The Effects of the Serotonin$_{1A}$ Receptor Agonist Buspirone on the Blood Glucose and Pancreatic Hormones in Rats

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ABSTRACT—The effects of the serotonin$_{1A}$ (5-HT$_{1A}$) receptor agonist buspirone on the plasma glucose and pancreatic hormones insulin and glucagon were investigated in rats. Buspirone elicited significant hyperglycemia and hyperglucagonemia, although it did not affect the insulin levels. Adrenodemedullation inhibited both the increase in blood glucose and glucagon levels. These results indicate that buspirone-induced hyperglycemia and hyperglucagonemia are mediated by adrenaline release from the adrenal gland.

Keywords: Buspirone, Serotonin$_{1A}$ receptor, Glucagon

The multiple serotonin (5-HT) receptor subtypes have been identified and several selective drugs have been developed in recent years. 5-HT$_1$ receptors are subdivided into 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$ and 5-HT$_{1E}$ receptors (1). It has been suggested that the 5-HT$_{1A}$ receptor may be involved in several physiological functions such as anxiety, food intake or thermoregulation (2). The activation of 5-HT$_{1A}$ receptors induces several pharmacological effects such as 5-HT syndrome, hypothermia or anxiolytic effects (2-4).

Buspirone has a high affinity for the 5-HT$_{1A}$ receptors, although buspirone acts as a partial agonist (2). Buspirone has been shown to be a new potent anxiolytic in humans and applied in clinical uses. Buspirone also elicits hyperglycemia in rats that is probably mediated by the activation of 5-HT$_{1A}$ receptors (5). Therefore, the treatment with buspirone may lead to the changes of glucose homeostasis. Blood glucose levels are regulated by several factors including catecholaminergic systems and pancreatic hormone insulin or glucagon. However, the effects of buspirone on insulin and glucagon are not yet clarified. The present study examined the effects of buspirone on blood glucose and pancreatic hormones insulin and glucagon.

Male SD rats weighing 180-240 g (SLC Japan, Inc., Japan) were used in all experiments. Rats were housed in a room with a controlled 12 hr/12 hr light/dark cycle, with lights on between 7:00 a.m. and 7:00 p.m., a temperature of 24 ± 1°C and at a humidity of 55 ± 5%. Experiments were performed between 1:00 p.m. and 4:00 p.m. Buspirone was purchased from Research Biochemicals Inc. (U.S.A.) and dissolved in saline. Buspirone was given s.c.

Blood samples were taken from the caudal vena cava under light ether anesthesia. Only one sample was removed from each rat. Plasma glucose and serum insulin levels were determined by the previously described method (6). Rat insulin (Novo, Denmark) was used as a standard for the determination of insulin. Plasma glucagon levels were determined by radioimmunoassay with a commercial available kit glucagon Daiichi (Daiichi Radioisotope Research Center, Japan) using the antiserum OAL 123 which is specific for pancreatic glucagon (7).

The operation of adrenodemedullation was performed under pentobarbital anesthesia. Buspirone at the dose of 20 mg/kg was injected 1 week after the operation.

Statistical significance was evaluated by Student’s t-test between two groups and by Dunnett’s test among three or more groups.

Effects of buspirone on plasma glucose are demonstrated in Fig. 1. Buspirone induced a significant hyperglycemia above the dosage of 10 mg/kg in rats. These results show that maximum hyperglycemia was elicited 15 min after the treatment. Therefore, insulin and glu-
Cagon levels were determined 15 min after the injection. Buspirone elicited the increases in plasma glucagon levels, although buspirone did not affect the serum insulin levels (Fig. 2). Buspirone at 20 mg/kg induced 47% increases in plasma glucagon levels compared to the control group.

Figure 3 demonstrates the effects of buspirone at a dose of 20 mg/kg on plasma glucose and glucagon levels in adrenoademulated rats. Buspirone produced an apparent hyperglycemia and hyperglucagonemia in sham-operated rats as well as in intact rats. Adrenoademulation abolished both hyperglycemia and hyperglucagonemia elicited by buspirone.

Our results demonstrate that buspirone affects plasma glucose and pancreatic hormone glucagon in rats. Buspirone induced an apparent hyperglycemia in rats which is in agreement with a previous study (5). Since the pancreatic hormones insulin and glucagon regulate the blood glucose levels, we studied the effects of buspirone on blood insulin and glucagon levels of rats. As shown in the results, buspirone did not affect insulin levels. However, buspirone apparently increased the
plasma glucagon levels of rats. This is the first study to demonstrate the hyperglucagonemic effects of buspirone. Therefore, the hyperglucagonemic effects of buspirone may participate in hyperglycemia.

A recent study suggests that the selective 5-HT<sub>1A</sub> receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) can induce hyperglycemic effects in rats and its effects are based on the adrenaline release from the adrenal gland (8). Buspirone is also an agonist of 5-HT<sub>1A</sub> receptors, and Chaouloff et al. (5) reported that buspirone can facilitate adrenaline release. We also determined the plasma adrenaline level 15 min after the treatment with 20 mg/kg buspirone by HPLC with electrochemical detection and found that buspirone significantly increased the level of plasma adrenaline (Saline: 1.9 ± 0.19 ng/ml, Buspirone: 5.9 ± 0.16 ng/ml, N = 6, **P < 0.01). It suggests that hyperglycemia induced by buspirone may be related to adrenaline release. Although adrenomedullated rats are available to clarify the involvement of adrenaline, there is no report examining the effects of buspirone in these rats. Therefore, we studied the effects of buspirone on plasma glucose levels in adrenomedullated rats. The results demonstrated that adrenomedullation completely abolished buspirone-induced hyperglycemia. This strongly suggests that hyperglycemia by buspirone depends on adrenaline release.

It is well-known that the adrenergic system regulates the pancreatic hormones and glucagon secretion is controlled by an adrenergic mechanism based on the activation of α or β adrenoceptors (9, 10). This suggests that the hyperglucagonemia caused by buspirone may be related to the adrenaline release from the adrenal gland. To confirm this, we determined the plasma glucagon levels in adrenomedullated rats. The present observations indicate that no hyperglucagonemia was elicited in adrenomedullated rats. This suggests that hyperglucagonemia elicited by buspirone was also related to the adrenaline release as well as hyperglycemia. Thus, it is considered that adrenaline released by buspirone from the adrenal medulla activates α and β adrenoceptors and this resulted in hyperglucagonemia.

Despite an apparent hyperglycemia, insulin release was not observed by the treatment with buspirone (Figs. 1 and 2), suggesting that there is an inhibition of insulin release, which is probably mediated by adrenaline. It has been reported that the 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT at a high dose decreases blood insulin levels (11). In our study, significant decreases in serum insulin levels were not observed after the treatment with buspirone. The reason for the difference between the effects of 8-OH-DPAT and buspirone on insulin levels is not yet clear. Further studies are required with glucose or other insulin releasing agents.

In this study, we have shown that the 5-HT<sub>1A</sub> recep-
tor agonist buspirone induces hyperglycemia and hyperglucagonemia, and these effects are strongly related to the adrenaline release. Buspirone has a high affinity to 5-HT$_{1A}$ receptors and also to dopamine$_{2}$ (D$_2$) receptors (12). However, we found that buspirone-induced hyperglycemia and hyperglucagonemia were unaffected by the D$_2$ receptor antagonist haloperidol at a dose of 0.5 mg/kg, which is sufficient to block the hyperlocomotion elicited by dopamine agonists (Y. Sugimoto et al., unpublished data). Therefore, this suggests that hyperglycemia and hyperglucagonemia induced by buspirone are not related to D$_2$ receptors.

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