Effects of Peripheral Administration of 5-Hydroxytryptamine (5-HT) on 2-Deoxy-β-glucose-Induced Hyperphagia in Rats

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Effects of peripheral administration of 5-HT (5-hydroxytryptamine, serotonin) on hyperphagia induced by 2-deoxy-β-glucose(2-DG) were studied in rats. It was found that 5-HT i.p. reduced 2-DG-elicited feeding in rats dose-dependently. The 5-HT-induced hypophagia was antagonized by the 5-HT2A receptor antagonist, ketanserin. It is known that 2-DG induces glucoprivation, resulting in hyperphagia and hyperglycemia. However, 5-HT did not affect hyperglycemia induced by 2-DG. These results suggest that peripheral injection of 5-HT reduces 2-DG-induced hyperphagia mediated by the peripheral 5-HT2A receptor and that its effects are not due to enhancement of hyperglycemia.

Key words 5-HT (5-hydroxytryptamine, serotonin); food intake; 2-deoxy-β-glucose; peripheral 5-HT2A receptor; glucoprivation

**MATERIALS AND METHODS**

**Animals** Male Sprague-Dawley rats (200–240 g) were obtained from SLC Japan. They were housed in individual cages and maintained under a controlled 12 h:12 h light/dark cycle (lights on at 07:00 h), with room temperature at 23 ± 1 °C and humidity at 55 ± 5% for at least 7 d prior to experiments. Rats were given free access to food and water.

**Drugs and Treatment** 2-DG and 5-HT creatinine sulfate were purchased from Wako Pure Chemical Co. (Japan), Merck (Germany), respectively. Ketanserin tartrate were obtained from Research Biochemicals Inc. (U.S.A.). 2-DG, 5-HT and ketanserin were dissolved in saline. All drugs were injected i.p. 2-DG and 5-HT were injected i.p. simultaneously at opposite sites. Ketanserin was injected 30 min before the injection of 5-HT. All drugs were administered in a volume of 0.2 ml/100 g.

**Measurement of Food Intake** Preweighed food was placed in the cage and the amount of remaining food was weighed 30 min, 1 h and 2 h after the injection of 2-DG. Drugs were injected between 13.00 h and 14.00 h.

**Determination of Blood Glucose Levels** Blood samples were taken from the caudal vena cava under light ether anesthesia. Only one sample was removed from each rat. Plasma glucose levels were determined by the method previously described.

**Statistical Analysis** Statistical significance was analyzed by two-way analysis of variance (ANOVA) followed by Tukey’s test.

**RESULTS**

Figure 1 shows the effects of 5-HT on 2-DG-induced hyperphagia in rats. In saline-treated rats, 5-HT did not affect food intake over 2 h. As shown in the results, 2-DG at a dose of 750 mg/kg induced marked hyperphagia in non-food-deprived rats. 5-HT significantly reduced 2-DG-induced hyperphagia for 30 min, 1 h and 2 h.

Figure 2 shows effects of the 5-HT2A receptor antagonist ketanserin on the inhibitory effects of 5-HT on 2-DG-elicited hyperphagia. Pretreatment with ketanserin (1 mg/kg) attenuated the suppressive effects of 5-HT on 2-DG-induced hyper-

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Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter and regulates several physiological functions. It is well established that 5-HT is an important factor controlling food intake and that 5-HT depresses food intake in animals and humans mediated by 5-HT receptors.1–3 Activation of central 5-HT1A, 5-HT2A and 5-HT2C receptors induces anorexia in rodents based on numerous results using 5-HT receptor agonists and antagonists.4–7 Direct administration of 5-HT into the brain also induces hypophagia in rodents and its effects may be elicited by these 5-HT receptors.3

Peripheral administration of 5-HT induces anorexia and this effect may be associated with peripheral 5-HT2 receptors, since it was antagonized by the peripheral 5-HT2 receptor antagonist xylamidine.8–10 We previously reported that the peripheral 5-HT2 receptor agonist α-methyl-5-HT, reduces food intake in fasted rats and that it is mediated by the peripheral 5-HT2A receptor.11 We also found that the peripheral 5-HT3 receptor agonist 2-methyl-5-hydroxytryptamine did not affect food intake in rats, which implying that the peripheral 5-HT3 receptor is not associated with food intake.11

It is known that 2-deoxy-β-glucose(2-DG) prevents utilization of intracellular glucose and elicits neuroglucopenia, leading to hyperphagia.12,13 To date, 2-DG-induced feeding serves as an animal model of hyperphagia. However, the effects of 5-HT itself on 2-DG-induced hyperphagia remain unclear. In the present study, therefore, we investigated the effects of peripheral administration of 5-HT on hyperphagia elicited by 2-DG in rats.

Since 2-DG induces glucoprivation by inhibition of glucose utilization of cells, it elevates plasma glucose levels to compensate it.12,13 2-DG-induced hyperphagia is elicited in response to low glucose levels in the brain. It suggests that facilitation of hyperglycemia may improve shortage of glucose in the brain by increasing glucose uptake to cells, which may lead to inhibition of hyperphagia. The peripheral 5-HT receptor participates in glucose regulation.14–17 We reported that peripheral 5-HT elicits hyperglycemia in rats.16 Thus, 5-HT may affect food intake in 2-DG-treated rats through modifying glucose levels. We also examined effects of 5-HT on blood glucose levels in 2-DG-treated rats.
Effects of 5-HT on 2-DG-elicited hyperglycemia are demonstrated in Fig. 3. 2-DG elicited an apparent hyperglycemia after the injection. 5-HT itself elicited significant hyperglycemia 15 min after the injection but no significant effect 30 min after the treatment. Coadministration of 5-HT did not alter 2-DG-induced hyperglycemia.

DISCUSSION

It is well recognized that the central 5-HT is involved in feeding behavior mediated by several 5-HT receptor subtypes. In the peripheral system, 5-HT may be related to the regulation of food intake, since peripherally administered 5-HT, which did not cross the blood brain barrier, elicits anorexia in rats. As shown in results, food intake gradually increased after the injection of 2-DG for 2 h. We previously found that 5-HT i.p. elevated plasma glucose levels and its effects abolished within 2 h. Thus, we examined effects of 5-HT on 2-DG-induced hyperphagia for 2 h.

The present study demonstrated that peripherally administered 5-HT apparently inhibited 2-DG-induced hyperphagia. The dose of 5-HT that inhibited 2-DG-elicited hyperphagia, did not affect food intake of satiated rats. Thus, peripheral 5-HT suppresses enhanced feeding with higher sensitivity than that in normal rats.

Although it was reported 5-HT itself induced hypophagia in food deprived rats that is blocked by the peripheral 5-HT receptor antagonist, xylamidine, it is not yet clear which 5-HT2 receptor subtypes, that is, 5-HT2A, 5-HT2B, 5-HT2C subtypes, are associated with it. Since the peripheral 5-HT2 receptor agonist a-methyl-5-HT induces hypophagia and it is antagonized by the 5-HT2A receptor antagonist, the peripheral 5-HT2A receptor may be involved in feeding behavior. Therefore, we studied effects of the peripheral 5-HT2A receptor antagonist ketanserin.

Inhibitory effects of 5-HT on 2-DG-elicited hyperphagia are blocked by pretreatment with the 5-HT2A receptor antagonist ketanserin. It is consistent with previous results that the a-methyl-5-HT inhibits 2-DG-elicited hyperphagia, which is antagonized by ketanserin. It suggests that the suppressive effects of 5-HT on 2-DG-induced hyperphagia are mediated by the peripheral 5-HT2A receptor. It is well known that 5-HT receptor is classified into many subtypes. The possibility that other 5-HT receptor subtypes may be related to anorexia induced by 5-HT cannot be excluded at present. However, ketanserin powerfully antagonized 5-HT-induced inhibition on 2-DG-induced hyperphagia and returned it to the control level. Therefore, it is likely that the peripheral 5-HT2A receptor plays a role in effects of 5-HT.

After 2-DG elicits neuroglucopenia, hyperglycemia is induced by activating the release of hyperglycemic hormones such as adrenaline or corticosterone. Hyperphagia elicited by 2-DG is caused by inhibition of glucose utilization in the hypothalamus, the center of feeding regulation. Therefore, suppressive effects of 5-HT on 2-DG-induced hyperphagia may be elicited by affecting glucose levels. We previ-
ously found that peripherally administered 5-HT elicits hyperglycemia, which is antagonized by the 5-HT<sub>2A</sub> receptor antagonist ketanserin<sup>16</sup>) similar to the effects on 2-DG-induced hyperphagia. Thus, we studied the effects of 5-HT on 2-DG-induced hyperglycemia.

As shown in the results, 2-DG at a dose of 750 mg/kg induced hyperglycemia. It was also shown that 5-HT itself induced significant hyperglycemia 15 min after the injection and its hyperglycemia abolished 30 min after the treatment, which are in agreement with our previous report<sup>16</sup>) However, 5-HT did not affect 2-DG-induced hyperglycemia. Therefore, it is likely that the inhibitory effects of 5-HT on 2-DG-induced hyperphagia are not caused by facilitating hyperglycemia.

The mechanism for peripheral 5-HT-induced anorexia has been reported. Hypophagia induced by the 5-HT releasing drug fenfluramine may be related to decreases in gastric emptying<sup>9,21</sup>) It has been suggested that 5-HT contracts the gastric pylorus<sup>22</sup>) Some effects of 5-HT on gastric emptying may be related to the suppressive effects of 5-HT on 2-DG-induced hyperphagia.

In conclusion, the present results demonstrate that peripherally administered 5-HT inhibited 2-DG-induced hyperphagia in rats mediated by the 5-HT<sub>2A</sub> receptor. Since 5-HT did not affect 2-DG-induced hyperglycemia, this effect is not derived from augmentation of hyperglycemia.

REFERENCES