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Altered Responses to Serotonergic Agents in Fawn-Hooded Rats

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GUDELSKY, G. A., J. I. KOENIG AND H. Y. MELTZER. *Altered responses to serotonergic agents in Fawn-Hooded rats*. PHARMACOL BIOCHEM BEHAV 22(3) 489–492, 1985.—The incidence of "wet dog" shakes elicited by quipazine, the hyperthermic response induced by 5-methoxy-N,N-dimethyltryptamine (5MeODMT) and the hypothermic response to 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) were compared in rats of the Fawn-Hooded (FH) and Sprague-Dawley (SD) strains. The behavioral responses of FH rats to quipazine and 5MeODMT were significantly greater than those of SD rats. On the other hand, the hypothermic effect of 8-OH-DPAT in FH rats was significantly less than that elicited in SD animals. The present results are supportive of the view that the responsiveness of serotonergic mechanisms in the CNS of FH rats differs markedly from those in SD animals.

Quipazine 5-Methoxy-N,N-dimethyltryptamine 8-OH-DPAT Fawn-Hooded rats Wet dog shakes Hyperthermia Hypothermia

RATS of the Fawn-Hooded (FH) strain possess a platelet storage pool deficiency [13, 15, 16], which is associated with a reduced platelet content of 5-HT [13,16]. A reduction of 5-HT uptake by blood platelets in these rats also has been noted [14], although this is not a consistent finding [1,13]. In addition, a reduction of the binding of ^{3}H-imipramine has been observed to platelets and brain tissue of FH rats compared to Sprague-Dawley (SD) and Wistar rats [1,5]. This is of interest in view of the possible allosteric relationship between the ^{3}H-imipramine binding site and the 5-HT uptake site in both brain and platelet [3].

Thus, the possibility exists for abnormal serotonergic function in the CNS, as well as the periphery, of FH rats. The purpose of the present study was to compare 5-HT-mediated behavioral responses of FH and SD rats. Serotonergic agents have been shown to elicit "wet dog" shakes [9,17] and alter body temperature [4,11]. In the present study, the incidence of "wet dog" shakes induced by quipazine and the alteration of rectal temperature produced by the 5-HT agonists 5-methoxy-N,N-dimethyltryptamine (5MeODMT) and 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) were examined in FH and SD rats.

METHOD

Male rats of the SD (Sprague-Dawley, Madison, WI) and FH (Dr. W. Jean Dodds, New York State Department of Health) strains, weighing 250–375 g, were used in these experiments. The animals were maintained in an air-conditioned room (22–24°C) with controlled lighting (lights on 0700 hr–1900 hr).

Animals were given quipazine (1, 3 or 10 mg/kg, IP) or the solvent vehicle (0.15 M NaCl) and were transferred to an observation cage where they were housed individually. The total number of "wet dog" shakes [2], including head and whole body shakes, was counted during a 3 min period 30 min after drug administration. Due to the limited number of available FH rats, the same animals of both strains were tested with the three doses of quipazine and the solvent vehicle. Drug treatments were administered in a randomized manner, and a period of at least six days was allowed between testing periods.

Rectal temperatures were recorded in other groups of SD and FH rats. A period of approximately 1 hr was allowed for the stabilization of the animal's temperature. Temperatures were recorded 15 min and immediately (0 time) before the injection of 5MeODMT (3 mg/kg, IP), 8-OH-DPAT (0.05 and 0.1 mg/kg SC) or the solvent vehicle. Another temperature measurement was made 15 min after 5MeODMT and 30 min after 8-OH-DPAT administration. All temperature measurements were performed at an ambient temperature of 24–26°C using a thermistor probe (Yellow Springs Instrument Co.) inserted approximately 5 cm into the rectum.

Statistical analysis of temperature measurements was performed using a one-way analysis of variance with consideration for repeated measures. Mean values were compared using the Newman-Keuls test. Quipazine-induced "wet dog" shakes were evaluated with the Student's *t*-test.

8-OH-DPAT was purchased from Research Biochemicals, Inc. (Wayland, MA). 5MeODMT was obtained from Sigma Chemical Co. (St. Louis, MO). Quipazine was obtained from Miles Laboratories, Inc. (Elkhart, IN).

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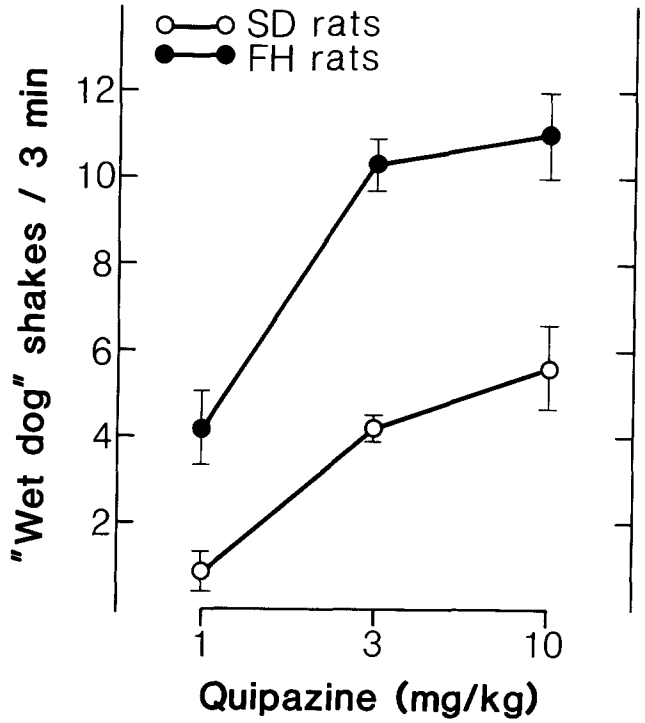

FIG. 1. "Wet dog" shakes induced by quipazine in SD and FH rats. "Wet dog" shakes were counted for a 3-min period commencing 30 min after the injection of quipazine. Each symbol represents the mean±S.E. of 7–12 animals.

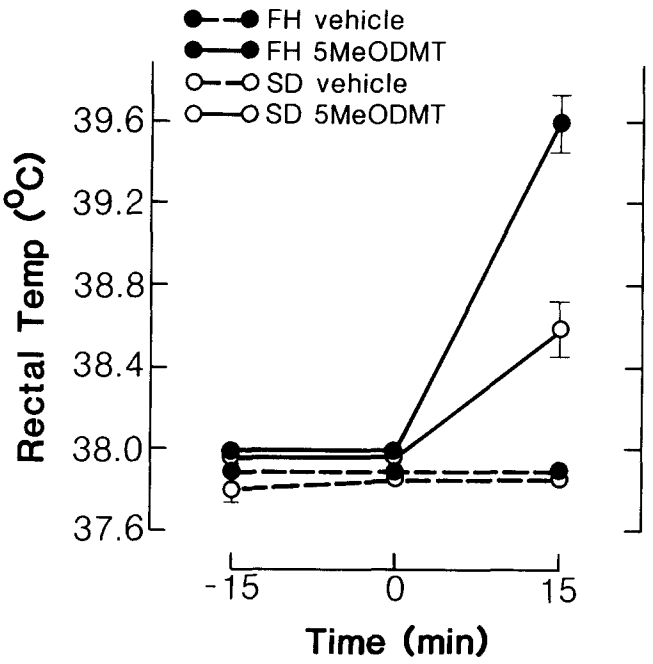

FIG. 2. Effect of 5MeODMT on the rectal temperatures of SD and FH rats. Rectal temperatures of SD and FH rats were recorded 15 min before (−15 min) and immediately prior to (0 time) the injection of 5MeODMT (3 mg/kg, IP) or the solvent vehicle. Another measurement was taken 15 min after this injection. Each symbol represents the mean±S.E. of 7–8 animals.

TABLE 1

8-OH-DPAT-INDUCED CHANGES IN BODY TEMPERATURES (Δ BT) OF SPRAGUE-DAWLEY (SD) AND FAWN-HOODED (FH) RATS

Strain	Dose (mg/kg)	Temperature (°C) 0 min	30 min	Δ BT
SD	0.05	37.2 ± 0.3	36.2 ± 0.2	−1.0 ± 0.2
FH	0.05	37.5 ± 0.2	37.2 ± 0.2*	−0.3 ± 0.1
SD	0.10	37.9 ± 0.1	35.3 ± 0.2	−2.6 ± 0.2
FH	0.10	37.8 ± 0.1	36.7 ± 0.1*	−1.1 ± 0.2

Rectal temperatures were taken immediately (0 min) before and 30 min after the SC administration of 8-OH-DPAT. Values represent the mean ± S.E. of 6 animals.
*$p<0.01$, vs. values for SD rats.

RESULTS

The dose response relationships for quipazine-induced "wet dog" shakes in SD and FH animals are presented in Fig. 1. At each of the doses (1, 3 and 10 mg/kg) of quipazine tested, rats of the FH strain exhibited a significantly ($p<0.01$) greater number of "wet dog" shakes than did rats of the SD strain. No "wet dog" shakes were observed in rats of either strain given the solvent vehicle (data not shown).

The increase in body temperature of SD and FH rats in response to 5MeODMT (3 mg/kg, IP) is shown in Fig. 2. Within 15 min after the administration of 5MeODMT, the rectal temperature of SD rats increased 0.6°C from 38.0±0.06°C (mean±S.E.) to 38.6±0.1°C. The response to 5MeODMT in FH rats was significantly ($p<0.01$) greater than that in SD animals. The mean rectal temperature of FH animals increased from 38.0±0.04°C to 39.6±0.1°C. Prior to the administration of 5MeODMT, no significant differences in the rectal temperatures of SD rats and FH rats were observed. In addition, rectal temperatures of both SD and FH rats were unaltered after the administration of the solvent vehicle.

The administration of 8-OH-DPAT (0.05 and 0.1 mg/kg, SC) resulted in a dose-related decrease in rectal temperature. At both of the doses of 8-OH-DPAT tested the hypothermic

response in FH rats was significantly ($p<0.01$) less than that in SD animals (Table 1).

DISCUSSION

Rats of the FH strain have a platelet storage disease that is associated with a greatly reduced platelet content of 5-HT [13,16]. However, the brain content of 5-HT in FH rats does not differ significantly from that of SD rats [7]. Nevertheless, in view of some of the similarities between blood platelets and serotonergic nerve terminals in the CNS, it was of interest to determine whether FH rats displayed abnormal behavioral responses to serotonergic agents.

In the present study, the effects of 5MeODMT and quipazine to induce hyperthermia and "wet dog" shakes, respectively, were significantly more pronounced in FH rats compared to SD animals. These results are suggestive of enhanced serotonergic receptor sensitivity in rats of the FH strain. The possibility that pharmacokinetic factors are involved in the enhanced responses to quipazine and 5MeODMT in FH rats cannot be excluded at the present time.

It has been suggested that the elicitation of "wet dog" shakes by quipazine or 5-HTP involves activation of 5-HT_2 receptors, as evidenced by the finding that ketanserin or pirenperone, selective antagonists at 5-HT_2 receptor sites [8], attenuates this behavioral response ([9,17], Gudelsky, Koenig and Meltzer, unpublished observations).

Ketanserin and pirenperone also antagonize the hyperthermia induced by 5MeODMT or the 5-HT agonists MK-212 and m-chlorophenyl-piperzine ([11], Gudelsky, Koenig and Meltzer, manuscript in preparation), which is suggestive that this response also is mediated by 5-HT_2 receptors.

In view of these findings, it seems reasonable to hypothesize that at least some receptors of the 5-HT_2 type in the CNS of FH rats are more responsive than those in SD rats.

Although the systemic administration of 5-HT agonists can produce hyperthermia, there is also evidence for the involvement of 5-HT in hypothermia [4]. Cox *et al.* [4] have shown that the intrahypothalamic administration of 5-HT to rats decreases rectal temperature, presumably due to activation of postsynaptic receptors. In the present study, a hypothermic response in FH and SD rats also was observed after the administration of the 5-HT agonist, 8-OH-DPAT (0.05 and 0.1 mg/kg).

In contrast to the enhanced hyperthermic response of FH rats to 5MeODMT, FH rats displayed a diminished hypothermic response to 8-OH-DPAT relative to SD animals. 8-OH-DPAT is a selective 5-HT agonist [6] which binds preferentially to 5-HT_{1A} recognition sites [10]. The hypothermic effect of 8-OH-DPAT is partially antagonized by metergoline and by spiperone (Koenig, Gudelsky and Meltzer, manuscript in preparation). It is noteworthy that spiperone also has been shown to bind to 5-HT_{1A} sites [12]. Thus, 8-OH-DPAT-induced hypothermia may involve activation of this subpopulation of 5-HT_1 receptors. In view of the present results, the responsiveness of 5-HT_1 receptors involved in thermoregulation in FH rats appears to be less than that in SD animals.

The differences in relative sensitivity of putative 5-HT_1 and 5-HT_2 receptors to 5-HT agonists between FH and SD rats is noteworthy. It is not possible to determine from the available data whether the enhanced responsiveness of 5-HT_2 receptors or decreased responsiveness of 5-HT_1 receptors represents a response to an abnormality of 5-HT in brain. We are presently characterizing 5-HT_1 and 5-HT_2 receptors in FH and SD rats with ligand binding methodology.

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