Effects of the Serotonergic Anxiolytic Buspirone on Plasma Glucose and Glucose-Induced Hyperglycemia in Mice

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Abstract. Effects of the serotonergic anxiolytic buspirone on plasma glucose and glucose-induced hyperglycemia were studied in mice. Buspirone did not affect plasma glucose levels of non-fasted mice, while it increased serum insulin levels. In fasted mice, buspirone significantly reduced glucose-induced hyperglycemia and enhanced insulin release elicited by glucose. This suggests that buspirone enhances insulin release, resulting in inhibition of glucose-induced hyperglycemia. The major metabolite of buspirone, 1-(2-pyrimidinyl)piperazine (1-PP) increased serum insulin levels and induced a slight hypoglycemia in non-fasted mice. 1-PP decreases glucose-induced hyperglycemia and amplifies insulin release elicited by glucose in fasted mice. Since buspirone is mainly metabolized to 1-PP and formation of 1-PP occurs quickly, the inhibitory effect of buspirone on glucose-induced hyperglycemia is likely mediated by 1-PP.

Keywords: buspirone, anxiolytic, glucose, insulin, 5-HT1A receptor

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) participates in controlling of mood and emotion and drugs affecting serotonergic neurotransmission are available as therapy for psychiatric disease (1, 2). Previous reports indicated that the 5-HT receptor is involved in glucose regulation. It has been suggested that several 5-HT-receptor agonists raise the plasma glucose levels of rats. The 5-HT1A- and 5-HT2-receptor agonists 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and 1-(2,5-dimethoxy-4-iodophenyl)2-aminopropane (DOI) or 1-(3-chlorophenyl)piperazine (mCPP) induce hyperglycemia in rats (3–8).

We previously reported that selective serotonin reuptake inhibitors (SSRIs), fluoxetine or fluvoxamine, which inhibit 5-HT reuptake and increase 5-HT levels in the synaptic cleft, increased blood glucose levels of mice (9, 10). We further demonstrated that tricyclic antidepressants, imipramine and clomipramine, also elevate plasma glucose levels (11, 12). These findings suggest that in the use of antidepressants affecting serotonergic neurotransmission, attention should be paid to glucose regulation.

The azapirone derivatives such as buspirone, ipsapirone, and tandospirone are known to act as 5-HT1A-receptor partial agonists (1). The 5-HT1A receptor is related to emotion and 5-HT1A receptor agonists induce anxiolytic and antidepressant effects in humans and animals (1). It is well recognized that stress induces hyperglycemia. Hyperglycemic responses to stress are recognized as an index of the sympathetic system (13). We previously reported that the azapirone derivative tandospirone suppresses immobilization stress-induced hyperglycemia in mice (14). Therefore, serotonergic anxiolytics may be available for inhibition of stress-induced hyperglycemia in addition to anxiolytic effects.

The 5-HT1A-receptor partial agonists including buspirone and ipsapirone elevate glucose levels of rats (5). We also previously reported that buspirone increases plasma glucose levels of rats (7). However, there is a species difference in glycemic responses to 5-HT1A-receptor agonists in rats and mice, since tandospirone or flesinoxan did not raise plasma glucose levels of mice (14–16). However, to date, the effects of buspirone on glucose levels on mice remain unclear. In the present study, therefore, we examined the effects of buspirone on plasma glucose levels in mice and...
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glucose-induced hyperglycemia. Since azapirone derivatives like buspirone are metabolized to 1-(2-pyrimidinyl)piperazine (1-PP) (17), we further studied the effects of 1-PP on glucose regulation in mice.

**Materials and Methods**

**Animals**

Male ddY mice weighing 28 – 32 g were obtained from SLC Japan, Inc. (Hamamatsu). Mice were fed with free access to food and water and 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 at 23 ± 1°C and humidity at 55 ± 5%. For experiments with glucose, mice were fasted for 20 h. The experimental procedure was approved by the Kobe Pharmaceutical University Animal Care and Use Committee.

**Drug treatment**

Buspirone HCl and 1-(2-pyrimidinyl)piperazine (1-PP) HCl were obtained from Sigma (St. Louis, MO, USA). D(+)-Glucose was purchased from Wako (Osaka). All drugs were dissolved in saline. Buspirone and 1-PP were injected s.c. Glucose was given i.p. Buspirone and 1-PP were given 30 min before the injection of glucose.

**Determination of plasma glucose and insulin levels**

Mice were decapitated and blood was collected in plastic tubes. For glucose determination, blood was collected in plastic tubes containing NaF. Plasma glucose was measured following the method described in our previous study (7). Serum insulin was measured using a commercially available ELISA kit (Morinaga insulin kit; Morinaga, Yokohama).

**Statistics**

Dose-related effects on plasma glucose and serum insulin levels were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett’s test. Other results were analyzed by two-way ANOVA followed by Tukey’s test.

**Results**

**Effects of buspirone on plasma glucose and serum insulin levels of non-fasted mice**

Effects of buspirone on plasma glucose and serum insulin levels of non-fasted mice are shown in Fig. 1. Buspirone did not affect plasma glucose levels. Buspirone above the dosage of 5 mg/kg induced significant hyperinsulinemia.

**Effects of buspirone on glucose-induced hyperglycemia and hyperinsulinemia in fasted mice**

Figure 2 shows the effects of buspirone on glucose-induced hyperglycemia in fasted mice. Buspirone reduced glucose-induced hyperglycemia, although it did not affect basal plasma glucose levels. Figure 3 shows the effects of buspirone on glucose-induced insulin release. Serum insulin levels were determined 15 min after the injection of glucose, since insulin release peaked at that time (data not shown). Buspirone was administered 30 min before the injection of glucose. Buspirone significantly facilitated glucose-induced hyperinsulinemia (Fig. 3).

**Effects of 1-PP on plasma glucose and serum insulin levels of non-fasted mice**

Effects of 1-PP on plasma glucose and serum insulin

![Fig. 1. Effects of buspirone on the blood glucose and insulin levels of non-fasted mice. Results are shown as the mean ± S.E.M. (n = 5 – 8). Buspirone was given s.c. *P<0.05, **P<0.01.](image)
levels of non-fasted mice were shown in Fig. 4. 1-PP induced a significant reduction of plasma glucose levels at doses of 0.5 and 1 mg/kg. 1-PP also induced a significant hyperinsulinemia at 0.5 and 1 mg/kg.

**Effects of 1-PP on glucose-induced hyperglycemia and hyperinsulinemia in fasted mice**

Figure 5 shows the effects of 1-PP on glucose-induced hyperglycemia. 1-PP was injected 30 min before glucose injection. At 1 mg/kg, 1-PP reduced both basal plasma glucose levels and glucose-induced hyperglycemia. 1-

Fig. 2. Effects of buspirone on glucose-induced hyperglycemia in fasted mice. Results are shown as the mean ± S.E.M. (n = 7 – 9). Glucose at 1 g/kg was given i.p. Buspirone at 10 mg/kg was injected s.c. 30 min before glucose. ***P<0.001 vs saline + saline-treated group. *P<0.05, **P<0.001 vs glucose + saline-treated group.

**Fig. 3.** Effects of buspirone on glucose-induced hyperinsulinemia in fasted mice. Results are shown as the mean ± S.E.M. (n = 7 – 9). Glucose at 1 g/kg was given i.p. Buspirone at 10 mg/kg was injected s.c. 30 min before glucose. Insulin levels were determined 15 min after the injection of glucose. *P<0.05 vs saline + saline-treated group. **P<0.001 vs glucose + saline-treated group. ***P<0.01 vs saline + buspirone-treated group.

PP significantly facilitated glucose-induced hyperinsulinemia 15 min after the injection of glucose (Fig. 6).

**Discussion**

The present results demonstrate that buspirone itself did not affect basal plasma glucose levels of non-fasted mice, although it induced significant hyperglycemia in rats (5, 7). Flesinoxan is another 5HT1A receptor agonist and displays anti-anxiety effects (15). Groenink et al. reported that flesinoxan did not affect glucose levels in mice, although they reported that it induced hyper-
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glycemia in rats (15, 16). Thus, there is a species difference in glycemic responses to the 5-HT\textsubscript{1A} receptor agonists between mice and rats. We previously reported that tandospirone, an azapirone derivative similar to buspirone, did not affect basal plasma glucose levels of non-fasted mice (14). Therefore, it is indicated that in mice, the serotonergic anxiolytics themselves do not elevate blood glucose levels. In the present study, buspirone significantly increased serum insulin levels in non-fasted mice. It has been reported that activation of the 5-HT\textsubscript{1A} receptor elicits hyperglycemia and hypoinsulinemia in rats (3, 18). These effects of 5-HT\textsubscript{1A} receptor agonists in rats are considered to be due to the facilitation of adrenaline release from the adrenal medulla (3, 18, 19). While buspirone elevated serum insulin levels in non-fasted mice, it did not alter plasma glucose levels. This may be caused by the hyperinsulinemic effects of buspirone, which counteract the hyperglycemic effects, based on facilitation of adrenaline release.

Our results have shown that buspirone apparently suppressed glucose-induced hyperglycemia in fasted mice. Buspirone did not affect plasma glucose levels in fasted mice, either. Thus, buspirone can suppress hyperglycemia elicited by glucose in mice, although it does not affect plasma glucose levels of either fasted or non-fasted mice. In the present study, buspirone significantly augmented glucose-induced insulin release in fasted mice. Therefore, buspirone increases insulin secretion, leading to inhibition of glucose-induced hyperglycemia.

Azapirone derivatives including buspirone are known to be metabolized to the major metabolite 1-PP. 1-PP is an active metabolite and it was reported that 1-PP may be involved in the anxiolytic effects of buspirone (17, 20). Buspirone is rapidly metabolized to 1PP, and 1-PP levels in the brain and plasma are 10- and 15-fold higher than those of buspirone 15 min after the injection of buspirone (21). This suggests that 1-PP may participate in the hyperinsulinemic effects of buspirone. Therefore, we examined the effects of 1-PP on glucose and insulin levels of non-fasted mice. As a result, 1-PP not only significantly reduced plasma glucose levels, but also significantly increased serum insulin levels in non-fasted mice. In addition, 1-PP inhibited glucose-induced hyperglycemia and facilitated insulin release elicited by glucose in fasted mice. Therefore, 1-PP may contribute to the preventive effects of buspirone on glucose-induced hyperglycemia and hyperinsulinemia.

1-PP has been reported to have an affinity to $\alpha_2$ receptors and acts as an agonist of $\alpha_2$ receptors (20). The $\alpha_2$ receptor is expressed in $\beta$ cells of the pancreas and its activation leads to inhibition of insulin release (22, 23). It was suggested that epinephrine elevates plasma glucose levels and decreases insulin release, which are antagonized by the $\alpha_2$ receptor antagonist (22, 23). Therefore, the hyperinsulinemic effects of 1-PP are considered to be due to inhibition of $\alpha_2$ receptors on $\beta$ cells, leading to hypoglycemia. In contrast, the 5-HT\textsubscript{1A} receptor agonist buspirone did not affect plasma glucose levels, while it increased serum insulin levels. It was reported that activation of the 5-HT\textsubscript{1A} receptor...
induces hyperglycemia (3, 18, 19). It is considered that the hyperglycemic effects based on activation of the 5-HT\textsubscript{1\textalpha} receptor may suppress hypoglycemia elicited by insulin.

As indicated above, in mice, buspirone did not affect basal glucose levels, while in rats, it induces hyperglycemia (5, 7). The reason for this remains unclear. There may be differences between mice and rats in the formation of 1-PP after treatment with buspirone. Anxiolytic effects of buspirone are suggested to be mediated by the central 5-HT\textsubscript{1\textalpha} receptor (1). As shown in the results, 1-PP may also be related to the hyperinsulinemic effects of buspirone. Experiments using 5-HT\textsubscript{1\textalpha} receptor antagonists may be helpful for discriminating the involvement of the 5-HT\textsubscript{1\textalpha} receptor and 1-PP in hyperinsulinemic effects of buspirone.

In conclusion, our results suggest that buspirone given to non-fasted mice increases serum insulin levels, while it does not affect plasma glucose levels and that buspirone suppresses glucose-induced hyperglycemia in fasted mice by enhancing glucose-elicited hyperinsulinemia. These effects of buspirone may be due to its major metabolite 1-PP, which blocks the \alpha\textsubscript{2} receptor. Stress is known to elevate glucose levels and it may be a factor causing diabetes mellitus. Buspirone can suppress stress-related anxiety in humans (1). Therefore, our results indicate that buspirone may be effective in controlling glucose regulation as well as anxiety.

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