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Effects of peripheral 5-HT_2 and 5-HT_3 receptor agonists on food intake in food-deprived and 2-deoxy-D-glucose-treated rats

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Abstract

Peripherally administered, the 5-HT_2 receptor agonist, α-methyl-5-hydroxytryptamine (α-methyl-5-HT), significantly suppressed the food intake of food-deprived rats. α-Methyl-5-HT also inhibited 2-deoxy-D-glucose-induced hyperphagia in rats. The α-methyl-5-HT-induced hypophagia was antagonized by the 5-HT_{2A} receptor antagonist, ketanserin. The α-methyl-5-HT-induced decrease in food intake of food-deprived rats was not inhibited by prior adrenodemedullation. The peripheral 5-HT_3 receptor agonist, 2-methyl-5-HT, did not affect food intake in food-deprived or 2-deoxy-D-glucose-treated rats. These results suggest that the peripheral 5-HT_{2A} receptor may participate in the regulation of food intake and that its hypophagic effects are not associated with its adrenaline-releasing effects from the adrenal gland. Lastly, the peripheral 5-HT_3 receptor did not participate in feeding control.

Keywords: α-Methyl-5-HT (α-methyl-5-hydroxytryptamine); 2-Methyl-5-HT (2-methyl-5-hydroxytryptamine); Food intake; 2-Deoxy-D-glucose; 5-HT_{2A} receptor, peripheral; 5-HT_3 receptor, peripheral

1. Introduction

It has been suggested that serotonergic systems influence feeding. The administration of 5-hydroxytryptamine (5-HT) precursors, reuptake inhibitors, or 5-HT receptor agonists suppresses food intake in rats (Blundell, 1984; Curzon, 1990). To date, much attention has been focused on the role of 5-HT receptors in the control of food intake in the central nervous system. It has been reported that the 5-$HT_{2A/2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI), or the 5-$HT_{2C/2B}$ receptor agonist, 1-(3-chlorophenyl)piperazine (mCPP), decreases food intake in rats and that these effects may be mediated by the central effects of 5-HT on food intake (Schechter and Simansky, 1988; Kennett and Curzon, 1991; Aulakh et al., 1992; Dourish, 1995). Furthermore, the central 5-HT_{1B} receptor is also related to hypophagia in rats, since the 5-HT_{1B} receptor agonists cause anorexia and the central injection of a 5-HT_{1B} receptor antagonist, metergoline, elicits feeding behaviour (Kennett et al., 1987; Coscina et al., 1994). In addition, the finding that the 5-HT_3 receptor antagonist, ondansetron, reduces food intake (Van der Hoek and Cooper, 1994), indicates that the 5-HT_3 receptor may also participate in the control of eating. However, it remains unclear whether the central or peripheral 5-HT_3 receptor is involved in feeding.

Previous findings indicate that peripheral 5-HT may be related to feeding. It has been reported that peripherally administered 5-HT induces anorexia and that this effect is associated with the peripheral 5-HT_2 receptor (Pollock and Rowland, 1981; Blundell, 1984; Fletcher and Burton, 1985; Edwars and Stevens, 1989). In addition, the peripherally acting 5-HT_1 receptor agonist, 5-carboxamidotryptamine, or the peripheral 5-HT_2 receptor agonist, α-methyl-5-HT, reduces food intake in rats (Simansky et al., 1989–1990; Simansky, 1991). However, the detailed mechanism for peripheral 5-HT receptor-mediated anorexia is not yet established.

α-Methyl-5-HT acts as a peripheral 5-HT_2 receptor agonist, since it can elicit hyperglycemic effects which are antagonized by the peripheral 5-HT_2 receptor antagonist (Chaouloff et al., 1990; Baudrie and Chaouloff, 1992).

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2-Deoxy-D-glucose is a glucose analog which prevents utilization of intracellular glucose, and is known to elicit eating in rats and 2-deoxy-D-glucose-induced feeding is an animal model of hyperphagia (Smith and Epstein, 1969). However, the effects of the peripheral 5-HT_2 receptor agonist on 2-deoxy-D-glucose-induced hyperphagia have not been investigated. In the present study, therefore, we investigated the effects of α-methyl-5-HT on food intake in both food-deprived and 2-deoxy-D-glucose-treated rats.

Adrenaline released from the adrenal gland is an anoretic factor and can elicit food-suppressive effects (Bellingerm and Williams, 1986). It has been shown that the 5-HT receptor relates to the sympathoadrenal system and facilitates adrenaline release (Bagdy et al., 1989; Chaouloff et al., 1992). Chaouloff et al. (1992) reported that α-methyl-5-HT can increase plasma adrenaline levels. This raises the possibility that α-methyl-5-HT-induced anorexia may be associated with adrenaline released from the adrenal gland. Thus, to clarify the involvement of adrenaline in the peripheral 5-HT_2 receptor-mediated anorexia, we examined the effects of α-methyl-5-HT on food intake in adrenodemedullated rats. We also studied the effects of the peripheral 5-HT_3 receptor agonist, 2-methyl-5-hydroxytryptamine (2-methyl-5-HT), on feeding in rats, because the role of the peripheral 5-HT_3 receptor in food intake remains unclear.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (200–240 g, SLC Japan) were housed in individual stainless-steel wire cages. They were maintained under a controlled 12-h/12-h light/dark cycle (light from 07:00 to 19:00 h), at a room temperature of 24 ± 1°C and humidity 55 ± 5% for at least 7 days prior to the experiments. The rats were allowed free access to food and water.

2.2. Drug treatment

α-Methyl-5-hydroxytryptamine maleate (α-methyl-5-HT), 2-methyl-5-hydroxytryptamine maleate (2-methyl-5-HT) and ketanserin tartrate were obtained from Research Biochemicals (USA). 2-Deoxy-D-glucose was purchased from Wako Pure Chemical (Japan). All drugs were dissolved in saline and injected i.p. at a volume of 0.2 ml/100 g. Ketanserin was given 30 min before the injection of α-methyl-5-HT. 2-Deoxy-D-glucose and α-methyl-5-HT or 2-methyl-5-HT were administered i.p. simultaneously on opposite sides of the abdomen, respectively. All doses refer to the weights of the respective free base.

2.3. Operation of adrenodemedullation

Bilateral adrenodemedullation was performed under anesthesia with sodium pentobarbital (50 mg/kg). Experiments were carried out 1 week after the operation.

2.4. Measurement of food intake

In experiments using food-deprived rats, food was removed for 20 h before the experiments, although water was allowed. Pre-weighed food was placed in the cage and the amount remaining was weighed 0.5, 1, 2 and 4 h after the injection of α-methyl-5-HT or 2-methyl-5-HT. In experiments involving 2-deoxy-D-glucose-induced feeding, food and water were freely supplied to rats. After the injection of 2-deoxy-D-glucose at a dose of 750 mg/kg, food was weighed after 0.5, 1, 2 and 4 h. Drugs were injected between 13:00 and 14:00 h.

2.5. Statistical analysis

Statistical significance was evaluated with Student's *t*-test for comparison of two groups. Dose-related effects of α-methyl-5-HT or 2-methyl-5-HT on feeding were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test. Effects of ketanserin on α-methyl-5-HT-induced effects or results obtained with 2-deoxy-D-glucose were analyzed by two-way ANOVA followed by Tukey's test.

3. Results

3.1. Effects of α-methyl-5-HT on food intake of food-deprived rats and ketanserin on α-methyl-5-HT-induced hypophagia

Fig. 1 shows the effects of α-methyl-5-HT on the food intake of food-deprived rats. α-Methyl-5-HT elicited apparent hypophagia in a dose-related manner. Fig. 2 demonstrates the effects of the 5-HT_{2A} receptor antagonist, ketanserin, on α-methyl-5-HT-induced hypophagia. As shown, ketanserin significantly antagonized the hypophagia elicited by α-methyl-5-HT. Ketanserin itself did not affect the food intake of food-deprived rats.

3.2. Effects of α-methyl-5-HT on 2-deoxy-D-glucose-induced hyperphagia and ketanserin on α-methyl-5-HT-induced inhibition of 2-deoxy-D-glucose-induced hyperphagia

Effects of α-methyl-5-HT on 2-deoxy-D-glucose-induced hyperphagia are shown in Fig. 3. Following the injection of 2-deoxy-D-glucose at a dose of 750 mg/kg,

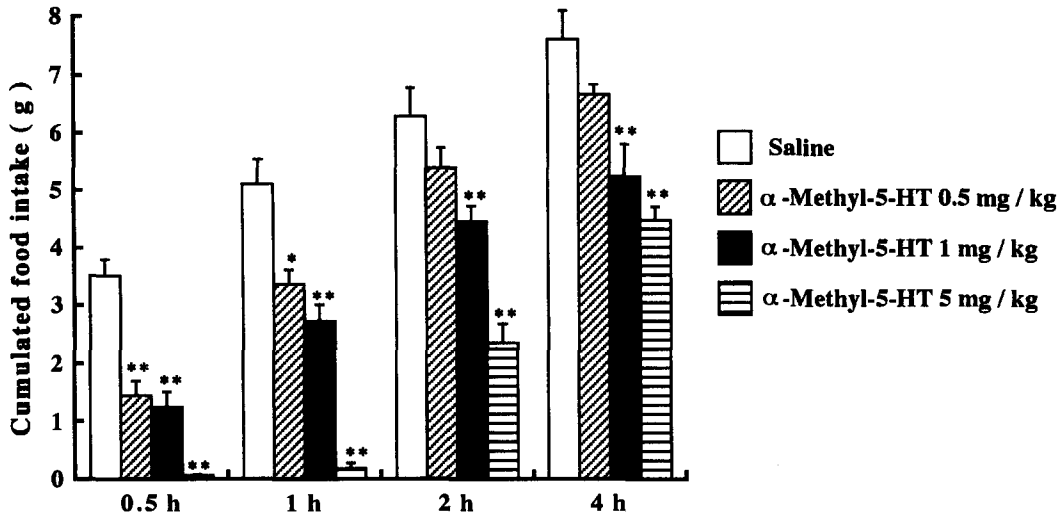

Fig. 1. Effects of α-methyl-5-HT on food intake of food-deprived rats. Results are shown as mean ± S.E. ($n = 6–9$). α-Methyl-5-HT was injected i.p. * $P < 0.05$, ** $P < 0.01$ by Dunnett's test following one-way ANOVA. F values: 0.5 h, $F(3,29) = 39.7$, $P < 0.0001$; 1 h, $F(3,29) = 70.6$, $P < 0.0001$; 2 h, $F(3,29) = 19.4$, $P < 0.0001$; 4 h, $F(3,29) = 13.6$, $P < 0.0001$.

marked hyperphagia was elicited in non-food-deprived rats. α-Methyl-5-HT above the dosage of 2.5 mg/kg apparently inhibited 2-deoxy-D-glucose-induced hyperphagia in rats, although it did not affect the food intake of non-food-deprived rats. Pre-treatment with ketanserin significantly antagonized the α-methyl-5-HT-induced inhibition of 2-deoxy-D-glucose-elicited hyperphagia (Fig. 4). Ketanserin did not affect the 2-deoxy-D-glucose-induced hyperphagia.

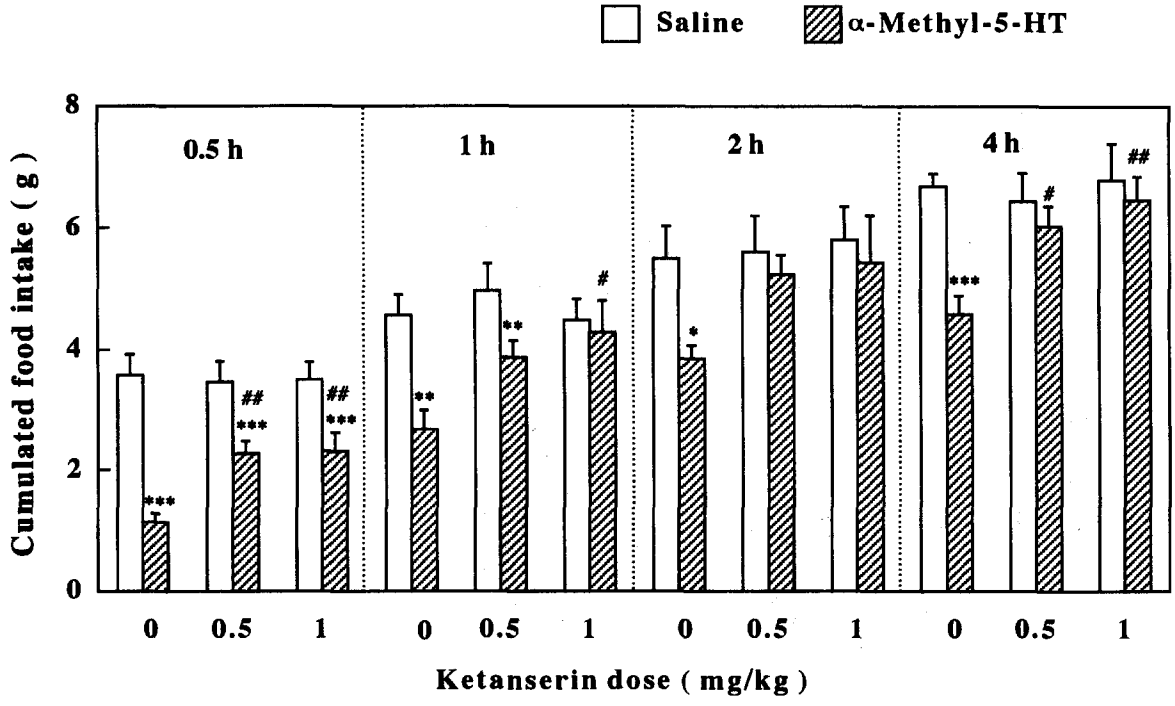

Fig. 2. Effects of ketanserin on α-methyl-5-HT-induced hypophagia in food-deprived rats. Results are shown as mean ± S.E. ($n = 6–7$). α-Methyl-5-HT, 1 mg/kg, was given i.p. Ketanserin was injected i.p. 30 min before α-methyl-5-HT. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. ketanserin + saline of respective group # $P < 0.05$, ## $P < 0.01$ vs. saline + α-methyl-5-HT of respective group by Tukey's test following two-way ANOVA. F values are as follows. 0.5 h: ketanserin $F(2,33) = 3.84$, $P < 0.05$, α-methyl-5-HT $F(1,33) = 56.8$, $P < 0.0001$, interaction $F(2,33) = 5.44$, $P < 0.01$. 1 h: ketanserin $F(2,33) = 9.72$, $P < 0.001$, α-methyl-5-HT $F(1,33) = 26.2$, $P < 0.0001$, interaction $F(2,33) = 3.37$, $P < 0.05$. 2 h: ketanserin $F(2,33) = 2.11$, N.S., α-methyl-5-HT $F(1,33) = 4.41$, $P < 0.05$, interaction $F(2,33) = 1.03$, N.S. 4 h: ketanserin $F(2,33) = 2.79$, N.S., α-methyl-5-HT $F(1,33) = 16.3$, $P < 0.001$, interaction $F(2,33) = 3.43$, $P < 0.05$.

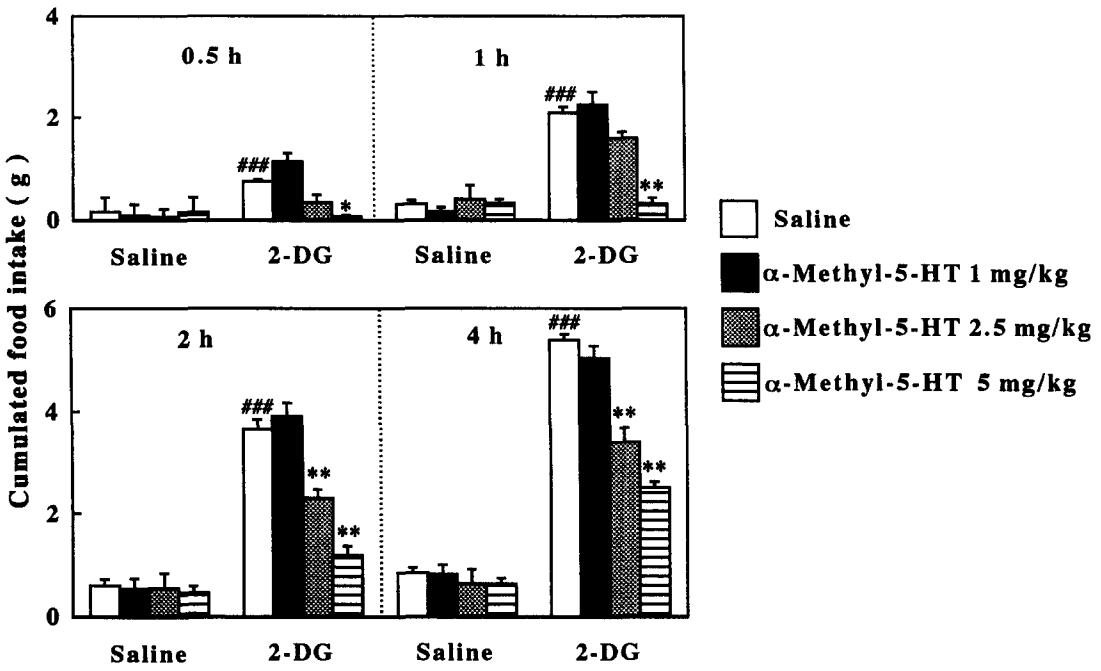

Fig. 3. Effects of α-methyl-5-HT on 2-deoxy-D-glucose (2-DG; 750 mg/kg)-induced hyperphagia in rats. Results are shown as mean ± S.E. ($n = 5–7$). 2-DG and α-methyl-5-HT were injected i.p. simultaneously. * $P < 0.05$, ** $P < 0.01$ vs. saline + 2-DG of respective group $^{###}$ $P < 0.001$ vs. saline + saline by Tukey's test following two-way ANOVA. F values are as follows. 0.5 h: α-methyl-5-HT, $F(3,38) = 10.2$, $P < 0.0001$; 2-DG, $F(1,38) = 42.6$, $P < 0.0001$; interaction, $F(3,38) = 10.6$, $P < 0.0001$. 1 h: α-methyl-5-HT, $F(3,38) = 13.7$, $P < 0.0001$; 2-DG, $F(1,38) = 130.0$, $P < 0.0001$; interaction, $F(3,38) = 20.5$, $P < 0.0001$. 2 h: α-methyl-5-HT, $F(3,38) = 19.9$, $P < 0.0001$; 2-DG, $F(1,38) = 229.2$, $P < 0.0001$; interaction, $F(3,38) = 17.0$, $P < 0.0001$. 4 h: α-methyl-5-HT, $F(3,38) = 13.1$, $P < 0.0001$; 2-DG, $F(1,38) = 270.8$, $P < 0.0001$; interaction, $F(3,38) = 9.53$, $P < 0.0001$.

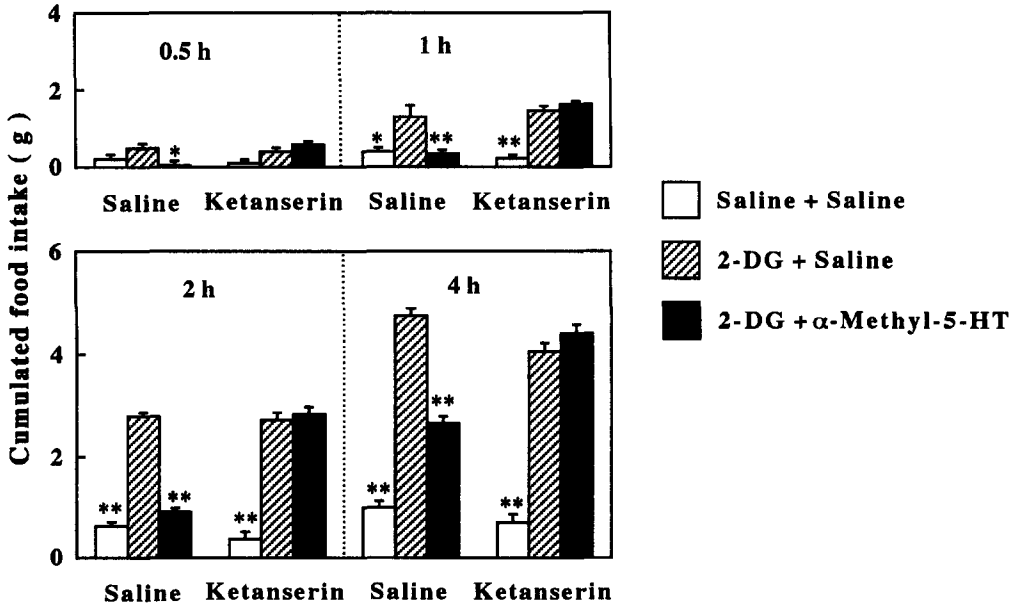

Fig. 4. Effects of ketanserin on α-methyl-5-HT-induced inhibition of hyperphagia elicited by 2-deoxy-D-glucose (2-DG) in rats. Results are shown as mean ± S.E. ($n = 5–8$). 2-DG at 750 mg/kg and α-methyl-5-HT at 5 mg/kg were injected i.p. Ketanserin at 1 mg/kg was injected i.p. 30 min before 2-DG and α-methyl-5-HT. * $P < 0.05$, ** $P < 0.01$ vs. saline + 2-DG of respective group by Tukey's test following two-way ANOVA. F values are as follows. 0.5 h: ketanserin $F(1,31) = 1.39$, N.S., α-methyl-5-HT $F(2,31) = 5.27$, $P < 0.05$, interaction $(2,31) = 6.67$, $P < 0.01$. 1 h: ketanserin $F(1,31) = 8.54$, $P < 0.01$, α-methyl-5-HT $F(2,31) = 23.8$, $P < 0.0001$, interaction $(2,31) = 10.5$, $P < 0.001$. 2 h: ketanserin $F(1,31) = 11.3$, $P < 0.01$, α-methyl-5-HT $F(2,31) = 93.1$, $P < 0.0001$, interaction $(2,31) = 24.5$, $P < 0.0001$. 4 h: ketanserin $F(1,31) = 0.36$, N.S. α-methyl-5-HT $F(2,31) = 87.6$, $P < 0.0001$, interaction $(2,31) = 13.0$, $P < 0.0001$.

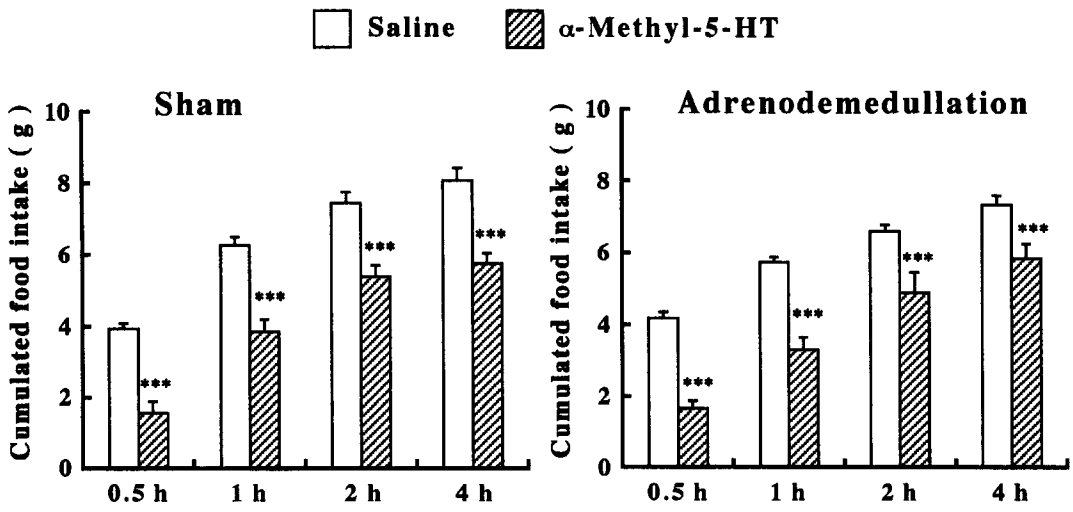

Fig. 5. Effects of adrenodemedullation on α-methyl-5-HT-induced hypophagia in food-deprived rats. Results are shown as mean ± S.E. ($n = 6–9$). α-Methyl-5-HT (1 mg/kg) was injected i.p. *** $P < 0.001$ by Student's t-test.

3.3. Effects of adrenodemedullation on α-methyl-5-HT-induced hypophagia in food-deprived rats

Fig. 5 shows the effects of α-methyl-5-HT on food intake of adrenodemedullated rats. Adrenodemedullation did not affect the food intake of food-deprived rats. In adrenodemedullated rats, α-methyl-5-HT elicited anoretic effects equal to that in sham-operated rats.

3.4. Effects of 2-methyl-5-HT on food intake of food-deprived and 2-deoxy-D-glucose-treated rats

2-Methyl-5-HT did not influence the food intake of food-deprived rats for 4 h (mean ± S.E. cumulated food intake g, $n = 6–7$. 0.5 h: saline 4.0 ± 0.24; 2-methyl-5-HT 1 mg/kg 3.8 ± 0.40; 2-methyl-5-HT 5 mg/kg 3.8 ± 0.44; $F(2,17) = 0.083$, N.S. 1 h: saline 5.7 ± 0.42; 2-methyl-5-HT 1 mg/kg 5.2 ± 0.49; 2-methyl-5-HT 5 mg/kg 5.5 ± 0.44; $F(2,17) = 0.27$, N.S. 2 h: saline 6.6 ± 0.26; 2-methyl-5-HT 1 mg/kg 6.2 ± 0.51; 2-methyl-5-HT 5 mg/kg 5.9 ± 0.49; $F(2,17) = 0.64$, N.S. 4 h: saline 8.1 ± 0.33; 2-methyl-5-HT 1 mg/kg 7.4 ± 0.50; 2-methyl-5-HT 5 mg/kg 7.6 ± 0.47; $F(2,17) = 0.71$, N.S.).

2-Methyl-5-HT, itself, did not affect the food intake of non-food-derived rats for 4 h. 2-Methyl-5-HT did not affect the hyperphagia elicited by 2-deoxy-D-glucose (mean ± S.E. cumulated food intake g, $n = 5–8$. 0.5 h: saline + saline 0.18 ± 0.10; saline + 2-methyl-5-HT 1 mg/kg 0.05 ± 0.03; saline + 2-methyl-5-HT 5 mg/kg 0.02 ± 0.02; 2-deoxy-D-glucose + saline 0.63 ± 0.14; 2-deoxy-D-glucose + 2-methyl-5-HT 1 mg/kg 0.90 ± 0.27; 2-deoxy-D-glucose + 2-methyl-5-HT 5 mg/kg 0.83 ± 0.18; F values, 2-methyl-5-HT, $F(2,30) = 0.11$, N.S.; 2-deoxy-D-glucose $F(1,30) = 30.1$, $P < 0.0001$; interaction, $F(2,30) = 0.98$, N.S. 1 h: saline + saline 0.25 ± 0.16; saline + 2-methyl-5-HT 1 mg/kg 0.23 ± 0.15; saline + 2-methyl-5-HT 5 mg/kg 0.31 ± 0.09; 2-deoxy-D-glucose + saline 1.4 ± 0.16; 2-deoxy-D-glucose + 2-methyl-5-HT 1 mg/kg 1.7 ± 0.25; 2-deoxy-D-glucose + 2-methyl-5-HT 5 mg/kg 1.8 ± 0.21; F values, 2-methyl-5-HT, $F(2,30) = 0.65$, N.S.; 2-deoxy-D-glucose $F(1,30) = 78.9$, $P < 0.0001$; interaction, $F(2,30) = 0.43$, N.S. 2 h: saline + saline 0.49 ± 0.18; saline + 2-methyl-5-HT 1 mg/kg 0.60 ± 0.20; saline + 2-methyl-5-HT 5 mg/kg 0.38 ± 0.11; 2-deoxy-D-glucose + saline 2.4 ± 0.22; 2-deoxy-D-glucose + 2-methyl-5-HT 1 mg/kg 2.8 ± 0.15; 2-deoxy-D-glucose + 2-methyl-5-HT 5 mg/kg 2.9 ± 0.19; F values, 2-methyl-5-HT, $F(2,30) = 0.71$, N.S.; 2-deoxy-D-glucose $F(1,30) = 205.6$, $P < 0.0001$; interaction, $F(2,30) = 1.03$, N.S. 4 h: saline + saline 0.95 ± 0.24; saline + 2-methyl-5-HT 1 mg/kg 0.88 ± 0.19; saline + 2-methyl-5-HT 5 mg/kg 1.0 ± 0.25; 2-deoxy-D-glucose + saline 3.9 ± 0.15; 2-deoxy-D-glucose + 2-methyl-5-HT 1 mg/kg 4.0 ± 0.23; 2-deoxy-D-glucose + 2-methyl-5-HT 5 mg/kg 3.9 ± 0.25; F values, 2-methyl-5-HT, $F(2,30) = 0.01$, N.S.; 2-deoxy-D-glucose $F(1,30) = 252.0$, $P < 0.0001$; interaction, $F(2,30) = 0.21$, N.S.).

4. Discussion

Our results demonstrate that the peripheral 5-HT_2 receptor agonist, α-methyl-5-HT, can decrease food intake in food-deprived rats. The anoretic effects of α-methyl-5-HT lasted for at least 4 h in rats receiving doses of > 1 mg/kg. Our results are consistent with previous findings of Hewson et al. (1987) and Simansky et al. (1989–1990) showing anoretic effects of α-methyl-5-HT in rats. α-Methyl-5-HT is known to cause hyperglycemia in rats and this effect is related to peripheral 5-HT_2 receptors (Baudrie and Chaouloff, 1992). As in previous studies (Hewson et al., 1987; Simansky et al., 1989–1990), we confirmed that

α-methyl-5-HT-induced decreases in food intake are antagonized by the pre-treatment with the 5-HT_2 receptor antagonist, ketanserin. This indicates that the hypophagic effects of α-methyl-5-HT are closely related to the peripheral 5-HT_2 receptor.

It has been found that several serotonergic drugs induce anorexia in humans under hyperphagic conditions such as bulimia (Freeman and Hampson, 1987; Blouin et al., 1988). However, it has not been determined whether the peripheral 5-HT_2 receptor agonist suppresses eating in hyperphagic models. Therefore, in the present study, we used a glucose analog (2-deoxy-D-glucose)-induced eating model of hyperphagia in rats. The present results demonstrated that α-methyl-5-HT significantly inhibits 2-deoxy-D-glucose-induced hyperphagia in rats, although this requires a higher dose than in food-deprived rats. The suppressive effects of α-methyl-5-HT on 2-deoxy-D-glucose-induced hyperphagia were antagonized by ketanserin. This suggests that the anoretic effects of α-methyl-5-HT on 2-deoxy-D-glucose-induced hyperphagia are also mediated by the peripheral 5-HT_2 receptor. It was recently found that the 5-HT_2 receptor can be subdivided into 5-$HT_{2A,2B,2C}$ receptors (Hoyer et al., 1994; Baxter et al., 1995). Although α-methyl-5-HT has an affinity for 5-HT_2 receptor subtypes, the affinity for the 5-HT_{2A} receptor is somewhat lower than for 5-HT_{2B} and 5-HT_{2C} receptors. Baxter et al. (1995) demonstrated that pEC_{50} values of α-methyl-5-HT for the 5-$HT_{2A,2B,2C}$ receptor are 6.1, 8.4 and 7.3, respectively. Furthermore, α-methyl-5-HT has an appropriate affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and 5-HT_4 receptor sites (Ismaiel et al., 1990; Saxena and Villalon, 1990). However, since ketanserin is known to have a high affinity for the 5-HT_{2A} receptor (Hoyer et al., 1994; Baxter et al., 1995), it is likely that suppression of food intake due to α-methyl-5-HT is mediated by the peripheral 5-HT_{2A} receptor. It should be noted that α-methyl-5-HT suppresses food intake in a hyperphagic model. This suggests that the peripheral 5-HT_{2A} receptor may be involved in the control of eating behaviour.

Adrenaline released from the adrenal gland is an anoretic factor and can suppress feeding (Bellingerm and Williams, 1986). It has been suggested that the 5-HT receptor relates to the sympathoadrenal system and that its activation facilitates adrenaline release (Bagdy et al., 1989). It has also been suggested that the effects of the clinically effective anoretic, fenfluramine, which releases neural 5-HT, may be connected to peripheral mechanisms (Davis et al., 1983; Baker et al., 1988; Francis et al., 1995). Chaouloff et al. (1992) reported that fenfluramine elevates plasma adrenaline levels, and also indicated that α-methyl-5-HT increases plasma adrenaline levels. We have previously found that the peripheral injection of 5-HT can cause a rise in plasma adrenaline levels in rats, which is mediated by the peripheral 5-HT_{2A} receptor (Yamada et al., 1995). Although the relation of peripheral 5-HT or adrenaline release to the suppressive effects of fenfluramine on eating behaviour has not yet been elucidated, these previous findings suggest that α-methyl-5-HT-induced anorexia may be associated with adrenaline release from the adrenal gland. Thus, we examined the effects of α-methyl-5-HT on food intake in adrenodemedullated rats. We found, however, that in adrenodemedullated rats, α-methyl-5-HT caused an apparent hypophagia similar to that in sham-operated rats. This suggests that α-methyl-5-HT-induced anorexia is not related to the adrenaline-releasing effects and that another mechanism is involved in the effects of α-methyl-5-HT. Some peripheral mechanisms of serotonergic drug-induced anorexia have so far been postulated. Previous findings suggest that decreases in gastric emptying may be related to the anoretic effects of fenfluramine (Davis et al., 1983; Baker et al., 1988; Francis et al., 1995) and that effects elicited by fenfluramine are antagonized by the peripheral 5-HT_2 receptor antagonist, xylamidine (Baker et al., 1988). Furthermore, Fletcher and Burton (1985) reported that 5-HT i.p. inhibits gastric emptying in rats. Since both 5-HT and α-methyl-5-HT cause anorexia through the peripheral 5-HT_2 receptor, α-methyl-5-HT-induced hypophagia may be connected to gastric emptying. However, there are contradictory reports as to whether the effects of peripheral 5-HT on gastric emptying depend on differences in doses or on experimental conditions (Fletcher and Burton, 1985; Gullikson et al., 1990; Francis et al., 1995). Since α-methyl-5-HT preferentially or selectively binds to 5-HT_2 receptor sites rather than to those for 5-HT (Hoyer et al., 1994), the effects of α-methyl-5-HT on motility of the gastric tract may provide some useful information on the peripheral hypophagic mechanism that involves the peripheral 5-HT_2 receptor.

It has recently been reported that the 5-HT_3 receptor agonist, 1-(m-chlorophenyl)-biguanide(mCPBG), induces hypophagia in rats, although the 5-HT_3 receptor antagonist, 1α H,3α,5α H-tropan-3-yl-3,5-dichlorobenzoate (MDL 72222), or ondansetron, did not affect it (Mazzola-Pomietto et al., 1995). In addition, systemic administration of the 5-HT_3 receptor antagonist, ondansetron, decreases the intake of palatable sweetened mash by freely feeding rats (Van der Hoek and Cooper, 1994). However, it is not clear whether the peripheral 5-HT_3 receptor is related to the feeding behaviour. Thus, to clarify the involvement of the peripheral 5-HT_3 receptor in food intake, we further investigated the effects of the peripheral 5-HT_3 receptor agonist, 2-methyl-5-HT, on food intake of food-deprived and 2-deoxy-D-glucose-treated rats. However, 2-methyl-5-HT did not affect food intake in either rat model. In addition, 2-methyl-5-HT did not change the food intake of non-food-deprived rats. This indicates that the peripheral 5-HT_3 receptor is not strongly linked with eating behaviour. Kennett and Grewal (1992) reported that 2-methyl-5-HT centrally injected did not affect food intake in rats. Therefore, it is suggested that the central 5-HT_3 receptor may also not be related to the control of food intake.

In summary, our results demonstrated that α-methyl-5-HT induces hypophagia in both food-deprived and 2-deoxy-D-glucose-induced hyperphagic rats. The effects of α-methyl-5-HT are closely connected to peripheral 5-HT_{2A} receptors, which indicates that these receptors are involved in the regulation of food intake. Our results also revealed that the adrenaline release induced by α-methyl-5-HT is not related to the latter's anoretic effects, but the mechanism of the suppressive effects of α-methyl-5-HT on food intake is not yet clear. Finally, the peripheral 5-HT_3 receptor is not associated with the food intake of rats.

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