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The Muscarinic M_1/M_4 Receptor Agonist Xanomeline Exhibits Antipsychotic-Like Activity in *Cebus apella* Monkeys

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Xanomeline is a muscarinic M_1/M_4 preferring receptor agonist with little or no affinity for dopamine receptors. The compound reduces psychotic-like symptoms in patients with Alzheimer's disease and exhibits an antipsychotic-like profile in rodents without inducing extrapyramidal side effects (EPS) at therapeutically relevant doses. In the present study, we examined whether the xanomeline-induced functional dopamine antagonism found in rodent studies could also be observed in nonhuman primates. In addition, we studied whether the lack of EPS observed in rodents also applies to primates. To this end, we investigated the effects of xanomeline on the behavior induced by D-amphetamine and (−)-apomorphine in drug-naive *Cebus apella* monkeys. Antipsychotic compounds antagonize amphetamine-induced motor unrest and stereotypies in this species. Xanomeline inhibited D-amphetamine-induced motor unrest, stereotypies and arousal as well as apomorphine-induced stereotypies and arousal in drug-naive *Cebus apella* monkeys. Xanomeline did not induce EPS but vomiting occurred in some monkeys at high doses, in accordance with emetic events observed in Alzheimer patients following xanomeline administration. Even when xanomeline was tested in EPS-sensitized *Cebus apella* monkeys, EPS were not observed at the dose range of xanomeline used in the D-amphetamine-apomorphine combination study (0.5–3 mg/kg). However, when xanomeline was tested at 4 mg/kg, moderate dystonia was seen in two out of three monkeys. It is concluded that xanomeline inhibits D-amphetamine- and (−)-apomorphine-induced behavior in *Cebus apella* monkeys at doses that do not cause EPS. These data further substantiate that muscarinic receptor agonists may be useful in the pharmacological treatment of psychosis.
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INTRODUCTION

The dopamine hypothesis of schizophrenia has had a pronounced effect on strategies for the development of antipsychotics. All efficacious antipsychotic compounds available for clinical use antagonize central dopamine receptors and the average antipsychotic dose correlates with the dopamine receptor blocking capacity of the compound measured in rat brain homogenates (Seeman *et al*, 1976; Seeman and Van, 1994; Seeman and Kapur, 2000). Even though these compounds clearly show antipsychotic efficacy they are not capable of alleviating all schizophrenic symptoms and consequently novel approaches to the pharmacological treatment of schizophrenia are warranted.

Previous studies have shown that cholinergic ligands exhibit antipsychotic effects in schizophrenics. Pfeiffer and Jenney (1957) administered the cholinomimetic compound arecoline by subcutaneous injection to 23 schizophrenic patients and clinical improvement described as 'lucid intervals' was reported in more than 80% of the patients. However, potent parasympatomimetic side effects confound the clinical use of nonselective cholinergic receptor agonists. More recently, it has been reported that acetylcholinesterase inhibitors as well as the muscarinic M_1/M_4 preferring receptor agonist xanomeline reduce psychotic-like symptoms in patients with Alzheimer's disease (Bodick *et al*, 1997; Cummings, 2000; White and Cummings, 1996). Even though these newer compounds have considerably less parasympatomimetic side effects, nausea and vomiting have been reported in Alzheimer patients taking these drugs (Doody *et al*, 2001; Bodick *et al*, 1997).

In the central nervous system, muscarinic receptors are involved in various functions, for example, motor control, nociception, and cognition (Felder *et al*, 2000). In the periphery, muscarinic receptors regulate heart rate, glandular secretion, and smooth muscle contraction (Eglen *et al*, 2001; Felder *et al*, 2000). Five muscarinic receptor subtypes (M_1–M_5) have been cloned and these receptor subtypes are widely distributed in the central nervous system including the prefrontal cortex and limbic areas, such as the nucleus accumbens, hypothesized to be associated with schizophre-

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nia (Levey *et al*, 1991). In addition, functional as well as anatomical studies suggest considerable interaction between the cholinergic and the dopaminergic systems (Di Chiara *et al*, 1994; Gomeza *et al*, 1999; Hartvig *et al*, 2002; Weiner *et al*, 1990).

Studies in rodents show that muscarinic receptor agonists can inhibit behavioral effects, as well as the Fos protein upregulation, induced by dopamine receptor stimulation (Shannon *et al*, 1999; Bymaster *et al*, 1998; Fink-Jensen *et al*, 1998). Recently, it was found that xanomeline, a muscarinic M_1/M_4 preferring receptor agonist, exhibits functional dopamine antagonism in rodents despite its lack of affinity for the dopamine transporter and dopamine receptors. Xanomeline inhibited apomorphine-induced climbing, dopamine agonist-induced rotation, and dopamine cell firing in the ventral tegmental area (Shannon *et al*, 2000). Xanomeline also inhibited conditioned avoidance responding (Shannon *et al*, 2000), a traditional preclinical test used to predict antipsychotic activity (Arnt, 1982; Arnt *et al*, 1982). Furthermore, similar to the effects of the antipsychotic compounds clozapine and olanzapine, xanomeline increased extracellular levels of dopamine and immediate-early gene expression, that is, Fos, in the rat prefrontal cortex (Perry *et al*, 2001). Finally, xanomeline has been shown to reverse apomorphine-induced reduction in prepulse inhibition in rats (Stanhope *et al*, 2001). Prepulse inhibition of the startle response has been found to be impaired in schizophrenic patients (Braff *et al*, 1978, 1992; Cadenhead *et al*, 2000; Glenthoj *et al*, 2001; Parwani *et al*, 2000), establishing this sensorimotor gating deficit as a central impairment of information processing in schizophrenia.

In the present study, we examined whether the xanomeline-induced functional dopamine inhibition observed in rodents is also found in nonhuman primates. To this end, we investigated the effects of xanomeline on the behavior induced by the dopamine releaser D-amphetamine and the nonselective direct dopamine receptor agonist (−)-apomorphine in drug-naive *Cebus apella* monkeys. Several studies from our laboratory have shown that drugs with antipsychotic activity antagonize amphetamine- and/or apomorphine-induced behaviors in *Cebus apella* monkeys (eg Gerlach and Casey, 1990; Peacock and Gerlach, 1993, 1999). In order to investigate the possible side effects of xanomeline, its effects were studied in drug-naive monkeys and in monkeys sensitized to extrapyramidal side effects (EPS) by earlier long-term treatment with classical antipsychotics. EPS observed in the Cebus monkeys are very similar to EPS induced by antipsychotics in humans and this model has shown to be predictive of EPS liability in the clinic (Peacock and Gerlach, 1993, 1999). In addition, possible gastrointestinal side effects such as emesis that cannot be properly examined in rodents can be investigated in monkeys.

MATERIALS AND METHODS

Animals

Seven male *Cebus apella* monkeys were used for the evaluation of the antidopaminergic effect and side effect profile of xanomeline. All seven monkeys received all treatments with at least 1 week between tests. Before start of the present experiment, the monkeys had been tested with single doses of D-amphetamine, (−)-apomorphine, and some selective dopamine ligands but had never received antipsychotics and never experienced EPS. For further evaluation of the EPS potential of xanomeline, the compound was tested in three monkeys sensitized to drug-induced EPS by previous chronic treatment with antipsychotic drugs (Peacock and Gerlach, 1999). The monkeys were housed in separate cages in a temperature-regulated environment at a 12-h light/dark cycle. The experimental procedures carried out in this study were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and with the Danish law regulating experiments on animals.

Compounds and Design

The test drugs were D-amphetamine sulfate (Nordisk Droge & Kemikalie A/S, Denmark), (−)-apomorphine hydrochloride (Nordisk Droge & Kemikalie A/S, Denmark), and xanomeline (synthesized at Eli Lilly, USA). D-Amphetamine was dissolved in physiological saline, (−)-apomorphine was dissolved in sterile water, and xanomeline in peanut oil. Physiological saline was used as vehicle for D-amphetamine and (−)-apomorphine, and peanut oil was used as vehicle for xanomeline. For the initial evaluation of side effects, xanomeline was tested alone in doses of 0.5, 1, 2, and 3 mg/kg. For the evaluation of antiamphetamine effects xanomeline was tested in doses of 1, 2, and 3 mg/kg in combination with 0.5 mg/kg of D-amphetamine. Owing to the induction of emesis in several monkeys when 3 mg/kg xanomeline was combined with D-amphetamine (see 'Results' for details), a lower dose range of 0.5, 1, and 2 mg/kg xanomeline was used in combination with 0.375 mg/kg (−)-apomorphine for the evaluation of antiapomorphine effects. Xanomeline or peanut oil was injected s.c. at approximately 9 am. Pretreatment time before injection of D-amphetamine (s.c.) was 60 min. Pretreatment time before injection of (−)-apomorphine (s.c.) was 120 min. On test days, the monkeys did not have access to food or water prior to or during the experiment.

Evaluation

The monkeys were videotaped in 90-s sessions at specific time points throughout the test sessions. The videotapes were rated for D-amphetamine- and (−)-apomorphine-induced behaviors and EPS by two experienced raters by means of a rating scale adapted from Peacock *et al* (1999) and Peacock and Gerlach (1999) (Table 1). When xanomeline was administered alone the monkeys were videotaped at $t_{xan} = 30$, 60, 75, 90, 105, 120, 150, 180, 240, and 300 min after injection (t_{xan} = time after xanomeline administration). For the combination studies, the monkeys were videotaped every 30 min in the time period between the first and the second drug injection. After administration of D-amphetamine or (−)-apomorphine, the monkeys were recorded at $t_{amp}/t_{apo} = 15$, 30, 45, 60, 90, 120, 180, and 240 min. Oral dyskinesia was measured in counts per 90 s. The severity of other behaviors and symptoms were rated on a scale ranging from 0 (not present) to 6 (extreme presence). The rated behaviors and symptoms were unrest, stereotypies, arousal, sedation, bradykinesia, and dystonia (see Table 1).

Table 1 Description of Behaviors and Rating Scales

Behavior	Description	Scale
Unrest	Restlessness including fidgeting and frequent changes of direction of movement or frequent changes between different behaviors	0–6
Stereotypies	Repeated futile movements, abrupt whole body movements and aborted behaviors	0–6
Arousal	Degree of vigilance ranging from not awake to extreme vigilance in relation to self or the environment	0–6
Sedation	Degree of drowsiness ranging from fully awake to heavy sleeping (cannot be awakened by gross stimuli)	0–6
Oral dyskinesia	Jaw movements and tongue protrusions	Counts/90 s
Bradykinesia	Slow and/or stiffened movements ranging from normal tempo and flexibility to fixed maintained postures	0–6
Dystonia	Clonic movement of head, neck, limbs, and trunk. Gaping and grimacing	0–6

Table 2 Overview of Xanomeline Side Effects

Treatment	Salivation	Emetic events (vomiting)	Sedation $2 \leqslant X \leqslant 5$
D-amphetamine 0.5 mg/kg (amp)	—	—	—
(−)apomorphine 0.375 mg/kg (apo)	—	—	—
Vehicle (veh)	—	—	—
Xanomeline 0.5 mg/kg/veh	—	—	—
Xanomeline 0.5 mg/kg/apo	—	—	—
Xanomeline 1.0 mg/kg/veh	—	—	2 in 7
Xanomeline 1.0 mg/kg/amp	—	—	—
Xanomeline 1.0 mg/kg/apo	1 in 7	—	2 in 7
Xanomeline 2.0 mg/kg/veh	—	1 in 7	4 in 7
Xanomeline 2.0 mg/kg/amp	6 in 7	1 in 7	3 in 6
Xanomeline 2.0 mg/kg/apo	3 in 7	2 in 7	5 in 7
Xanomeline 3.0 mg/kg/veh	2 in 7	2 in 7	6 in 7
Xanomeline 3.0 mg/kg/amp	6 in 7	5 in 7	4 in 7

Data Analysis

The seven monkeys all received all treatments and they were used as their own controls. The data were analyzed for overall treatment effects at each time point by means of the nonparametric Friedman's test for repeated measures. Student–Newman–Keuls multiple comparison procedure was used to analyze for specific dose effects. Data collected at $t_{xan} = 60$, 90, and 180 min are presented when xanomeline was administered alone. Data collected at $t_{amp} = 30$, 60, 90, and 180 min ($t_{xan} = 90$, 120, 150, and 240 min) are presented for the D-amphetamine/xanomeline study. (−)-Apomorphine has a short-lasting effect and for that reason data collected at $t_{apo} = 30$ and 60 min ($t_{xan} = 150$ and 180 min) are presented for the (−)-apomorphine/xanomeline study. The accepted level of significance was $p < 0.05$ for all tests.

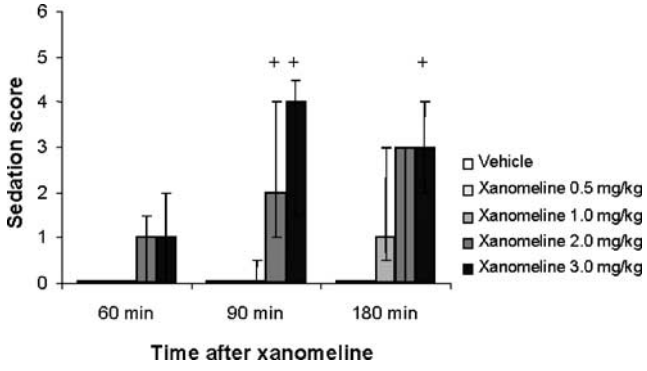

Figure 1 Sedation after injection of xanomeline ($n = 7$). Sedation was rated on a scale ranging from 0 to 6. Data are shown as medians ± quartiles. $^{+}p < 0.05$ relative to vehicle (Student–Newman–Keuls test).

RESULTS

Xanomeline

Xanomeline produced sedation at all three test times ($p < 0.01$ for all). As shown in Figure 1, only the highest doses were significantly different from vehicle. At $t_{xan} = 90$ and 180 min there was a concomitant dose-dependent decrease in unrest ($p < 0.05$ and $p < 0.01$, respectively) and in arousal ($p < 0.01$ for both). Stereotypies, oral dyskinesia, bradykinesia, or dystonia were not observed at any of the tested doses. Salivation and vomiting were observed in two monkeys after 3 mg/kg xanomeline. Salivation was not observed at lower doses, while one monkey vomited after 2 mg/kg xanomeline (see Table 2).

Xanomeline and D-Amphetamine

Unrest was significantly affected by drug treatment at all four test times ($t_{amp} = 30$ and 60 min: $p < 0.01$, $t_{amp} = 90$ and 180 min: $p < 0.05$). D-Amphetamine specifically increased unrest at $t_{amp} = 30$, 60, and 180 min. Concurrent administration of xanomeline (1, 2, and 3 mg/kg) inhibited the D-amphetamine-induced unrest as illustrated in Figure 2a. D-Amphetamine-induced stereotypies were counteracted by all tested doses of xanomeline at all four time points ($p < 0.01$ for all), as shown in Figure 2b. As shown in Figure 2c, arousal was likewise significantly increased by D-amphetamine and the effect was counteracted by xanomeline at all four test times ($p < 0.01$ for all). Slight sedation was observed after administration of 2 and 3 mg/kg of

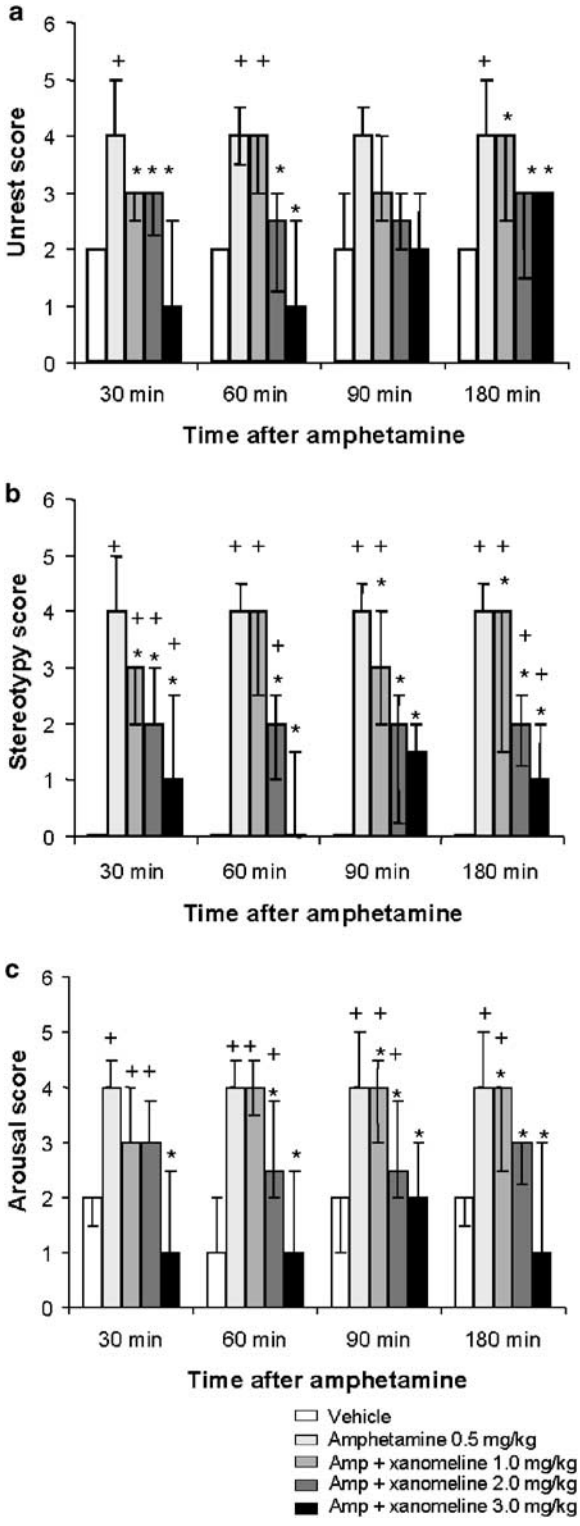

Figure 2 Effect of xanomeline on amphetamine-induced unrest (a), stereotypies (b), and arousal (c) ($n=7$). The behaviors were rated on a scale ranging from 0 to 6. Data are shown as medians ± quartiles. Amp = 0.5 mg/kg D-amphetamine. $^{+}p<0.05$ relative to vehicle, $^{*}p<0.05$ relative to amphetamine (Student–Newman–Keuls test).

xanomeline in combination with D-amphetamine (data not shown), but the effect was only significant at $t_{amp}=30$ and 60 min ($p<0.05$). Neither D-amphetamine alone nor the combination of D-amphetamine with xanomeline induced

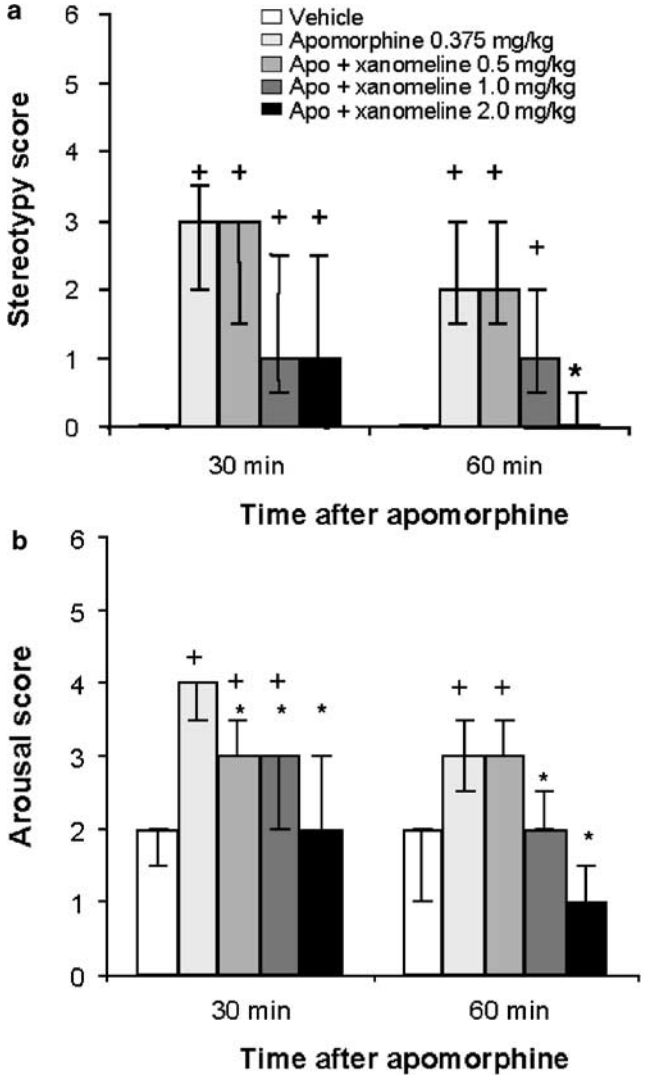

Figure 3 Effect of xanomeline on apomorphine-induced stereotypies (a) and arousal (b) ($n=7$). The behaviors were rated on a scale ranging from 0 to 6. Data are shown as medians ± quartiles. Apo = 0.375 mg/kg (−)-apomorphine. $^{+}p<0.05$ relative to vehicle, $^{*}p<0.05$ relative to apomorphine (Student–Newman–Keuls test).

oral dyskinesia, bradykinesia, or dystonia. In combination with amphetamine, one monkey vomited after 2 mg/kg and five monkeys vomited after 3 mg/kg of xanomeline. Salivation was observed in six monkeys at both of these doses (see Table 2).

Xanomeline and (−)-Apomorphine

(−)-Apomorphine treatment did not significantly increase unrest (data not shown) but induced stereotypies at $t_{apo}=30$ min ($p<0.05$) and 60 min ($p<0.01$) as shown in Figure 3a. This effect was significantly counteracted by 2 mg/kg of xanomeline at $t_{apo}=60$ min. Arousal was also significantly increased by (−)-apomorphine at both time points ($p<0.01$) and this effect was inhibited by all three doses of xanomeline (0.5, 1, and 2 mg/kg) at $t_{apo}=30$ min and by 1 and 2 mg/kg xanomeline at $t_{apo}=60$ min (Figure 3b). Sedation was observed after 2 mg/kg xanomeline at both time points ($p<0.01$, data not shown). (−)-Apomor-

phine-induced oral dyskinesia did not reach the level of significance ($p > 0.05$, data not shown). However, when (−)-apomorphine was combined with the lowest dose of xanomeline (0.5 mg/kg), oral dyskinesia at $t_{apo} = 60$ min was significantly increased above basal level (ie the level observed when no drugs were given). However, when (−)-apomorphine was administered together with higher doses of xanomeline, oral dyskinesia was at basal level. Salivation was observed in one monkey when (−)-apomorphine was combined with 1 mg/kg xanomeline and in three monkeys when combined with 2 mg/kg xanomeline. The latter dose also produced vomiting in three monkeys (see Table 2).

Xanomeline in EPS-Sensitive Monkeys

When xanomeline was tested in three EPS-sensitized monkeys, EPS were observed at the highest dose of 4 mg/kg xanomeline, but not in the dose range used in the dopamine agonist/xanomeline combination experiments (0.5–3 mg/kg). At 4 mg/kg, two animals developed dystonia with a score of 4 (out of six possible points, see Table 1). One of these displayed oral dyskinesia before the onset of dystonia. One monkey did not display any motor side effects.

DISCUSSION

In the present study, D-amphetamine induced behavioral unrest, stereotypies, and arousal in *Cebus apella* monkeys, while (−)-apomorphine induced stereotypies and arousal. These effects were antagonized by the muscarinic M_1/M_4 receptor agonist xanomeline in accordance with studies demonstrating functional antidopaminergic effects in rodents (Shannon *et al*, 2000; Stanhope *et al*, 2001), supporting the notion of an antipsychotic potential of xanomeline.

To our knowledge, the present study demonstrates for the first time that dopamine agonist-induced behaviors in monkeys can be inhibited by a cholinergic (muscarinic) receptor agonist. Several muscarinic receptor agonists, for example, milameline (Schwarz *et al*, 1999), sabcomeline (Harries *et al*, 1998), and WAY-132983 (Bartolomeo *et al*, 2000) have been tested in monkeys. The experiments focused on cognition, while possible antidopaminergic effects of these compounds have not been addressed. In one study, spontaneous movements were reduced following administration of the cholinesterase inhibitor tacrine or the muscarinic M_1 receptor agonist AF102B (Fitten *et al*, 1999). However, the compounds were not tested in combination with any direct or indirect dopamine receptor agonists.

The antidopaminergic effects of xanomeline in primates are in accordance with an unpublished clinical trial evaluating the efficacy of xanomeline in 20 inpatients with a diagnosis of either schizophrenia or schizoaffective disorder (Shekhar *et al*, 2001). In this double-blind, placebo-controlled, randomized clinical trial a 1-week placebo lead-in was followed by xanomeline or placebo treatment for 3 additional weeks. Employing the CGI definition of responders (CGI $\leqslant 3$) the patients treated with xanomeline did significantly better than the placebo treated group. Interestingly, even though gastrointestinal side effects were observed, they occurred to a considerably lesser extent than in the Alzheimer patient study (Bodick *et al*, 1997).

In the present study, we have investigated the antidopaminergic effects of xanomeline most likely predicting efficacy against the positive symptoms of schizophrenia. Antipsychotic treatment is generally effective in alleviating positive symptoms of schizophrenia. However, effects on negative symptoms and cognitive deficits are more modest and classical antipsychotics seem to have minimal effects and may even worsen the symptoms (Kane and Freeman, 1994; Meltzer and McGurk, 1999). Even though newer antipsychotics have more pronounced effects against negative symptoms and cognitive deficits compared to most of the older compounds, they do not eliminate these symptoms (Meltzer *et al*, 1999; Meltzer and McGurk, 1999). As xanomeline improved cognitive function in patients with Alzheimer's decease (Bodick *et al*, 1997), a positive effect on cognition in schizophrenic patients could be anticipated. However, whether xanomeline is effective against cognitive deficits and negative symptoms in schizophrenic patients has to be investigated in clinical trials.

Xanomeline is a direct muscarinic M_1/M_4 preferring receptor agonist with little or no binding affinity for dopamine receptors (Bymaster *et al*, 1994, 1997). In mice and rats xanomeline shows functional dopamine antagonism and an antipsychotic-like profile (Shannon *et al*, 2000; Stanhope *et al*, 2001). In man xanomeline reduces psychotic-like symptoms, for example, hallucinations and delusions, similar to cholinesterase inhibitors, in patients with Alzheimer's disease (Bodick *et al*, 1997). We have earlier reported functional dopamine antagonism of the muscarinic M_2/M_4 receptor partial agonist PTAC in rats (Bymaster *et al*, 1998) and suggested that this effect might result from an interaction between dopamine D_1 and muscarinic M_4 receptors at the striatal level (Fink-Jensen *et al*, 1998). A similar interaction may be involved in the antidopaminergic effects of the muscarinic M_1/M_4 receptor agonist xanomeline. In the rat basal ganglia, muscarinic and dopaminergic receptors are colocalized on medium spiny GABAergic projection neurons. The colocalization of dopamine D_1 receptors and muscarinic M_4 receptors are of special interest. Dopamine D_1 receptors are positively coupled to adenylate cyclase whereas M_4 receptors are negatively coupled to this enzyme (Hulme *et al*, 1990). In agreement with these biochemical observations, behavioral studies have demonstrated that muscarinic M_4 knockout mice exhibit increased locomotor activity and are hypersensitive to dopamine D_1 receptor stimulation (Gomeza *et al*, 1999). Whether the same interaction exists in the primate basal ganglia is at present unknown. However, most GABAergic projection neurons in the monkey striatum express either dopamine D_1 or D_2 receptor mRNA (Aubert *et al*, 2000). Moreover, muscarinic M_4 receptors have been localized in the human striatum (Flynn *et al*, 1995). In addition, PET studies have shown that [^{11}C]xanomeline binds in the monkey striatum (Farde *et al*, 1996). An interaction between the dopaminergic and the cholinergic system might well take place in the primate striatum in a manner similar to that observed in rat brains.

The behavioral parameter 'arousal' comprises increased vigilance and attention that appears different from the control situation. Examples of increased arousal are fixated

staring at a specific point in space, rapid and continuous scanning of the environment, and increased reactivity to disturbances and noise. We have earlier reported that monkeys, following injection of apomorphine, 'were more reactive and alert to sounds outside the cage' (Gerlach *et al*, 1984). In a later study apomorphine was shown to increase 'reactivity' in monkeys when rated on a 7-point reactivity scale (0–6) (Lublin *et al*, 1992). A similar effect was observed following administration of the dopamine D_2 receptor agonist quinpirole but not following administration of the dopamine D_1 receptor agonists SKF 38393, SKF 75670, or SKF 81297 (Lublin *et al*, 1992; Peacock *et al*, 1990), indicating that this reactivity is mediated through dopamine D_2 receptors. Since arousal, as measured in our study, is very similar to the above-mentioned reactivity, xanomeline-induced inhibition of arousal may involve an interaction with dopamine D_2-mediated effects. In contrast to PTAC, xanomeline stimulates M_1 receptors and M_1 receptor knockout mice show increased spontaneous locomotor activity and increased locomotor response to amphetamine compared with their wild-type littermates (Gerber *et al*, 2001). Moreover, *in situ* hybridization studies of the rat basal ganglia have shown that all striatal cells expressing D_2 mRNA also express M_1 mRNA (Bernard *et al*, 1992; Weiner *et al*, 1990). Consequently, besides the M_4/D_1 interaction, proposed previously, an interaction between M_1 receptors and D_2 receptors may exist at the cellular level in the striatum. However, to our knowledge such an interaction has not been demonstrated.

At high doses xanomeline induced salivation and vomiting in some monkeys (see Table 2) but did not produce EPS at doses required to antagonize D-amphetamine and (−)-apomorphine effects. Salivation is recognized as a cholinergic side effect and has also been observed in rats after injection of M_1 receptor agonists including xanomeline (Bartolomeo *et al*, 2000). The emetic events are in accordance with clinical observations in Alzheimer patients where adverse events were predominantly gastrointestinal side effects (Bodick *et al*, 1997). However, potent antidopaminergic effects were observed in monkeys at 1 mg/kg of xanomeline, a dose that did not induce side effects. At high doses xanomeline induced sedation, to a greater extent when tested alone than in combination with the dopaminergic drugs. EPS were not observed in the drug-naive monkeys, which is in accordance with a previous study in rats (Bymaster *et al*, 1998). Even in the EPS-sensitized monkeys, that is, monkeys that have been sensitized to drug-induced EPS by prolonged exposure to dopamine antagonists, EPS were not observed in the dose range demonstrating antidopaminergic effects (0.5–3 mg/kg). However, when the dose of xanomeline was increased to 4 mg/kg, dystonia was observed. In comparison, the classical antipsychotic haloperidol produced dystonia in four out of seven monkeys at 0.015 mg/kg, which was also the minimal effective dose to reduce amphetamine-induced behavior. The therapeutic index between the minimal dose inducing dystonia and the minimal antiamphetamine dose was thus 1. The atypical antipsychotic clozapine produced other side effects, but did not induce dystonia, while quetiapine produced dystonia at high doses. The therapeutic index of these drugs were 4 and 3, respectively (Peacock and Gerlach, 1999). At clinically relevant doses (75–750 mg daily) quetiapine did not cause EPS in schizophrenic patients (Arvanitis and Miller, 1997). Like quetiapine xanomeline produced dystonia at a high dose (4 mg/kg) with a therapeutic index of 4.

In conclusion, despite its lack of binding to dopamine receptors, the direct muscarinic M_1/M_4 preferring receptor agonist xanomeline inhibited D-amphetamine- and (−)-apomorphine-induced psychotic-like behavior in *Cebus apella* monkeys at doses that did not cause EPS. Even though emetic events were observed, the doses of xanomeline that induced vomiting could be separated from the lowest antiamphetamine and antiapomorphine doses. The results are in accordance with earlier studies in rodents (Shannon *et al*, 2000; Stanhope *et al*, 2001) and humans (Bodick *et al*, 1997), and further substantiate that muscarinic receptor agonists may serve as a new tool in the pharmacological treatment of psychosis.

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