Pharmacology Biochemistry and Behavior, Vol. 58, No. 1, pp. 103–108, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(96)00478-9

Dopaminergic and Cholinergic Interaction in Cataleptic Responses in Mice

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Received 13 March 1995; Revised 17 September 1996; Accepted 17 September 1996

USHIJIMA, I., M. KAWANO, H. KANEYUKI, K. USAMI, M. SUETSUGI, H. HIRANO, Y. MIZUKI AND M. YAMADA. *Dopaminergic and cholinergic interaction in cataleptic responses in mice.* PHARMACOL BIOCHEM BEHAV **58**(1) 103–108, 1997.—The cataleptogenic effects of haloperidol, a dopamine D2 receptor antagonist; SCH23390, a D1 receptor antagonist; physostigmine, a cholinesterase inhibitor; and pilocarpine, a muscarinic M1 receptor agonist, were challenged by pretreatment of mice with SKF38393, a dopamine D1 receptor agonist; apomorphine, a dopamine D1/D2 receptor agonist (mainly D2 receptor); pirenzepine, a muscarinic M1 receptor antagonist; and scopolamine, a muscarinic M1/M2 receptor antagonist. The effect of physostigmine and pilocarpine on haloperidol and SCH23390 cataleptic responses was also examined. Each of the challenging agents blocked one or more of the cataleptogenic agents, but only scopolamine blocked all four. Pirenzepine blocked cataleptic responses induced by SCH23390 and pilocarpine, but not those by haloperidol and physostigmine. The results of this study suggest that the action of physostigmine (endogenous acetylcholine) on M2 receptors might be more potent than that on muscarinic M1 receptors. A further interesting observation was that the haloperidol-induced catalepsy was enhanced by physostigmine pretreatment, but not by pilocarpine pretreatment, whereas the SCH23390-induced catalepsy showed the opposite spectrum of enhancement by the two cholinergic agonists. We conclude that, although the four cataleptogenic agents act via the dopaminergic-cholinergic systems, their pharmacological differences may be due largely to the different receptor subtypes that are involved in the mediation of catalepsy produced by each agent. Thus, dopamine receptors not only influence the cholinergic muscarinic receptors, but muscarinic M1 and M2 receptors also might mediate dopamine D1 and D2 receptor responses, respectively. The results suggest that there are, at the least, relationships between muscarinic M1 receptors and dopaminergic D1 receptors, and between muscarinic M2 receptors and dopaminergic D2 receptors. Dopamine D1 and D2 receptors may interact in a synergistic fashion on dopaminergic systems, but act independently of each other in influencing other system such as cholinergic neurons. © 1997 Elsevier Science Inc.

Catalepsy Haloperidol SCH23390 Physostigmine Pilocarpine Mice

IT has been postulated that neuroleptic catalepsy results from the blockade of dopamine receptors in the striatum (4,7) and nucleus accumbens (7). The ability of neuroleptics to elicit catalepsy has been shown to correlate with their potency in ameliorating the symptoms of neuropsychiatric illness, and the antipsychotic action of the drugs in turn correlates with their binding potency on the D2 dopamine receptors (17). The D1 receptor antagonist SCH23390 also induces catalepsy in animals (11,12,14). The cataleptic effect induced by SCH23390 is potentiated by D2 receptor antagonist spiroperidol or haloperidol, and inhibited by D2 agonist apomorphine, i.e., the cataleptic responses induced by D1 and D2 receptor antagonists share common features (12,14,20). D1 and D2 receptor antagonists potentiated each other's effect in producing catalepsy, i.e., the presence of synergistic effects between D1 and D2 receptor blockade (24). It appears that dopamine D1 and D2 receptors are closely associated either on the same neurons or on the same effector system, because specific D1 and D2 antagonists are equally effective in blocking the synergistic effects (hyperlocomotion and stereotypy) of the combination of SKF38393, a D1 receptor agonist, and quinpirole, a D2 receptor agonist (19). Furthermore, selective D2 receptor agonists cannot reverse

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the akinesia produced by reserpine unless D1 receptors are concurrently stimulated by D1 receptor agonists (5,8,25). On the other hand, the antinociceptive effect of cocaine in rats is modified in an opposite manner by the dopamine agonists, i.e., the D1 agonist increases, and D2 agonist decreases, the antinociceptive effect that is mediated by NMDA system. These effects of the dopamine agonists are reversed by their respective antagonists. Because of this opposing nature of the D1 and D2 systems, it was suggested that these two receptor subtypes are independent of each other in influencing cocaine-induced antinociception (21). Furthermore, with regard to the interaction between opioid (dynorphin) and the dopamine systems, there is evidence that neostriatal dynorphin levels are decreased by D2 agonists, whereas stimulation of the D1 receptors result in an increase in nigral dynorphin levels (13). This evidence suggests that dopamine D1 and D2 receptors can interact in either a synergistic fashion or an antagonistic fashion.

It is well established that an extrapyramidal syndrome results from a disturbance of a dopaminergic-cholinergic balance in basal ganglia. Under normal conditions, dopamine, acting as an inhibitory transmitter, functions to regulate the activity of cholinergic interneurons in neostriatum (16). Neuroleptics, such as haloperidol, by blocking dopamine receptors on cholinergic cell bodies and/or dendrites, reduce dopamine's inhibitory control of cholinergic neuron activity, thus causing an overactivity of cholinergic neurons, which in turn sends abnormal messages to thalamus and other areas controlling motor function. For this reason, anticholinergic drugs, by antagonizing the extra acetylcholine released from cholinergic neuron terminals (3,16), reduces much of the symptoms of neuroleptic-induced extrapyramidal syndrome. On the other hand, tardive dyskinesia induced by long-term treatment with neuroleptics appears to involve up-regulation of dopamine receptors in neostriatum resulting from their prolonged blockade. Upon withdrawal of the neuroleptic, the increased number of receptors exhibit a supersensitive response to released dopamine. Tardive dyskinesia is therefore a condition of excessive dopamine activity in neostriatum, resulting from an excessive inhibition of acetylcholine release from cholinergic interneurons. For this reason, anticholinergic antiparkinson drugs are ineffective in reducing the symptoms; in fact, they may worsen the condition. It would thus be of great clinical benefit to develop antipsychotic agents that did not also promote such changes in receptor sensitivity. Although the clinical potency of neuroleptics correlates with their affinity for D2 receptors, the therapeutic efficacy of neuroleptics in the treatment of schizophrenia may also be caused by subsensitivity of D1 receptors. The detailed interaction between dopaminergic and cholinergic systems should be clarified.

Cholinomimetics can antagonize some of the behavioral effects of dopamine agonists and enhance the effects of dopamine antagonists (6,22). More recently, it was shown that the cataleptic action of SCH23390 was inhibited by muscarinic M1/M2 receptor antagonist atropine, unaffected by nicotinic receptor antagonist mecamylamine and markedly potentiated by pilocarpine (9,10). Haloperidol catalepsy was inhibited by hemicholinium, an acetylcholine synthesis inhibitor, but not by mecamylamine (9). Thus, the cholinergic role in cataleptic effects induced by dopamine antagonists may involve predominantly muscarinic systems. However, pilocarpine was unable to potentiate the action of fluphenazine or spiroperidol significantly (20). Accordingly, dopamine D1 and D2 receptors might also act independently of each other in influencing cholinergic systems (muscarinic M1 and M2 receptors), like NMDA (21) and opioid (13) systems. The present studies were designed to clarify the relationship between dopaminergic D1 or D2 receptor and cholinergic M1 or M2 receptor systems involved in cataleptic responses induced by haloperidol, SCH23390, physostigmine, or pilocarpine.

METHOD

Animals

Healthy male ddY albino mice (7 week-old mice; 30–35 g), purchased from Kyudo Animal Laboratory (Kumamoto, Japan), were allowed free access to food and water. The mice were housed and all trials were conducted at an environmental temperature of 23 ± 1°C, with a 12 L:12 D cycle (0700–1900). All experiments were performed by using 8-week-old mice weighing 35–40 g.

Measurement of Catalepsy

Catalepsy responses were measured using the suspended bar method. Mice were placed individually on a plastic board (25 × 35 cm) with a horizontal wire bar (3 mm o.d., covered with vinyl) suspended 5 cm above the floor. The animals' front paws were placed gently on the bar, and the time taken for the mouse to remove both paws from the bar was recorded.

Administration of Drugs

To observe drug effects on cataleptic responses, we selected the challenge dose of SCH23390 (0.3 mg/kg), haloperidol (0.3 mg/kg), physostigmine (0.75 mg/kg), or pilocarpine (50 mg/kg), and the time intervals used were taken from previous reports (9,11,12,23) in which the dose response effects of these drugs on the cataleptic response were observed. Mice received physostigmine (0.75 mg/kg IP) or pilocarpine (50 mg/kg IP) 60 min after pretreatment with N-methyl atropine (2.0 mg/kg IP). We administered saline (10 ml/kg), SKF38393 (1.0–10 mg/kg), apomorphine (0.01–0.5. mg/kg), or scopolamine (0.01–0.5 mg/kg) 15 min before, or pirenzepine dihydrochloride (1.0–20 mg/kg) 45 min before, SCH23390 (0.3 mg/kg IP), and simultaneously and 30 min before the other cataleptogenic agents, respectively. We observed cataleptic responses 15 min after SCH23390 (0.3 mg/kg) and 30 min after the other cataleptogenic agents. We did not repeat tests on the same mice.

Drugs

The drugs used were (R)-(+)-SCH23390 (RBI, Natick, MA, USA), haloperidol hydrochloride, physostigmine sulfate (Wakoh, Osaka, Japan), pilocarpine hydrochloride (Wakoh, Osaka, Japan), N-methyl atropine nitrate (Sigma, St. Louis, MO, USA), SKF38393 (RBI, Natick, MA), apomorphine hydrochloride (Sigma), scopolamine hydrobromide (Sigma), pirenzepine dihydrochloride (Sigma) and N-methyl atropine nitrate (Sigma). All drugs were dissolved in saline, and an equal volume of vehicle (10 ml/kg) was injected IP except for pirenzepine, which was given IV. Doses are expressed as authentic substances.

Statistics

Catalepsy scores are expressed as mean ± SEM. Each group consisted of 8–11 animals. The significance of differences between data for saline- and cataleptogenic agent-injected groups was analyzed using Mann–Whitney *U*-tests. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Effects of Dopamine Receptor Agonists on Cataleptic Responses Induced by SCH23390 or Haroperidol

As shown in Fig. 1, pretreatment with SKF38393 (1.0–10 mg/kg IP) did not affect haloperidol (0.3 mg/kg) catalepsy, but inhibited SCH23390 (0.3 mg/kg) catalepsy in a U-shape fashion, the significant doses being at 1.0, 2.5, and 5.0 mg/kg (Fig. 1A).

Apomorphine (0.01–1.0 mg/kg IP) itself induced cataleptic responses and exhibited a small bell-shaped dose-response curve. Apomorphine at 0.01–0.1 mg/kg altered the haloperidol catalepsy response in a bell-shaped manner, at 0.25 and 0.5 mg/kg decreasing, but at 0.01 and 0.1 mg/kg not affecting, as compared with the saline-injected group (0 point) (Fig. 1B).

Effects of Cholinergic Muscarinic Receptor Antagonists on Cataleptic Responses Induced by Physostigmine or Pilocarpine

As demonstrated in Fig. 2, pirenzepine (5–20 mg/kg IV) inhibited pilocarpine catalepsy, but did not affect physostigmine catalepsy (Fig. 2A). Scopolamine (0.01–0.5 mg/kg IP) inhibited the cataleptic effects of physostignime (0.75 mg/kg IP) and pilocarpine (50 mg/kg IP) (Fig. 2B).

Effects of Cholinergic Drugs on Cataleptic Responses Induced by Haloperidol or SCH23390

As indicated in Table 1, pirenzepine (1–20 mg/kg) inhibited SCH23390-induced but not haloperidol-induced catalepsy in a dose dependent fashion, whereas scopolamine (0.1–0.5 mg/kg IP) inhibited both cataleptic responses.

The pretreatment with a low dose of physostigmine (0.2 mg/kg IP) increased haloperidol catalepsy significantly, but did not affect SCH23390 catalepsy, whereas a low dose of pilocarpine (4.0 mg/kg IP) increased SCH23390 catalepsy, but not haloperidol catalepsy. Neither physostigmine (0.2 mg/kg) nor pilocarpine (4.0 mg/kg) produced catalepsy by themselves with the challenge doses.

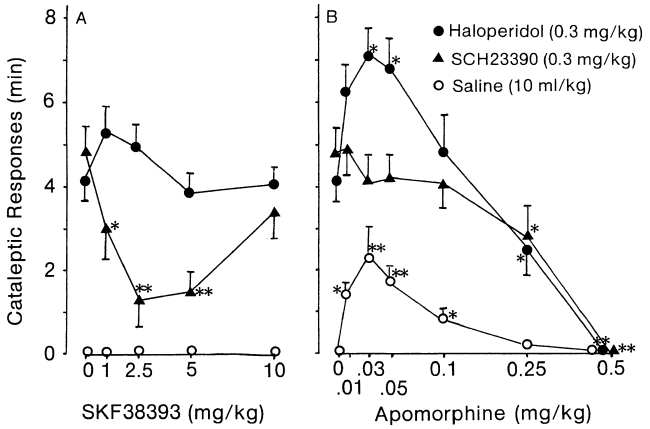

FIG. 1. Dose–response of catalepsy induced by haloperidol or SCH23390 to SKF38393 (A) or apomorphine (B). Mice received saline (10 ml/kg IP), SKF38393 (1.0–10 mg/kg IP), and apomorphine (0.01–0.5 mg/kg IP) 15 min before SCH23390 (0.3 mg/kg IP), and immediately before haloperidol (0.3 mg/kg IP). Cataleptic responses were counted 15 min after SCH23390 (0.3 mg/kg) and 30 min after haloperidol (0.3 mg/kg IP). Each value indicated the mean ± SEM. $*p < 0.05$, $**p < 0.002$ as compared with saline-injected group (0 point).

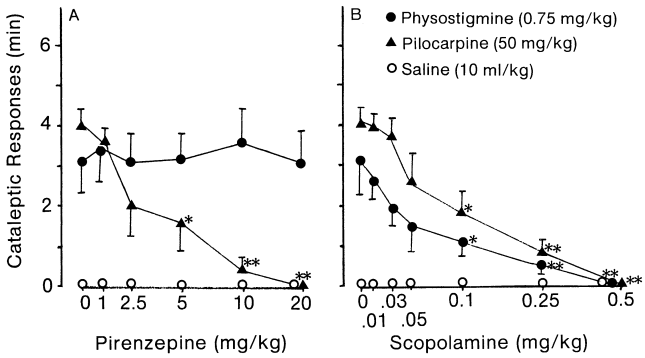

FIG. 2. Dose–response of catalepsy induced by physostigmine or pilocarpine to pirenzepine (A) or scopolamine (B). Mice received saline or pirenzepine (1.0–20 mg/kg IP) 30 min and scopolamine (0.01–0.5 mg/kg IP) immediately before physostigmine (0.75 mg/kg IP) or pilocarpine (50 mg/kg IP). Catalepsy was counted 30 min after the cataleptogenic drugs. Further explanation as in Fig. 1.

Effects of Dopaminergic Drugs on Cataleptic Responses Induced by Physostigmine or Pilocarpine

As shown in Table 2, SKF38393 (1.0–10 mg/kg IP) inhibited physostigmine (0.75 mg/kg)- and pilocarpine (50 mg/kg)-induced cataleptic responses. The inhibitory effect of SKF38393 on physostigmine catalepsy was a U-shaped dose-related curve, the most pronounced effect being produced by a dose of 5.0 mg/kg, whereas the inhibitory effect on pilocarpine catalepsy was in a dose-dependent fashion. Only the effect of SKF38393 (5 mg/kg IP) on physostigmine catalepsy was significantly different from saline pretreatment group, $F(1,19) = 9.884$, $p < 0.001$. However, in all five treatment groups, ANOVA of the data showed no significant difference, $F(4,47) = 1.812$, $p > 0.1$).

Apomorphine (0.01–0.5 mg/kg IP) exerted a biphasic effect on physostigmine catalepsy. Low doses of apomorphine (0.01–0.05 mg/kg IP) increased physostigmine catalepsy, the peak appearing at a dose of 0.03 mg/kg, but high doses of apomorphine (0.1–0.5 mg/kg IP) decreased the physostigmine response in a dose-dependent fashion. Apomorphine did not have any effect on pilocarpine catalepsy.

DISCUSSION

The results of this study suggest that SCH23390, haloperidol, physostigmine, and pilocarpine exert their cataleptogenic action via dopaminergic and cholinergic mechanisms, but none of them has the identical mechanism as the others.

Although D1 and D2 receptor antagonists exert synergistic effects between D1 and D2 receptor blockade (24), in this study, SCH23390 catalepsy was altered by SKF38393 in a U-shaped manner, whereas haloperidol catalepsy was not affected. SKF38393 may be a partial dopamine D1 receptor agonist, with intrinsic activity being shifted in the striatum from D1 receptor agonistic to D1 receptor antagonistic activity (15,18). Apomorphine, a D1/D2 receptor agonist (mainly D2 receptor), exerted a biphasic effect on haloperidol catalepsy, that is, an increase at low doses and a decrease at higher doses. Low doses of apomorphine activate the presynaptic dopamine D2 receptor preferentially, which results in an inhibition of dopamine release and consequent decrease in its synthesis, whereas higher doses stimulate postsynaptic receptors (26). Accordingly, catalepsy

TABLE 1

THE PRETREATMENT EFFECTS OF CHOLINERGIC DRUGS ON CATALEPTIC RESPONSES NDUCED BY HALOPERIDOL OR SCH23390

Pretreatment (mg/kg)	Cataleptic responses (min)					
	Saline (10 ml/kg)	(N)	Haloperidol (0.3 mg/kg)	(N)	SCH23390 (0.3 mg/kg)	(N)
Saline (10 ml/kg)	0.0 ± 0.0	(8)	4.2 ± 0.5	(10)	4.8 ± 0.6	(10)
Pirenzepine (1.0)	0.0 ± 0.0	(8)	4.0 ± 0.9	(10)	3.2 ± 0.9	(10)
Pirenzepine (2.5)	0.0 ± 0.0	(8)	4.3 ± 0.8	(10)	2.5 ± 0.7*	(10)
Pirenzepine (5.0)	0.0 ± 0.0	(8)	4.4 ± 0.9	(10)	1.3 ± 0.8*	(10)
Pirenzepine (10)	0.0 ± 0.0	(8)	4.7 ± 1.5	(10)	0.7 ± 0.2†	(10)
Pirenzepine (20)	0.0 ± 0.0	(8)	4.1 ± 1.1	(10)	0.1 ± 0.0†	(10)
Scopolamine (0.05)	0.0 ± 0.0	(8)	2.2 ± 0.7	(10)	3.0 ± 1.0	(10)
Scopolamine (0.1)	0.0 ± 0.0	(8)	1.6 ± 0.9*	(10)	1.8 ± 0.7*	(10)
Scopolamine (0.25)	0.0 ± 0.0	(8)	0.9 ± 0.3†	(10)	1.1 ± 0.7†	(10)
Scopolamine (0.5)	0.0 ± 0.0	(8)	0.0 ± 0.0†	(9)	0.0 ± 0.0†	(9)
Physostigmine (0.2)	0.0 ± 0.0	(8)	10.1 ± 1.2†	(10)	3.5 ± 0.6	(10)
Pilocarpine (4.0)	0.0 ± 0.0	(8)	4.0 ± 1.1	(10)	8.5 ± 0.9*	(10)

Mice received pirenzepine 45 min before SCH23390 (0.3 mg/kg IP) and 30 min before haloperidol (0.3 mg/kg IP). Scopolamine was administered 15 min before SCH23390 and immediately before haloperidol. Catalepsy was counted 15 min after SCH23390 and 30 min after haloperidol. Each value indicates the mean ± SEM *$p < 0.05$, †$p < 0.002$ as compared with saline-injected group.

elicited by low doses of apomorphine (1) seems to be due to an activation of presynaptic D2 receptors, and inhibitory effect of higher doses on haloperidol catalepsy an activation of postsynaptic D2 receptors. Furthermore, high doses of apomorphine inhibited SCH23390 catalepsy, as reported previously (11,14), but lower doses did not. These results suggest that SCH23390 catalepsy may be mediated at least by postsynaptic D2 receptors, whereas haloperidol catalepsy appears not to involve D1 receptor activity. We also reported previously that SCH23390 catalepsy was affected by chronic treatment with haloperidol, but haloperidol catalepsy was unaltered at any time after long-term SCH23390 treatment, suggesting that SCH23390 catalepsy may be mediated by indirect blockade of D2 receptor function through its D1 blocking action, whereas haloperidol catalepsy may be unaffected by desensitization of D1 receptors (23).

In this study, the cataleptic effect of pilocarpine was blocked by either pirenzepine, a specific muscarinic M1 receptor antagonist, or scopolamine, a muscarinic M1/M2 receptor antagonist. Because the cataleptic effect of physostigmine, an acetylcholinesterase inhibitor, which has both muscarinic and nicotinic actions, was blocked by scopolamine, but not by pirenzepine or mecamylamine, a nicotinic receptor antagonist (unpublished

TABLE 2

THE PRETREATMENT EFFECTS OF DOPAMINERGIC AGONISTS ON CATALEPTIC RESPONSES INDUCED BY PHYSOSTIGMINE OR PILOCARPINE

Pretreatment (mg/kg)	Cataleptic responses (min)					
	Saline (10 ml/kg)	(N)	Physostigmine (0.75 mg/kg)	(N)	Pilocarpine (50 mg/kg)	(N)
Saline (10 ml/kg)	0.0 ± 0.0	(8)	3.1 ± 0.9	(10)	4.1 ± 0.5	(10)
SKF38393 (1.0)	0.0 ± 0.0	(8)	3.5 ± 1.2	(10)	2.8 ± 0.7	(10)
SKF38393 (2.5)	0.0 ± 0.0	(8)	1.8 ± 0.9	(10)	1.3 ± 0.3*	(10)
SKF38393 (5.0)	0.0 ± 0.0	(8)	0.4 ± 0.1*	(11)	0.9 ± 0.0†	(10)
SKF38393 (10)	0.0 ± 0.0	(8)	2.5 ± 1.1	(11)	0.0 ± 0.0†	(10)
Apomorphine (0.01)	1.4 ± 0.2*	(8)	4.5 ± 1.1	(10)	4.5 ± 1.4	(10)
Apomorphine (0.03)	2.3 ± 0.8†	(10)	6.3 ± 1.0*	(11)	4.1 ± 1.8	(10)
Apomorphine (0.05)	1.7 ± 0.5†	(10)	3.1 ± 0.9	(10)	4.2 ± 1.5	(10)
Apomorphine (0.1)	0.8 ± 0.2*	(10)	1.9 ± 0.3*	(11)	4.0 ± 1.3	(10)
Apomorphine (0.25)	0.2 ± 0.1	(10)	0.3 ± 0.0†	(11)	4.1 ± 1.7	(10)
Apomorphine (0.5)	0.0 ± 0.0	(10)	0.0 ± 0.0†	(10)	3.8 ± 1.0	(10)

Mice received SKF38393 or apomorphine immediately before physostigmine (0.75 mg/kg IP) or pilocarpine (50 mg/kg IP). Cataleptic responses were counted 30 min after the cateleptogenic drugs. Further explanation as in Table 1.

observation), the indirect action of physostigmine (endogenous acetylcholine) on muscarinic M2 receptors might be more potent than that on muscarinic M1 or nicotinic receptors.

Regarding the interaction between dopaminergic and cholinergic systems, the pretreatment with higher doses of apomorphine or scopolamine, but not pirenzepine, inhibited the cataleptic effects of subsequently administered haloperidol and physostigmine, respectively. Low doses of apomorphine increased the physostigmine catalepsy as well as haloperidol catalepsy, suggesting that the stimulatory effects of low doses on these cataleptic responses may be mediated by cholinergic activation secondary to the inhibition of dopamine transmission. These results suggest that dopamine D2 receptors may mediate the sites activated by endogenous acetylcholine (mainly M2 receptor), and muscarinic M2 receptors regulate the D2 receptor effects. On the other hand, the cataleptic effect of SCH23390 or pilocarpine was inhibited by pretreatment with either scopolamine or pirenzepine, and SCH23390 catalepsy was potentiated by pilocarpine but not by physostigmine. SKF38393 also inhibited pilocarpine catalepsy. Neither of the cholinergic agonists produced catalepsy by themselves with the challenge doses. It implies that D1 receptor responses may be mediated by M1 receptors. It has been reported that pilocarpine markedly potentiates haloperidol catalepsy, but is unable to significantly potentiate the actions of the other dopamine D2 receptor antagonists, such as fluphenazine and spiroperidol (20). However, in this study, pilocarpine catalepsy was not affected by apomorphine, and haloperidol catalepsy was not affected by pirenzepine or low doses of pilocarpine. On the other hand, physostigmine catalepsy was blocked by either SKF38393 or apomorphine. This inhibition profile was similar to that seen with SKF38393 inhibition of SCH23390 catalepsy, and with apomorphine inhibition of haloperiedol catalepsy (Fig. 1). Accordingly, the muscarinic M2 receptor responses may be mediated by both dopamine D1 and D2 receptors. However, dopamine D1 receptor effects may not be mediated by muscarinic M2 receptors, because SCH23390 catalepsy was not affected by a low dose of physostigmine. The inhibitory effect of SKF38393 (5 mg/kg IP) on physostigmine catalepsy may be due to the indirect enhancement of D2 receptor function via direct D1 receptor activation, which is consistent with the finding that SCH23390 catalepsy may be mediated by D2 receptor actions (11,14,23). There appears to be no interaction between dopaminergic D2 receptors and muscarinic M1 receptors, because pirenzepine was ineffective in altering haloperidol-induced catalepsy. Furthermore, there is a report suggesting that acetylcholine release is controlled by the dopamine D2 receptors (2). Tardive dyskinesia seems to result from an imbalance of the dopaminergic–cholinergic system, and is based on an excessive dopamine D2 receptor activation (supersensitivity) and muscarinic M2 receptor inhibition (subsensitivity), resulting from an excessive inhibition of acetylcholine release from cholinergic interneuron, in neostriatum. There is supportive evidence that physostigmine-induced yawning is potentiated by fluphenazine, a long-acting neuroleptic, but is inhibited by higher doses of apomorphine, whereas pilocarpine-induced yawning is not affected by either drug (26). Thus, the results suggest that there are, at the least, relationships between muscarinic M1 receptors and dopaminergic D1 receptors, and between muscarinic M2 receptors and dopaminergic D2 receptors. Dopamine D1 and D2 receptors may interact in a synergistic fashion on dopaminergic systems (24), but act independently of each other in influencing other systems, such as NMDA (21), opioid (13), and cholinergic neurons.

ACKNOWLEDGEMENTS

This work was supported in part by a grant-in aid for scientific research (no. 06670964) from the Ministry of Education Sciences and Culture, Japan.

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