Effects of the 5-HT_{2A} Receptor Agonist 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on Plasma Glucose and Glucagon Levels of Rats

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Effects of the 5-hydroxytryptamine (5-HT)$_{2A}$ receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on plasma glucagon levels were studied in rats. Systemic injection of DOI induces significant increases in plasma glucagon levels. Hyperglucagonemia induced by DOI was dose-dependently prevented by the 5-HT_{2A} receptor antagonist ketanserin. Adrenodemedullation abolished hyperglucagonemia elicited by DOI. Previous report demonstrated that the peripheral 5-HT_{2A} receptor agonist induces hyperglycemia in rats but does not increase plasma glucagon levels at doses inducing hyperglycemia. Therefore, our findings suggest that DOI-induced glucagon release was elicited by stimulation of the central 5-HT_{2A} receptor, which in turn increasing adrenaline release.

Key words DOI; glucagon; 5-HT; 5-HT_{2A} receptor; adrenaline

The phenylisopropylamine compound 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) has a structure similar to the hallucinogens 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) or 1-(2,5-dimethoxy-4- methylphenyl)-2-aminopropane (DOM) and is well recognized to be a central 5-hydroxytryptamine (5-HT)$_2$ receptor agonist.[1] The 5-HT_2 receptor is divided into 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} subtypes and DOI preferentially binds with 5-HT_{2A} receptors.[1,2] Administration of DOI induces head twitch responses in rodents, which are elicited by stimulation of the central 5-HT_{2A} receptors.[3] DOI also stimulates the release of several hormones, such as corticosterone and prolactin, and these responses are involved in the central 5-HT_{2A} receptor.[4]

Previous findings accumulated evidence that 5-HT in the central nervous system is involved in glucose regulation, because several central 5-HT receptor agonists can elicit hyperglycemia in rats and mice.[5—7] The 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetrulin (8-OH-DPAT) 8-OH-DPAT or buspirone elevates blood glucose levels in rats and mice.[5—7] Moreover, the 5-$HT_{2C/2B}$ receptor agonist *m*-chlorophenylpiperazine (mCPP) induces hyperglycemia in rats.[8] Our previous report has shown that DOI also elicits hyperglycemia in rats mediated by the 5-HT_{2A} receptor.[8] It is well known that pancreatic hormone glucagon elicits hyperglycemia. Although DOI elicits hyperglycemia, little is known about whether it affects circulating glucagon levels. In this paper, we investigated effects of DOI on glucagon secretion in rats and involvement of glucagon in hyperglycemia induced by DOI.

MATERIALS AND METHODS

Male Sprague-Dawley rats (180—230 g) were purchased from SLC Japan, Inc. (Japan). Rats were maintained under a controlled 12 h/12 h light dark cycle (light from 7:00 a.m. to 7:00 p.m.), with a room temperature of 23±1 °C and 55±5% humidity. All animals were given free access to food and water before the experiments.

DOI, ritanserin and ketanserin tartrate were obtained from Research Biochemicals Inc. (USA). DOI and ketanserin were dissolved in saline. Ritanserin was suspended in 1% carboxymethylcellulose-Na. All drugs were injected i.p. and 5-HT receptor antagonists were given 30 min before the injection of DOI.

Blood samples were taken from the caudal *vena cava* under ether anesthesia. Only one sample was removed from each rat. Plasma glucose levels were determined by the method previously described.[9] Glucagon levels were measured by radioimmunoassay using the commercially available kit, Glucagon Daiichi (Daiichi Radioisotope Center, Japan).

Bilateral adrenodemedullation was performed under anesthesia with pentobarbital Na at 50 mg/kg. A small incision was made along the apex of the cortex. Slight pressure applied, thus popping out the medulla. Experiments were carried out one week after the operation. After the experiments, the adrenodemedullated rats were killed and it was verified that the adrenal medulla was removed and that the adrenal cortex was preserved.

Statistical significance was evaluated by Student's *t*-test for comparisons of 2 groups. Dose-related effects of DOI on plasma glucose and glucagon levels were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test. Effects of 5-HT receptor antagonists on DOI-induced effects were analyzed by two-way ANOVA followed by Tukey's test.

RESULTS

Figures 1A and 1B show time course changes in plasma glucose and glucagon levels following the treatment with DOI 10 mg/kg. DOI elevated plasma glucose and glucagon levels and these responses reached the maximum 15 min after the injection. Dose response studies of DOI-elicited hyperglycemia and hyperglucagonemia are shown in Fig. 2. DOI increased plasma glucose and glucagon levels in dose dependent manner.

Figure 3 shows the effects of the 5-$HT_{2A/2B/2C}$ receptor antagonist ritanserin and the 5-HT_{2A} receptor antagonist ketanserin on hyperglucagonemia caused by DOI. Both ritanserin and ketanserin apparently reduced hyperglucagonemia elicited by DOI.

Figure 4 shows the effects of adrenodemedullation on

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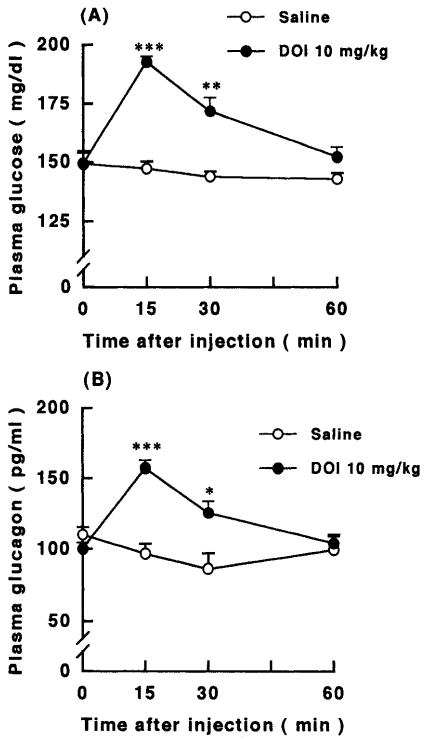

Fig. 1. Effects of DOI on Plasma Glucose and Glucagon Levels of Rats

(A) Plasma glucose, (B) plasma glucagon. Results are shown as the means±S.E. (n=5−7). DOI at 10 mg/kg was injected i.p. * p<0.05, ** p<0.01, *** p<0.001.

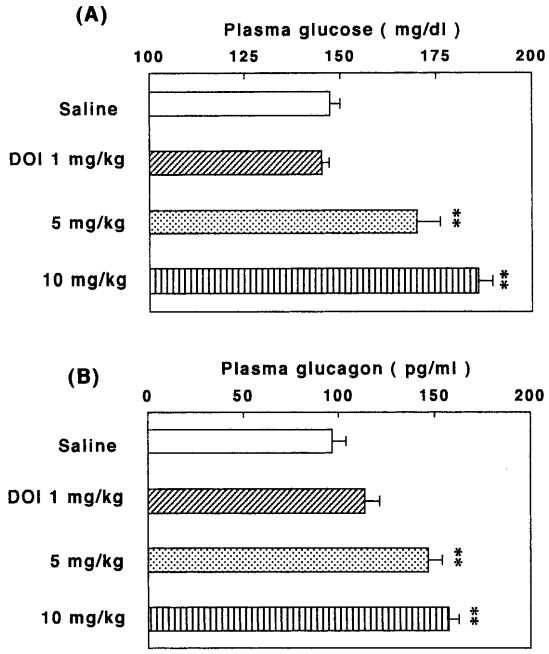

Fig. 2 Dose Response Studies of DOI on Plasma Glucose and Glucagon Levels of Rats

(A) Plasma glucose, (B) plasma glucagon. Results are shown as the means±S.E. (n=5−7). DOI was injected i.p. Plasma glucagon levels were determined 15 min after the injection of DOI. ** p<0.01.

DOI-induced hyperglycemia and hyperglucagonemia in rats. In sham operated rats, DOI increased plasma glucose and glucagon levels. Adrenodemedullation completely abolished both hyperglycemia and hyperglucagonemia.

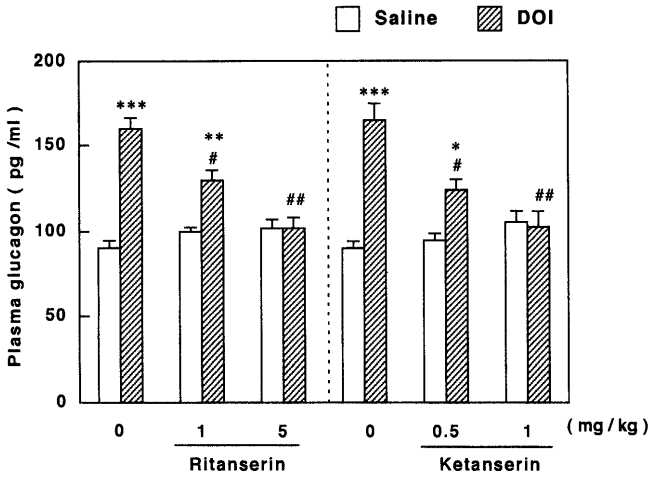

Fig. 3. Effects of Ritanserin and Ketanserin on DOI-Induced Hyperglucagonemia in Rats

Results are shown as the means±S.E. (n=5−7). Ritanserin and ketanserin were given i.p. 30 min before DOI. DOI at 10 mg/kg was injected i.p. * p<0.05, ** p<0.01, *** p<0.001 *vs.* saline of respective groups. # p<0.05, ## p<0.01 *vs.* saline+DOI.

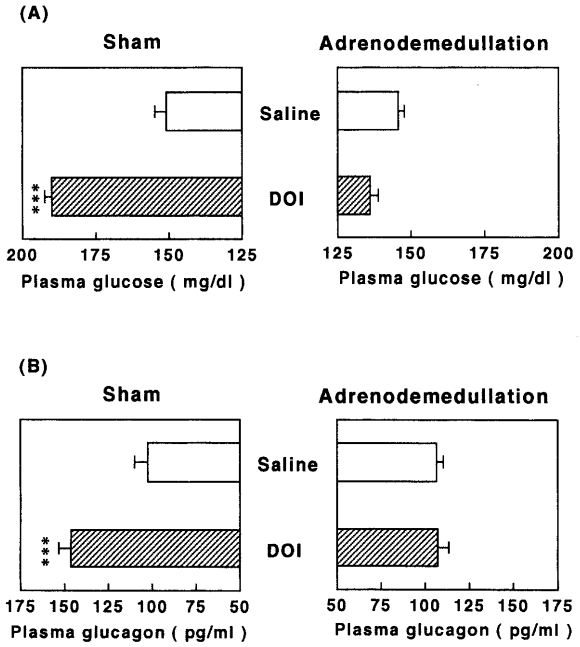

Fig. 4. Effects of DOI on Plasma Glucose and Glucagon Levels in Adrenodemedullated Rats

(A) Plasma glucose, (B) plasma glucagon. Results are shown as the means±S.E. (n=5−7). DOI at 10 mg/kg was injected i.p. Plasma glucose and .glucagon levels were determined 15 min after the injection of DOI. *** p<0.001.

DISCUSSION

Our present results have shown that DOI elevates plasma glucagon levels in rats. Maximum hyperglucagonemic effects of DOI were observed 15 min after the injection and disappeared within 60 min. As shown in results, time course changes in glucose levels following treatment with DOI are comparable with hyperglucagonemia. Moreover, dose response effects of DOI on plasma glucose levels are also similar to those on glucagon levels. Therefore, these results suggest that hyperglucagonemia may be associated with hyperglycemia induced by DOI.

DOI strongly stimulates the 5-HT_{2A} receptor and adminis-

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tration of DOI to rats was reported to suppress food intake, induce hyperthermia and these responses are mediated by the 5-HT_{2A} receptor.[10,11] It was also reported that DOI increases adenocorticotropic hormone (ACTH) or corticosterone levels of blood by stimulation of the 5-HT_{2A} receptor.[4,12] As shown in the results, DOI-induced hyperglucagonemia was strongly prevented by both the 5-$HT_{2A/2B/2C}$ receptor antagonist ritanserin and the 5-HT_{2A} receptor antagonist ketanserin. The doses of ritanserin and ketanserin used in the present study are those blocking the 5-HT_{2A} receptor-mediated head shake responses elicited by 5-hydroxytryptophan.[13] It indicates that DOI-induced hyperglucagonemia is elicited by stimulation of the 5-HT_{2A} receptor. Our previous report demonstrated that DOI-induced hyperglycemia is mediated by the 5-HT_{2A} receptor, since the 5-HT_{2A} receptor antagonist ketanserin inhibited hyperglycemia induced by DOI.[8] Taken together with previous findings, both hyperglucagonemia and hyperglycemia induced by DOI were blocked by ketanserin and these responses are elicited by activation of the 5-HT_{2A} receptor. It indicates that hyperglucagonemia induced by DOI may contribute to its hyperglycemic effects. We previously demonstrated that the peripheral 5-HT_{2A} receptor agonist α-methyl-5-HT induces hyperglycemia in rats but does not increase plasma glucagon levels at doses inducing hyperglycemia.[14] It suggests that DOI-induced hyperglucagonemia is mediated by the central 5-HT_{2A} receptor.

To date, the 5-HT_{1A} receptor agonist 8-OH-DPAT or ipsapirone, buspirone induces hyperglycemia, which is elicited by facilitation of adrenaline release.[9,15,16] The 5-$HT_{2C/2B}$ receptor agonist mCPP also raises blood glucose levels and adrenaline release from the adrenal gland is associated with its glycemic effects.[8] Thus, it is suggested that 5-HT receptor is related to glucose regulation by modifying adrenaline release. Bagdy *et al.* reported that DOI stimulates the sympathoadrenomedullary system and it can increase the plasma adrenaline levels of rats, although it was without effect on noradrenaline levels.[17] As shown in the results, DOI-induced hyperglycemia was prevented by adrenodemedullation. Hyperglucagonemic effects of DOI were inhibited by adrenodemedullation similar to hyperglycemia. Therefore, it is indicated that both DOI-induced hyperglycemia and hyperglucagonemia are mediated by facilitation of adrenaline release. Adrenaline increases blood glucose levels by stimulating glycogenolysis, inhibiting glucose uptake and insulin release.

In summary, the present findings suggest that DOI increases glucagon secretion in rats by stimulation of the central 5-HT_{2A} receptor and that hyperglucagonemia is closely related to its hyperglycemic effects. These responses are mediated by adrenaline release, since they were strongly prevented by prior adrenodemedullation. Our findings suggest that the central 5-HT_{2A} receptor participates glucagon release through adrenaline release and that hyperglucagonemia induced by DOI plays a role in its hyperglycemic effects.

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