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European Journal of Pharmacology 359 (1998) 81–86

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Effects of the non-selective 5-HT receptor agonist, 5-carboxamidotryptamine, on plasma glucose levels in rats

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Received 2 July 1998; revised 14 August 1998; accepted 18 August 1998

Abstract

The effects of the 5-$HT_{1A/1B/1D/5/7}$ receptor agonist, 5-carboxamidotryptamine (5-CT), on blood glucose, insulin and glucagon levels in rats were investigated. 5-CT above the dosage of 0.05 mg/kg elicited significant hyperglycemic effects and 0.1 mg/kg, induced a 35% increase in plasma glucose levels. 5-CT did not affect plasma glucagon, and serum insulin levels increased following the high dose of 5-CT. Adrenodemedullation abolished the 5-CT-induced hyperglycemia. Hyperglycemia induced by 5-CT was prevented by pretreatment with the 5-$HT_{1/2/7}$ receptor antagonist, metergoline, and the 5-$HT_{1/2/5/7}$ receptor antagonist, methysergide, although the 5-HT_{2A} receptor antagonist, ketanserin, the 5-$HT_{2A/2B/2C}$ receptor antagonist, ritanserin, and the 5-$HT_{3/4}$ receptor antagonist, tropisetron, had no effect. Although 5-CT has a high affinity with 5-HT_{1A} receptors, the 5-HT_{1A} and 5-HT_{1B} and β receptor antagonist, (−)-popranolol, did not affect 5-CT-induced hyperglycemia. These results indicate that 5-CT-induced hyperglycemia is elicited by facilitation of adrenaline release from the adrenal gland and that 5-CT-induced hyperglycemia is mediated by the 5-HT_7 receptor unrelated to 5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-HT_2, 5-HT_3, 5-HT_4 or 5-HT_5 receptors.

Keywords: 5-Carboxamidotryptamine; Hyperglycemia; 5-HT_7 receptor; (Rat); Adrenaline

1. Introduction

Previous findings indicate that stimulation of the central 5-HT_{1A}, or the 5-HT_2 receptor results in hyperglycemia in rats, on the basis of results with several 5-HT receptor agonists. The 5-HT_{1A} receptor agonist, 8-hydroxy-2-di-*n*-(propylamino)tetralin (8-OH-DPAT), and 5-HT_{1A} receptor partial agonists including buspirone and ipsapirone induce hyperglycemia in rats (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990a,b; Sugimoto et al., 1992). Furthermore, hyperglycemic effects were elicited in rats following the administration of a 5-$HT_{2A/2B/2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI), and a 5-$HT_{2C/2B}$ receptor agonist, 1-(3-chlorophenyl)piperazine (mCPP) (Baudrie and Chaouloff, 1992; Sugimoto et al., 1996b). Peripheral 5-HT receptors are also involved in glycemic control, since the peripheral administration of 5-HT or a peripheral 5-HT_{2A} receptor agonist can elevate plasma glucose levels of rats (Baudrie and Chaouloff, 1992; Yamada et al., 1995; Sugimoto et al., 1996a). Furthermore, there was a previous report that the peripherally acting 5-$HT_{1A/1D}$ receptor agonist, *N*,*N*-dipropyl-5-carboxamidotryptamine (DP-5-CT), at a high dose elicits hyperglycemia in rats (Laude et al., 1990).

5-Carboxamidotryptamine (5-CT) has a high affinity with 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D} and 5-HT_5 receptors (Hoyer et al., 1994). 5-CT is also recognized as a 5-HT_7 receptor (formerly 5-HT_1-like receptor) agonist (Eglen et al., 1997) and it elicits relaxation of vascular muscle and hypotension in rats, probably mediated by the peripheral 5-HT_7 receptor subtype (Saxena and Lawang, 1985 Treventhick and Humphrey, 1986; Terron, 1997). Simansky (1991) reported that 5-CT inhibits food intake and elicits drinking in rats, as a result of activation of the peripheral 5-HT_7 (5-HT_1-like) receptor. However, glycemic responses to 5-CT have not yet been clarified. We, therefore, now report on the effects of 5-CT on glucose regulation and several 5-HT

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0014-2999/98/$ - see front matter
PII: S0014-2999(98)00617-7

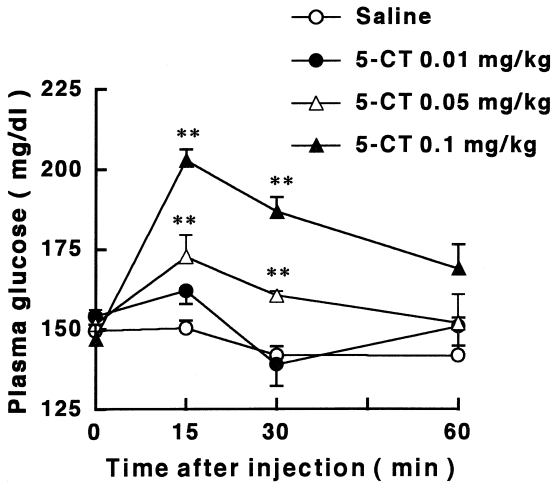

Fig. 1. Effects of 5-CT on plasma glucose levels of rats. Results are shown as means ± S.E. ($n = 5–9$). 5-CT was injected i.p. $*P < 0.05$, $**P < 0.01$.

receptor antagonists on glycemic effects of 5-CT investigated in rats.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (190–220 g) were purchased from SLC Japan (Japan). They were housed under a controlled 12-h/12-h light–dark cycle (light from 7:00 a.m. to 7:00 p.m.), with room temperature 24 ± 1°C and humidity 55 ± 5%. The rats were given food and water ad libitum.

2.2. Drug treatment

5-Carboxamidotryptamine maleate (5-CT), methysergide hydrogen maleate, metergoline, ritanserin, ketanserin tartrate, tropisetron, 8-hydroxy-2-di-*n*-(propylamino)tetralin hydrobromide (8-OH-DPAT) and (−)-popranolol hydrochloride were obtained from Research Biochemicals (USA). Methysergide, ketanserin and (−)-popranolol were dissolved in saline. Tropisetron was dissolved in a few drops of 0.1 M HCl and diluted with saline. Ritanserin and metergoline were suspended in 1% carboxymethylcellulose-Na. All drugs except 8-OH-DPAT were injected i.p. 8-OH-DPAT was given s.c. 5-HT receptor antagonists were given 30 min before the injection of 5-CT or 8-OH-DPAT.

2.3. Determination of blood glucose, insulin and glucagon levels

Blood samples were taken from the caudal vena cava under light ether anesthesia. Only one sample was taken from each rat. Plasma glucose levels were determined with methods described in a previous report (Sugimoto et al., 1992). The pancreatic hormones insulin and glucagon, were measured by radioimmunoassay using commercially available kits, Phadeseph Insulin (Pharmacia, Sweden) and glucagon Daiichi (Daiichi Radioisotope Center, Japan), respectively (Sugimoto et al., 1992).

2.4. Adrenodemedullation

Bilateral adrenodemedullation was performed under anesthesia with pentobarbital Na, 50 mg/kg. Experiments were carried out one week after the operation.

2.5. Statistics

Statistical significance was evaluated by Student's *t*-test for comparisons of two groups. Dose-related effects of 5-CT on plasma glucose levels were evaluated by One-way analysis of variance (ANOVA) followed by Dunnett's test. Effects of 5-HT receptor antagonists on 5-CT-induced

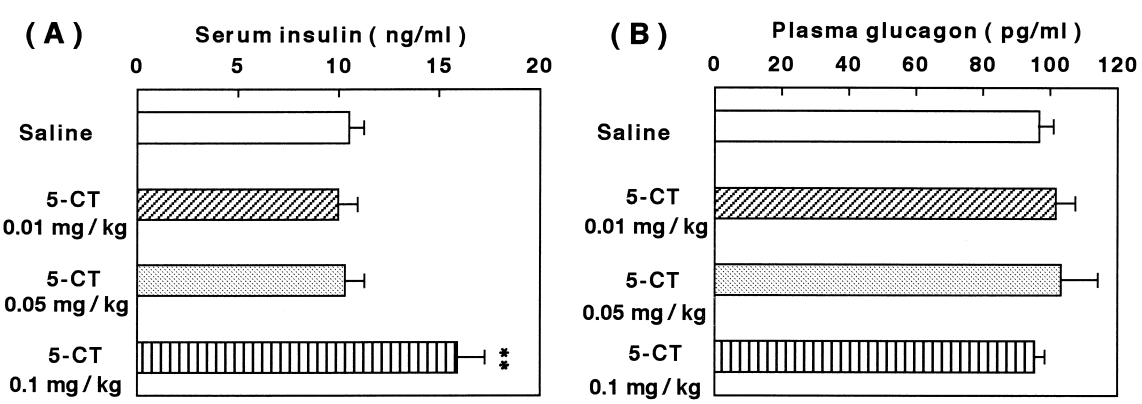

Fig. 2. Effects of 5-CT on serum insulin and plasma glucagon levels in rats. Results are shown as means ± S.E. ($n = 5–8$). 5-CT was injected i.p. Insulin and glucagon levels were determined 15 min after injection of 5-CT. $**P < 0.01$.

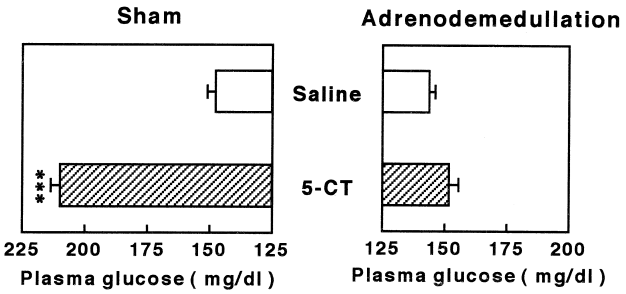

Fig. 3. Effects of 5-CT on plasma glucose levels in adrenodemedullated rats. Results are shown as means ± S.E. ($n = 5–6$). 5-CT was injected i.p. at 0.1 mg/kg. Plasma glucose levels were determined 15 min after injection of 5-CT. $***P < 0.001$.

effects were analyzed by Two-way ANOVA followed by Tukey's test.

3. Results

3.1. Effects of 5-CT on blood glucose, insulin and glucagon levels of rats

Fig. 1 shows the time-course changes of plasma glucose levels after treatment with 5-CT. At doses above 0.05 mg/kg, 5-CT elicited a significant hyperglycemia. The hyperglycemic effects of 5-CT lasted for 30 min. Fig. 2

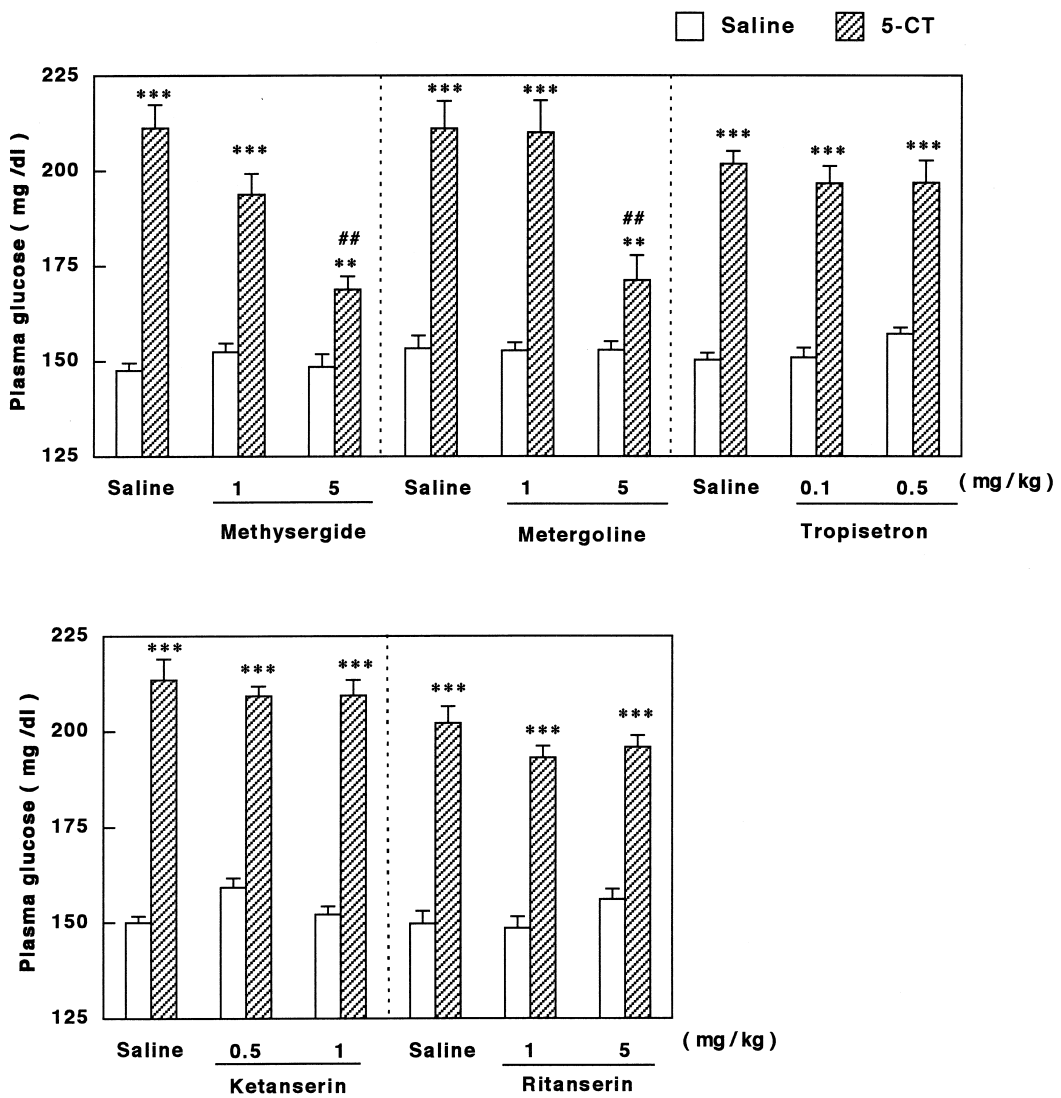

Fig. 4. Effects of 5-HT receptor antagonists on 5-CT-induced hyperglycemia in rats. Results are shown as means ± S.E. ($n = 5–8$). 5-CT was injected i.p. at 0.1 mg/kg. Plasma glucose levels were determined 15 min after injection of 5-CT. $**P < 0.01$, $***P < 0.001$ vs. antagonist + saline in respective group. $\#\#P < 0.01$ vs. saline + 5-CT.

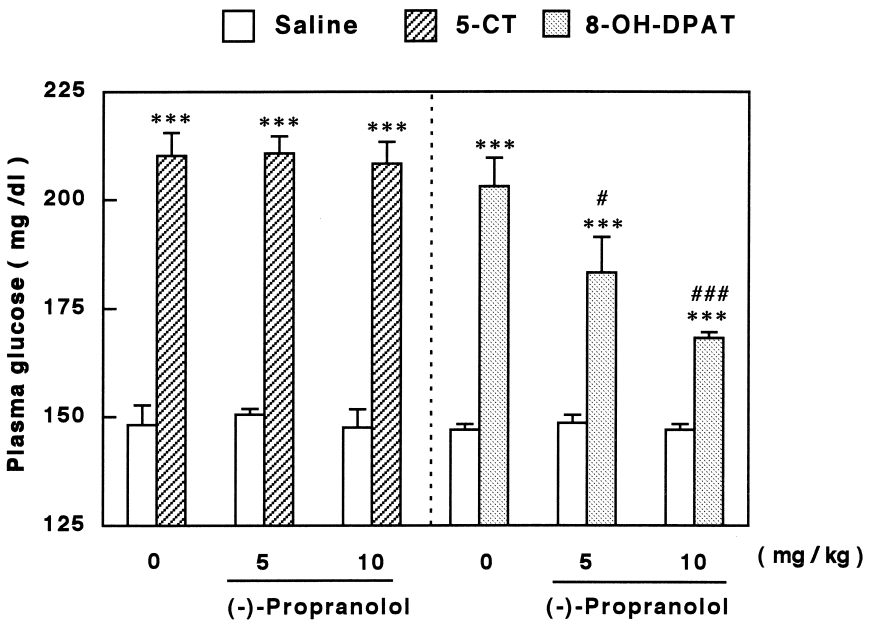

Fig. 5. Effects of (−)-propranolol on 5-CT and 8-OH-DPAT-induced hyperglycemia in rats. Results are shown as means ± S.E. ($n = 5–9$). 5-CT was injected i.p. at 0.1 mg/kg. 8-OH-DPAT was injected s.c. at 0.5 mg/kg. Plasma glucose levels were determined 15 min after injection of 5-CT or 8-OH-DPAT. $***P < 0.001$ vs. saline in respective group. $\#P < 0.05$, $\#\#\#P < 0.001$ vs. saline + 8-OH-DPAT.

shows the effects of 5-CT on serum insulin and plasma glucagon levels 15 min after the injection of 5-CT. Serum insulin was significantly elevated only by the 0.1-mg/kg dose of 5-CT, which did not affect plasma glucagon levels.

3.2. Effects of 5-CT on plasma glucose levels in adrenodemedullated rats

The effects of adrenodemedullation on 5-CT (0.1 mg/kg)-induced hyperglycemia are shown in Fig. 3. Prior adrenodemedullation clearly reduced the hyperglycemia induced by 5-CT, although it elicited an apparent hyperglycemia in sham-operated rats.

3.3. Effects of 5-HT receptor antagonists on 5-CT-induced hyperglycemia in rats

The effects of several 5-HT receptor antagonists on 5-CT-induced hyperglycemia are shown in Fig. 4. The 5-$HT_{1/2/7}$ receptor antagonist, metergoline, and the 5-$HT_{1/2/5/7}$ receptor antagonist, methysergide, at a dose of 5 mg/kg significantly reduced the hyperglycemia elicited by 5-CT. However, neither the 5-HT_{2A} receptor antagonist, ketanserin, the 5-$HT_{2A/2B/2C}$ receptor antagonist, ritanserin, affected 5-CT-induced hyperglycemia. The 5-$HT_{3/4}$ receptor antagonist, tropisetron, was ineffective.

3.4. Effects of (−)-propranolol on 5-CT and 8-OH-DPAT-induced hyperglycemia in rats

Fig. 5 shows the effects of (−)-propranolol on 5-CT and 8-OH-DPAT-induced hyperglycemia. (−)-Propranolol did not alter 5-CT-induced hyperglycemia, although the hyperglycemia induced by the central 5-HT_{1A} receptor agonist, 8-OH-DPAT, was apparently inhibited by pretreatment with (−)-propranolol.

4. Discussion

Our results demonstrated that the peripherally acting 5-HT receptor agonist, 5-CT, apparently elicited hyperglycemia in rats. Above the low dose of 0.05 mg/kg, 5-CT induced significant hyperglycemia. The doses of 5-CT eliciting hyperglycemia were similar to those inducing other pharmacological effects such as hypophagia or drinking in rats (Simansky, 1991). Since the pancreatic hormones, insulin and glucagon, play a major role in glucose regulation, we determined blood levels of these hormones following the injection of 5-CT. Glucagon is not related to the hyperglycemia elicited by 5-CT, since 5-CT did not affect plasma glucagon levels. Although a dose of 0.05 mg/kg 5-CT induced hyperglycemia, serum insulin levels were not increased. Thus, it is suggested that insulin release is inhibited after this dose of 5-CT. However, serum insulin levels increased following a dose of 0.1 mg/kg. This suggests that an apparent hyperglycemia induced by 5-CT 0.1 mg/kg may trigger insulin release. Therefore, it is likely that 5-CT-induced hyperglycemia is not strongly related to inhibition of insulin release.

Several central 5-HT receptor agonists including the 5-HT_{1A} receptor agonist, 8-OH-DPAT, the 5-$HT_{2C/2B}$ receptor agonist, mCPP, and the 5-$HT_{2A/2B/2C}$ receptor

agonist, DOI, have been reported to elevate plasma glucose levels in rats (Chaouloff and Jeanrenaud, 1987; Baudrie and Chaouloff, 1992; Chaouloff et al., 1992; Sugimoto et al., 1996b). Furthermore, peripherally administered 5-HT and peripheral 5-HT_2 receptor agonists like α-methyl-5-HT elicit hyperglycemia mediated by the peripheral 5-HT_{2A} receptor in rats (Baudrie and Chaouloff, 1992; Yamada et al., 1995; Sugimoto et al., 1996a). This 5-HT receptor agonist-induced hyperglycemia is closely related to adrenaline release from the adrenal gland, since the agonists increase adrenaline levels in blood, and since adrenalectomy or adrenodemedullation can block the hyperglycemia induced by these drugs (Chaouloff et al., 1990a,b,c; Baudrie and Chaouloff, 1992; Sugimoto et al., 1992, 1996b; Yamada et al., 1995). This indicates that the 5-HT receptor may participate in glucose regulation by releasing adrenaline. Thus, the effects of adrenodemedullation on 5-CT-induced hyperglycemia were investigated. Adrenodemedullation did not affect basal plasma glucose levels in our experiments, which is consistent with previous results (Bouhelal and Mir, 1992), possibly as a result of homeostasis of plasma glucose levels. As we showed, 5-CT-induced hyperglycemia was clearly prevented by prior adrenodemedullation. Therefore, 5-CT-elicited hyperglycemia is induced by a facilitation of adrenaline release, similar to the effects of other 5-HT receptor agonists. We demonstrated that 5-CT elicits hyperglycemia in ether-anesthetized rats. Since ether itself stimulates adrenaline release, synergistic effects of ether with 5-CT may enhance hyperglycemia.

5-CT has a high affinity to various 5-HT receptor subtypes (Hoyer, 1991; Hoyer et al., 1994) and produces several pharmacological effects, such as hypotensive effects or relaxation of the vascular smooth muscle, which are mediated by the 5-HT_7 receptor (Saxena and Lawang, 1985; Treventhick and Humphrey, 1986; Terron, 1997). To evaluate the involvement of 5-HT receptor subtypes, effects of 5-HT receptor antagonists on 5-CT-induced hyperglycemia were investigated. The 5-$HT_{1/2/7}$ receptor antagonist, metergoline, and the 5-$HT_{1/2/5/7}$ receptor antagonist, methysergide, at a dose of 5 mg/kg significantly inhibited 5-CT-elicited hyperglycemia. In addition, the 5-HT_{2A} receptor antagonist, ketanserin, the 5-$HT_{2A/2B/2C}$ receptor antagonist, ritanserin, and the 5-$HT_{3/4}$ receptor antagonist, tropisetron, did not affect 5-CT-induced hyperglycemia. These results suggest that 5-HT_2, 5-HT_3 and 5-HT_4 receptors are not related to 5-CT-induced hyperglycemia. As metergoline, which inhibited 5-CT-induced hyperglycemia, has less affinity with 5-HT_5 receptors (Hoyer et al., 1994), it is likely that the 5-HT_5 receptor is unrelated to the effect. Together, these results indicate that the 5-HT_1 or the 5-HT_7 receptor may be related to 5-CT-induced hyperglycemia.

Glycemic responses to centrally acting 5-HT_1 receptor agonists have been reported. The 5-HT_{1A} receptor agonist, 8-OH-DPAT, is well known to elicit hyperglycemia in rats and mice by stimulating the central 5-HT_{1A} receptor (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990c; Durcan et al., 1991). Since Laude et al. (1990) showed that the 5-$HT_{1B/1D}$ receptor agonist, 7-trifluoromethyl-4-(4-methyl-1-piperazinyl)-pyrrolo(1,2-*a*)quinoxaline (CGS 12066B), affects neither plasma glucose nor plasma adrenaline levels, they concluded that the 5-$HT_{1B/1D}$ receptor does not participate in glucose regulation. Furthermore, the peripherally acting 5-$HT_{1A/1D}$ receptor agonist, *N*,*N*-dipropyl-5-carboxamidotryptamine (DP-5-CT), at a high dose causes hyperglycemia in rats (Laude et al., 1990). However, it was supposed that hyperglycemic effects of DP-5-CT are involved in the central 5-HT_{1A} receptor and that DP-5-CT penetrated to the brain and acted as a 5-HT_{1A} receptor agonist. It was reported that systemic injection of 5-CT can induce some central effects, such as inhibition of firing in the dorsal raphe nuclei in guinea pigs (Wright et al., 1992). Since 5-CT has a high affinity for 5-HT_{1A} receptors (Hoyer, 1991; Hoyer et al., 1994), the possibility arises that 5-CT-induced hyperglycemia is mediated by the central 5-HT_{1A} receptor. Thus, we compared the effects of (−)-popranolol, which blocks the central 5-HT_{1A} receptor, on 8-OH-DPAT- and 5-CT-induced hyperglycemia. 8-OH-DPAT-induced hyperglycemia is recognized as a result of stimulation of the central 5-HT_{1A} receptor, since it was prevented by (−)-popranolol or the selective 5-HT_{1A} receptor antagonist, WAY 100135 (Chaouloff and Jeanrenaud, 1987; Critchley et al., 1994). Although 5-$HT_{1A/1B}$ and the β receptor antagonist, (−)-popranolol, reduced the hyperglycemia induced by central 5-HT_{1A} receptor agonist, 8-OH-DPAT, it did not affect the 5-CT-induced hyperglycemia. This suggests that the central 5-$HT_{1A/1B}$ receptor is not involved in 5-CT-induced hyperglycemia. Furthermore, it is likely that the peripheral 5-$HT_{1A/1B}$ receptor is not related to the hyperglycemic effects of 5-CT.

As shown in Section 3, 5-CT-induced hyperglycemia was blocked by the 5-$HT_{1/2/5/7}$ receptor antagonist, methysergide, and the 5-$HT_{1/2/7}$ receptor antagonist, metergoline. It was reported that 5-CT, methysergide and metergoline have a high affinity with 5-HT_7 receptor subtypes (Hoyer et al., 1994). Simansky (1991) showed that 5-CT-induced anorexia in rats was prevented by methysergide but not affected by the 5-$HT_{1A/1B}$ receptor antagonist, (−)-popranolol, or the 5-$HT_{2A/2B/2C}$ receptor antagonist, ritanserin. It was demonstrated that 5-CT has a high affinity with 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors. Thus, it was suggested that 5-CT-induced hypophagia is mediated by the 5-HT_7 (5-HT_1-like) or 5-HT_{1D} receptor. The effects of 5-HT receptor antagonists on 5-CT-induced anorexia were comparable to these effects on 5-CT-induced hyperglycemia. Involvement of the 5-HT_{1D} receptor can probably be excluded, because the 5-$HT_{1B/1D}$ receptor agonist did not affect glycemia (Laude et al., 1990). Together, our results suggest that the 5-HT_7 receptor may be related to 5-CT-induced hyperglycemia.

A recent report suggests that 5-HT_7 receptor mRNA has not been detected in the adrenal gland in rats (Eglen et al., 1997). Thus, it is unlikely that 5-CT acts directly in the adrenal gland. The 5-HT_7 receptor is expressed in other tissues such as vascular smooth muscle (Eglen et al., 1997). Since 5-CT elicits relaxation of vascular smooth muscle and hypotensive effects mediated by the 5-HT_7 receptor (Treventhick and Humphrey, 1986; Eglen et al., 1997) hyperglycemia and adrenaline release elicited by 5-CT may be associated with responses to vasodilator effects. As shown in Section 3, the antagonistic effects of methysergide and metergoline were moderate. Therefore, an unknown mechanism independent of 5-HT receptors may be related to 5-CT-induced hyperglycemia.

In conclusion, our results demonstrated that the non-selective 5-HT receptor agonist, 5-CT, elicits hyperglycemia in rats. 5-CT-induced hyperglycemia is elicited by facilitation of adrenaline release. Furthermore, 5-CT-induced hyperglycemia is mediated by 5-HT_7 receptors unrelated to 5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-$HT_{1D,}$ 5-HT_2, 5-$HT_{3,}$ 5-HT_4 or 5-HT_5 receptors. Therefore, the 5-HT_7 receptor may be involved in the adrenaline release, like other 5-HT receptor subtypes.

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