.001$), dose ($P < 0.01$), and a significant group by dose interaction ($P < 0.05$). The ED_{50} was 0.15 mg/kg (c.i. 0.07 to 0.34 mg/kg).

4. Discussion

The present data confirm previous similar findings from our laboratory that drug-naive mice dose-dependently self-administer intravenous infusions of cocaine (Rasmussen and Swedberg, 1998). However, the major finding was that the selective muscarinic receptor ligand PTAC, exhibiting partial agonist mode of action at muscarinic M_2 and M_4 and antagonist mode of action at muscarinic M_1, M_3 and M_5 receptor subtypes, dose-dependently decreased rates of intravenous self-administration of the indirect dopamine receptor agonist cocaine in drug naive mice. The more or less non-selective muscarinic receptor agonists oxotremorine and pilocarpine (Richards and Van Giersbergen, 1995; Schwarz et al., 1993) and the dopamine receptor antagonists olanzapine, clozapine, risperidone, fluphenazine and haloperidol (Bymaster et al., 1996; Roth et al., 1994; Schotte et al., 1996) induced similar dose-dependent decreases in rates of cocaine self-administration.

In the present study, PTAC had no significant effects on nose poking of yoked control mice up to at least 0.003 mg/kg, compared to vehicle control, suggesting that the dose-dependent decrease in nose poking of contingent mice was caused by a decrease in operant behaviour and not by non-specific drug-induced side effects. Based on the present data it is difficult directly to address whether the PTAC induced decrease in cocaine self-administration rates reflects a decrease or an enhancement of drug reward. However, it is well established that dopamine release in the nucleus accumbens is important for the reinforcing properties of drugs of abuse (Koob, 1992) and earlier results from our laboratory have shown than PTAC blocks Fos protein immunoreactivity in the rat nucleus accumbens, induced by another drug of abuse, the indirect dopamine receptor agonist d-amphetamine (Bymaster et al., 1998). This result as well as the observations that PTAC dose-dependently inhibited d-amphetamine (3 mg/kg, s.c.) and apomorphine (2 mg/kg., s.c.) induced hyperlocomotion (data not shown) and apomorphine (2 mg/kg, s.c.) induced climbing in mice (Bymaster et al., 1998), indicate that the effect of PTAC on cocaine self-administration reflects a decrease in drug reward. The locomotor activity data are in agreement with an earlier study reporting that oxotremorine inhibits d-amphetamine (2.5 mg/kg, s.c.) induced hyperlocomotion in rats (Wang and McGinty, 1996). In the Fos protein immunoreactivity study (Bymaster et al., 1998), equipotent inhibitory effects were obtained at the two doses of PTAC tested (0.01 and 0.1 mg/kg), indicating that even lower doses of PTAC may have been effective in this test. However, PTAC inhibited

Table 1
Rank order of ED_{50}'s for decrease in cocaine self-administration rates in drug-naive mice. Shown are comparative values for inhibition of apomorphine (2 mg/kg, s.c.) induced climbing in mice

	ED_{50} (mg/kg)	
	Decrease in cocaine self-administration rate	Inhibition of apomorphine induced climbing
PTAC	0.003	0.04[a]
Haloperidol	0.003	0.08[b]
Oxotremorine	0.01	0.09[b]
Fluphenazine	0.06	0.12[b]
Risperidone	0.08	0.15[b]
Olanzapine	0.15	0.42[b]
Pilocarpine	0.41	3.87[c]
Clozapine	2.89	3.1[b]

[a] Bymaster et al., 1998.
[b] Rasmussen et al., 1998b.
[c] Sauerberg et al., 1998.

d-amphetamine and apomorphine-induced hyperlocomotion as well as apomorphine-induced climbing in mice with ED_{50} values of 0.02 mg/kg, 0.02 mg/kg (data not shown) and 0.04 mg/kg (Bymaster et al., 1998), respectively. Thus, more potent effects of PTAC were obtained in the cocaine self-administration model (ED_{50}: 0.003 mg/kg) compared to its effects against d-amphetamine- and apomorphine-induced behaviours.

As mentioned above, the antipsychotic compounds presently investigated are all dopamine receptor antagonists, which may explain why they all decreased cocaine self-administration. We have earlier shown that PTAC can elicit central functional dopamine receptor antagonism (Bymaster et al., 1998, 1999; Fink-Jensen et al., 1998; Sauerberg et al., 1998) even though the compound has very low affinity for the dopamine transporter and for dopamine receptors (Bymaster et al., 1998). These findings may explain the present results: If the effects of cocaine self-administration are mediated by dopaminergic mechanisms, functional dopamine receptor antagonism by muscarinic agonists may decrease such self-administration. Also in mice, decrease in cocaine self-administration rates and inhibition of apomorphine induced climbing displayed similar rank order of potencies for the compounds presently investigated (Table 1). This suggests that similar mechanisms of action, i.e., dopaminergic, underlie inhibition of cocaine (dopamine re-uptake inhibitor) self-administration and inhibition of apomorphine (direct dopamine receptor agonist) induced climbing.

PTAC has very low affinity for the dopamine transporter and dopamine receptors (Bymaster et al., 1998), providing in vitro evidence for the functional nature of its dopamine receptor antagonism in functional assays. The precise mechanisms underlying such antagonism by muscarinic receptor agonists remain, however, to be elucidated. Occupancy of muscarinic autoreceptors on neurons of the laterodorsal tegmental nucleus (Ch6) has been suggested to inhibit acetylcholine release to dopaminergic neurons of the mesocorticolimbic pathway, resulting in decreased dopaminergic activity (Bymaster et al., 1999; Yeomans, 1995). This would also explain why scopolamine is self-administered in drug-naive mice (Rasmussen and Fink-Jensen, 2000) because a muscarinic receptor antagonist could, in contrast, disinhibit cholinergic autoreceptors on neurons of the Ch6 nucleus, resulting in increased dopaminergic activity. Alternatively, interaction with potential inhibitory muscarinic heteroreceptors on dopamine neurons in the ventral tegmental area has been suggested (Bymaster et al., 1999). Moreover, earlier results from our laboratory demonstrated that PTAC-induced inhibition of spontaneous locomotor activity in rats could be mimicked by bilateral injection of PTAC into the ventral striatum (Bymaster et al., 1998), indicating that the nucleus accumbens may be involved in certain of its pharmacological effects. The inhibitory effect of PTAC on d-amphetamine-induced Fos protein immunoreactivity in the nucleus accumbens (Bymaster et al., 1998) is in accordance with these results. Interestingly, Chapman et al. (1997) found that systemic administration of the non-specific muscarinic receptor antagonist scopolamine increased dopamine release in the striatum. Muscarinic M_4 receptors and dopamine D_1 receptors are colocalized on medium spiny striatal output neurons (for review, Di Chiara et al., 1994), and we have earlier suggested that the functional dopamine antagonism of PTAC could be explained by opposing effects of muscarinic M_4 receptors and dopamine D_1 receptors on second messenger systems in the striatum (Fink-Jensen et al., 1998).

In conclusion, the present results suggest that systemically administered muscarinic compounds with M_2/M_4 partial receptor agonist mode of action, not endowed with parasympathomimetic side effects, may be a novel approach in the medical treatment of cocaine abuse.

Parts of the present data were presented at the 28th annual meeting of Society for Neuroscience, Los Angeles, USA (Rasmussen et al., 1998a).

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