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Hyperthermia Induced by the Dopamine D_1 Receptor Agonist SK&F38393 in Combination With the Dopamine D_2 Receptor Agonist Talipexole in the Rat

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NAGASHIMA, M., K. YAMADA, H. KIMURA, S.-I. MATSUMOTO AND T. FURUKAWA. *Hyperthermia induced by the dopamine D_1 receptor agonist SK&F38393 in combination with the dopamine D_2 receptor agonist talipexole in the rat.* PHARMACOL BIOCHEM BEHAV 43(4) 993–997, 1992. – The present experiments were performed to investigate the effects of dopamine D_1 receptor agonists given alone or in combination with dopamine D_2 receptor agonists on body temperature in rats. The selective dopamine D_1 receptor agonist, 1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SK&F38393), produced hyperthermia. However, the dopamine D_2 receptor agonist, B-HT 920 (talipexole), and the newly synthesized dopamine D_2 receptor agonist, (*S*)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (SND 919), did not change the temperature. Interestingly, the SK&F38393-induced hyperthermia was enhanced by talipexole and SND 919. The drastic hyperthermia induced by combined administration of dopamine D_1 and D_2 receptor agonists was blocked by either the dopamine D_1 receptor antagonist, SCH23390, or the dopamine D_2 receptor antagonist, spiperone. On the other hand, treatment with prazosin, yohimbine, propranolol, scopolamine, or methysergide failed to affect the marked hyperthermia. The present results suggest that a functional link between dopamine D_1 and D_2 receptors may be synergistic in the regulation of body temperature and that concurrent stimulation of both dopamine D_1 and D_2 receptors thereby produces marked hyperthermia in the rat.

Body temperature Dopamine D_1 and D_2 receptors Talipexole B-HT 920 SND 919 SK&F38393

BIOCHEMICAL and pharmacological evidence indicates the presence of at least two dopamine receptor subtypes: dopamine D_1 and D_2 receptors (10,23,27). According to the classification, 1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SK&F38393) is a dopamine D_1 receptor agonist (11,15,20) and B-HT 920 (talipexole) (Fig. 1) is a dopamine D_2 receptor agonist (1,7,12,13,31,32). Recently, (*S*)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (SND 919) (Fig. 1) has been reported to be a compound possessing talipexole-like dopamine D_2 receptor agonistic activities (3,12,31,32), and is almost devoid of α-adrenoceptor-stimulating effects (M. H. Jennewein, personal communication, Boehringer Ingelheim, Germany).

Ample evidence has indicated that the dopaminergic neuronal system is importantly participated in brain functions. In this respect, it is of interest that dopamine D_1 and D_2 receptors mutually interact in eliciting functional alterations. Recently, it was reported that concurrent stimulation of both dopamine D_1 and D_2 receptors was required for the appearance of stereotypy (8,15,19). We have also confirmed that the combined treatment with SK&F38393 and talipexole or SND 919 induces marked stereotypy (32). On the contrary, yawning responses to talipexole or SND 919 was dose dependently reduced by simultaneous administration of SK&F38393 (32), implying that a functional link between dopamine D_1 and D_2 receptors is synergistic in producing stereotypy and is antagonistic in evoking yawning.

The dopaminergic neuronal system appears to play an important role in the central regulation of body temperature in animals (2). The selective dopamine D_2 agonists such as quinpirole and bromocriptine have been reported to induce hypothermia in rodents that is blocked by dopamine D_2 recep-

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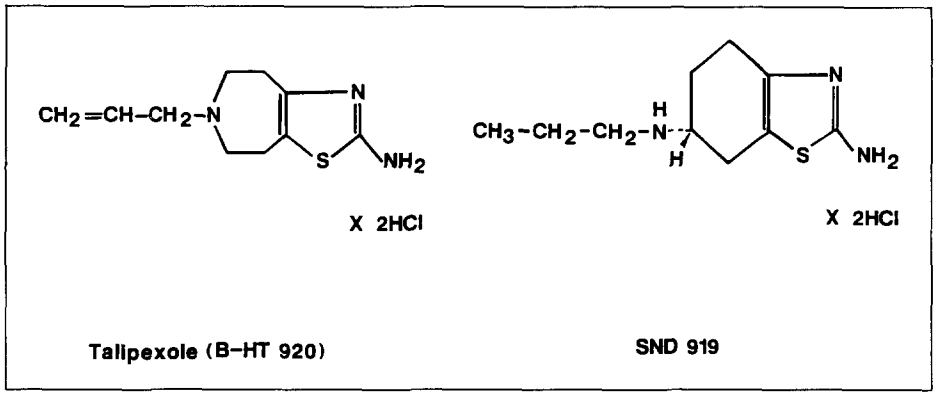

FIG. 1. Chemical structures of talipexole (B-HT 920) and SND 919.

tor antagonists (5,14,16,21,33). On the basis of such findings, it has been proposed that dopamine D_2 receptors are involved in thermoregulation (14,16,18,33).

We noticed that after combined administration of SK&F38393 and talipexole or SND 919 rectal temperature increased, accompanied by the occurrence of stereotypy. The present experiments were therefore performed to investigate change in body temperature of rats by administration of dopamine D_1 or D_2 receptor agonists alone or in combination.

METHOD

Animals

Male Wistar rats (250–300 g) were obtained from Kyudo Animal Laboratory (Kumamoto, Japan). They were kept in an animal room with a 12 L : 12 D cycle (lights on at 7:00 a.m.). Commercial food (CE-2, Clea Japan Ltd.) and tapwater were freely available except during experiments. All experiments were carried out at an environmental temperature of 23 ± 1°C.

Measurement of Temperature

Groups of four rats were placed in plastic boxes (33 × 30 × 17 cm) containing wood shavings. The rectal temperature of rats was measured using a thermistor (Nihon Kohden, Type P) before and after drug administration. The probe was inserted into the animal's rectum to a constant depth of 4 cm and removed after each reading. A change in body temperature (°C) represented a difference from the predrug value.

Administration of Drugs

Rats were treated SC in the neck area with saline, SK&F38393 (5 and 10 mg/kg), talipexole (0.25 and 0.5 mg/kg), or SND 919 (0.5 and 1 mg/kg) given alone or in combination. These drug dosages were selected according to our previous experiments (12,31,32), which showed that SK&F38393 (0.1–8 mg/kg, SC) in combination with talipexole (5–100 μg/kg, SC) or SND 919 (25–500 μg/kg, SC) elicited stereotypy or yawning. For IP pretreatment with various antagonists, prazosin (2 mg/kg), yohimbine (2 mg/kg), propranolol (20 mg/kg), *R*(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-*ol* (SCH23390) (0.5 mg/kg), spiperone (0.5 mg/kg), scopolamine (0.5 mg/kg), or methysergide (10 mg/kg) was injected 10 min before injecting the dopamine receptor agonists. These antagonist dosages were selected according to our previous experiments (12,13,30).

Drugs

The following drugs were used: SK&F38393 HCl [Research Biochemicals, Inc. (RBI), Natick, MA], talipexole (B-HT 920)

TABLE 1

EFFECTS OF SK&F38393, TALIPEXOLE, OR SND 919 ON RECTAL TEMPERATURE IN RATS

	Change in Rectal Temperature (°C)					
Drugs (mg/kg)	0.5 h	1 h	1.5 h	2 h	2.5 h	24 hr
Saline	−0.1 ± 0.1	0.0 ± 0.1	−0.1 ± 0.1	0.0 ± 0.1	−0.1 ± 0.2	−0.3 ± 0.1
SK&F38393 (5)	1.4 ± 0.2*	1.7 ± 0.2*	1.6 ± 0.2*	1.3 ± 0.2*	1.2 ± 0.2*	0.2 ± 0.2
SK&F38393 (10)	1.5 ± 0.1*	2.1 ± 0.1*	2.1 ± 0.1*	2.0 ± 0.1*	1.8 ± 0.1*	0.3 ± 0.1
Talipexole (0.25)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.3 ± 0.2	−0.1 ± 0.1
Talipexole (0.5)	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.2	0.3 ± 0.3	0.3 ± 0.1	−0.2 ± 0.1
SND 919 (0.5)	0.3 ± 0.1	−0.3 ± 0.2	−0.4 ± 0.2	0.1 ± 0.2	0.4 ± 0.1	0.1 ± 0.1
SND 919 (1)	−0.1 ± 0.2	−0.1 ± 0.2	−0.2 ± 0.2	−0.2 ± 0.3	0.2 ± 0.2	−0.1 ± 0.1

Various dopamine receptor agonists were given subcutaneously. Values represent means ± SEM of changes of rectal temperature from six to eight rats 0.5, 1, 1.5, 2, 2.5, and 24 h after administration of drugs.

*$p < 0.01$, significant difference from saline-injected control groups.

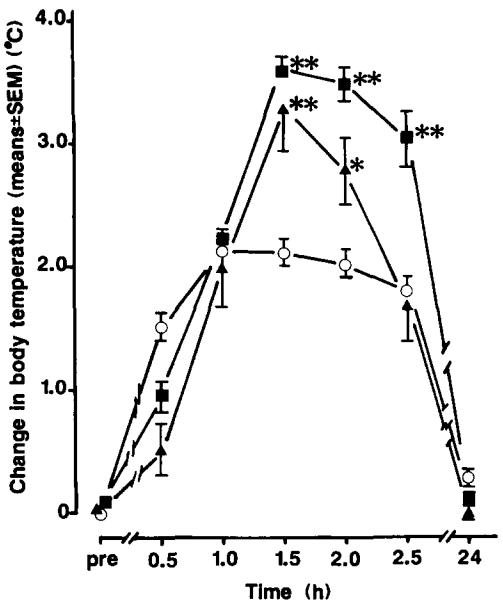

FIG. 2. Potentiation of SK&F38393-induced hyperthermia by talipexole or SND 919. All drugs were administered concurrently. Values represent means ± SEM of changes of rectal temperature from 8-10 rats. (○), SK&F38393 10 mg/kg plus saline; (▲), SK&F38393 10 mg/kg plus talipexole 0.5 mg/kg; (■), SK&F38393 10 mg/kg plus SND 919 1 mg/kg. *$p < 0.05$, **$p < 0.01$, significant difference from SK&F38393 plus saline group.

2HCl (Boehringer Ingelheim, Kawanishi, Japan), SND 919 2HCl (Boehringer Ingelheim), prazosin HCl (Tokyo Kasei, Tokyo, Japan), yohimbine HCl (Nakarai, Kyoto, Japan), propranolol HCl (Sigma Chemical Co., St. Louis, MO), SCH23390 HCl (RBI), spiperone (Spiropitan Injection, Eisai, Tokyo, Japan), scopolamine HBr (Nakarai), and methysergide bimaleate (Sandoz, Basel, Switzerland). Drugs were dissolved or diluted in saline with the exception of prazosin, which was dissolved in an excess of equimolar tartaric acid solution, with subsequent dilution in saline. Doses were expressed in terms of salt with the exception of spiperone.

Statistical Analysis

Changes in body temperature were expressed as mean values ± SEM. Statistical analysis was done using one-way analysis of variance (ANOVA) followed by the two-tailed Dunnett's *t*-test (difference between a control and all means) (28).

RESULTS

Change in Body Temperature After Administration of SK&F38393, Talipexole, or SND 919 in Rats

The mean body temperature in nontreated rats was 37.1 ± 0.1°C. As shown in Table 1, body temperature in control rats treated subcutaneously with saline was not changed. Administration of SK&F38393 at doses of 5 and 10 mg/kg (SC) produced a dose-related increase in temperature. The hyperthermic effects reached a maximum 1 h after administration and the elevations in body temperatures were 1.7 ± 0.2 and 2.1 ± 0.1°C at doses of 5 and 10 mg/kg, respectively. These hyperthermic effects disappeared 24 h after the treatment. Talipexole (0.25 and 0.5 mg/kg, SC) and SND 919 (0.5 and 1 mg/kg, SC) did not exert significant effects on body temperature.

Potentiation of SK&F38393-Induced Hyperthermia by Talipexole or SND 919 in Rats

As depicted in Fig. 2, the SK&F38393 (10 mg/kg, SC)-induced increase in body temperature was enhanced by treatment with talipexole (0.5 mg/kg, SC) or SND 919 (1 mg/kg, SC) in rats. Hyperthermia peaks were seen 1.5 h after the combined treatments and elevations in body temperature were

TABLE 2

EFFECTS OF VARIOUS RECEPTOR ANTAGONISTS ON HYPERTHERMIA INDUCED BY SK&F38393 IN COMBINATION WITH TALIPEXOLE OR SND 919 IN RATS

	Change in Rectal Temperature (°C)		
Drugs (mg/kg)	Saline	SK&F + Talipexole	SK&F + SND 919
Saline	0.1 ± 0.1	3.3 ± 0.3	3.6 ± 0.1
Prazosin (2)	0.2 ± 0.1	3.9 ± 0.2	4.4 ± 0.3
Yohimbine (2)	−0.3 ± 0.1	4.1 ± 0.3	3.7 ± 0.5
Propranolol (20)	−0.1 ± 0.2	3.1 ± 0.2	3.6 ± 0.2
SCH23390 (0.5)	0.6 ± 0.3	1.0 ± 0.2*	1.4 ± 0.2*
Spiperone (0.5)	0.2 ± 0.2	0.5 ± 0.2*	1.2 ± 0.1*
Scopolamine (0.5)	0.8 ± 0.2	3.9 ± 0.2	3.5 ± 0.7
Methysergide (10)	−0.1 ± 0.2	2.7 ± 0.4	3.5 ± 0.2

Various receptor antagonists were given intraperitoneally 10 min before administration of SK&F38393 (10 mg/kg, SC) in combination with talipexole (0.5 mg/kg, SC) or SND 919 (1 mg/kg, SC). Values represent means ± SEM of changes of rectal temperature from 8-12 rats 1.5 h after administration of dopamine receptor agonists.
*$p < 0.01$, significant difference from respective control groups.

3.3 ± 0.3°C with talipexole and 3.6 ± 0.1°C with SND 919. The hyperthermia terminated 24 h after treatments.

Effects of Various Receptor Antagonists on the Hyperthermia Induced by SK&F38393 in Combination with Talipexole or SND 919 in Rats

As demonstrated in Table 2, body temperature was not altered by injection of various receptor antagonists per se, such as prazosin (2 mg/kg, IP), yohimbine (2 mg/kg, IP), propranolol (20 mg/kg, IP), SCH23390 (0.5 mg/kg, IP), spiperone (0.5 mg/kg, IP), scopolamine (0.5 mg/kg, IP), or methysergide (10 mg/kg, IP). However, the hyperthermia induced by SK&F 38393 (10 mg/kg, SC) in combination with talipexole (0.5 mg/kg, SC) or SND 919 (1 mg/kg, SC) was inhibited by pretreatment with SCH23390 or spiperone but unaffected by the other receptor antagonists.

DISCUSSION

It has been reported that talipexole does not exert any postsynaptic dopaminergic effects, such as induction of stereotypy and locomotor hyperactivity, in naive animals with normosensitive brain dopamine receptors (1,7). However, recent observations have shown that talipexole does exhibit postsynaptic dopamine receptor agonistic actions when administered simultaneously with the selective dopamine D_1 receptor agonist, SK&F38393, because this combined administration of talipexole and SK&F38393 induces strong stereotypy in naive rats (8,15,32). This effect of producing behavioral changes is analogous to the postsynaptic effect of high doses of apomorphine, which stimulates both dopamine D_1 and D_2 receptors (29). Our previous experiments have also shown that administration of very high doses of talipexole (0.5 mg/kg, SC) or SND 919 (1 mg/kg, SC) in combination with SK&F38393 (5 and 10 mg/kg, SC) evokes marked stereotypy (32). In the present experiments, talipexole and SND 919 were administered at doses that were able to produce stereotypy. Accordingly, these agents at the doses used in this study are able to stimulate postsynaptic dopamine D_2 receptors.

Apomorphine was reported to cause a dose-dependent reduction in body temperature of naive rodents that was blocked by a variety of dopamine D_2 receptor antagonists, such as haloperidol and sulpiride, but not by the dopamine D_1 receptor antagonist, SCH23390 (9,14,16,18). The dopamine D_2 receptor agonist, quinpirole, also induced hypothermia in mice and rats (5,14,16,21). Therefore, it has been proposed that stimulation of dopamine D_2 receptors produces hypothermia in naive rodents (14,18,21,33). Our previous reports have shown that talipexole and SND 919 are effective in eliciting yawning and decreasing serum prolactin levels via stimulation of dopamine D_2 receptors (3,12,31,32). However, in the present experiments administration of talipexole or SND 919 at such behavioral and endocrinologic effective doses did not affect body temperature in rats. These results seem to be incompatible with the previous findings (14,18,33) that other dopamine D_2 receptor agonists induce hypothermia in rodents. At present, we have no adequate explanation for this discrepancy in these results. However, recent genomic cloning experiments have interestingly shown that there are two isoforms of dopamine D_2 receptor, termed D_{2A} and D_{2B} receptors (6,17), in addition to dopamine D_1 receptors. Furthermore, some investigators have reported that D_3 (22), D_4 (25), and D_5 receptors (24) are present in the brain, although their functional roles are still unknown. At present, we cannot dismiss the possibility that these new dopamine receptor subtypes are involved in thermoregulation. Therefore, the above discrepancy may be due to, at least in part, differences of new dopamine receptor subtypes, species, and/or strain.

It was recently reported that SK&F38393 increased body temperature in a dose-dependent manner in reserpine-treated mice and this increase was completely antagonized by SCH23390 (4). Moreover, the hypothermia in mice induced by quinpirole was attenuated by SK&F38393 (16,21). Thus, previous findings have shown that SK&F38393 reverses the hypothermia induced by reserpine or quinpirole in mice. In our experiments, SK&F38393 given alone increased body temperature in naive rats. These results seem to be consistent with the recent findings (21,26) that SK&F38393 given alone induced hyperthermia in naive mice. Combined, it is assumed that stimulation of dopamine D_1 receptors is involved in hyperthermia in rodents as a possible neuronal mechanism.

Interestingly, the SK&F38393-produced hyperthermia was enhanced by talipexole or SND 919. The marked hyperthermia induced by combined administration of dopamine D_1 and D_2 receptor agonists was antagonized by either SCH23390 or spiperone. Some nondopaminergic antagonists have been reported to induce a slight hypothermia in mice (33), but treatment with prazosin, yohimbine, propranolol, scopolamine, or methysergide at pharmacologically effective doses used in this study did not change basal body temperature and failed to block the marked hyperthermia induced by combined administration of dopamine D_1 and D_2 receptor agonists in rats.

The present results suggest that both dopamine D_1 and D_2 receptors are related to the regulation of body temperature and that a synergistic function of dopamine D_1 and D_2 receptors is involved in hyperthermia in a manner identical to stereotypy in the rat.

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