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Selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induce hyperglycemia by different mechanisms

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Abstract

The effects of the selective serotonin reuptake inhibitors, fluoxetine and fluvoxamine, on plasma glucose levels were investigated in mice. Both fluoxetine and fluvoxamine elicited significant hyperglycemia, while a selective noradrenaline reuptake inhibitor maprotiline had no effect. Fluoxetine and fluvoxamine did not change serum insulin levels, although they elicited hyperglycemia. Pretreatment with the serotonin (5-hydroxytryptamine, 5-HT) depleter, *p*-chlorophenylalanine (*p*CPA), abolished fluvoxamine-induced hyperglycemia, although *p*CPA did not affect the fluoxetine-induced glycemic effects. These results suggest that the selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induce hyperglycemia by inhibition of insulin release. Moreover, our findings indicate that the glycemic effects of these drugs are differentially associated with serotonergic mechanisms.

Keywords: Fluoxetine; Fluvoxamine; 5-HT (5-hydroxytryptamine, serotonin); Selective serotonin reuptake inhibitor; Maprotiline; Hyperglycemia; Insulin; *p*-Chlorophenylalanine; (Mouse)

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has been demonstrated to participate in glucose regulation. The central 5-HT_{1A}, 5-HT_{2A} and 5-$HT_{2B/2C}$ receptors are considered to be involved in glucose regulation, since agonists of these receptor can elicit hyperglycemic effects in rats and mice (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990a, 1992; Durcan et al., 1991; Sugimoto et al., 1996a). The peripheral 5-HT_{2A} receptor is also involved in glycemic control, since the peripheral administration of a peripheral 5-HT_{2A} receptor agonist elevates plasma glucose levels in rats (Chaouloff et al., 1990a; Yamada et al., 1995; Sugimoto et al., 1996b). Hyperglycemia induced by stimulation with these 5-HT receptors is related to adrenaline release from the adrenal gland (Chaouloff et al., 1990a, 1990b, 1992; Sugimoto et al., 1992, 1999a).

5-HT is considered to be involved in several psychiatric diseases such as depression and schizophrenia, and enhancement of 5-HT neurotransmission improves depressive illness (Montgomery, 1990). Selective serotonin reuptake inhibitors, which increase 5-HT neurotransmission, have been used in clinical therapy and are effective against depression in humans (Montgomery, 1990). In animal studies, selective serotonin reuptake inhibitors show antidepressant effects in forced swimming tests (Borsini, 1995; Redrobe et al., 1996).

Since selective serotonin reuptake inhibitors are known to enhance 5-HT neurotransmission, they may modify glucose regulation. Therefore, we investigated the effects of fluoxetine and fluvoxamine, typical selective serotonin reuptake inhibitors, on plasma glucose levels in mice.

2. Materials and methods

2.1. Animals

Male ddY mice weighing 28–32 g were obtained from SLC Japan (Japan). Mice were given free access to food and water and they were housed under a controlled 12-h/12-h light–dark cycle (light from 0700 h to 1900 h), with room temperature at 23 ± 1°C and humidity at 55 ± 5%.

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2.2. Drug treatment

Fluoxetine hydrochloride and fluvoxamine hydrochloride were obtained from Tocris (UK). Maprotiline and *p*-chlorophenylalanine methylester hydrochloride (*p*CPA) were purchased from RBI (USA) and Sigma (USA), respectively. All drugs were given i.p. at a volume of 0.1 ml/10 g. *p*CPA was injected i.p. at a dose of 400 mg/kg, 5, 3 and 1 days before the administration of fluoxetine and fluvoxamine.

2.3. Determination of plasma glucose and insulin levels

Mice were decapitated and blood was collected in tubes containing NaF. Plasma glucose was measured following the method described in our previous study (Sugimoto et al., 1992). Serum insulin levels were determined using a commercially available ELISA insulin kit (Morinaga Institute of Biological Science, Japan).

2.4. Determination of brain 5-HT and its metabolite

Mice treated with *p*CPA (400 mg/kg × 3) were decapitated and their brains were removed and frozen on dry ice. 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were determined using high-performance liquid chromatography (HPLC) with electrochemical detection (+700 mV). Brains were homogenized in 0.1 N perchloric acid containing 50 μM EDTA and centrifuged (10,000 × *g* for 20 min). Ten microliters of supernatant was injected into the HPLC apparatus.

2.5. 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. The effects of *p*CPA on fluoxetine and fluvoxamine-induced effects were analyzed by two-way ANOVA followed by Tukey's test.

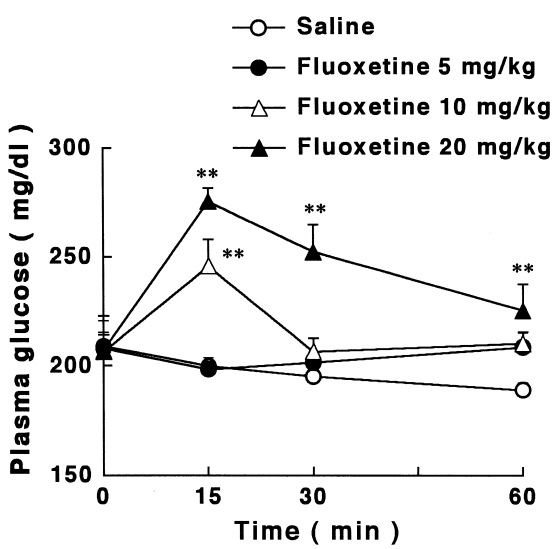

Fig. 1. Effects of fluoxetine on the plasma glucose level in mice. Results are shown as means ± S.E. ($N = 5–9$). Fluoxetine was given i.p. $^{**}P <$ 0.01.

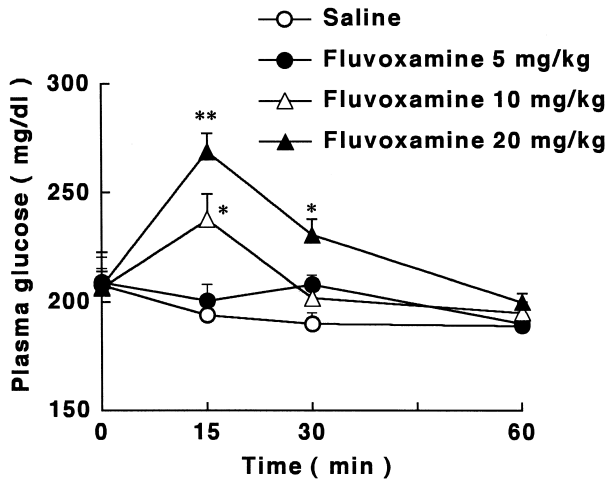

Fig. 2. Effects of fluvoxamine on the plasma glucose level in mice. Results are shown as means ± S.E. ($N = 5–9$). Fluvoxamine was given i.p. $^{*}P < 0.05$, $^{**}P < 0.01$.

3. Results

3.1. Effects of fluoxetine and fluvoxamine on plasma glucose levels of mice

Figs. 1 and 2 show the time course of changes in plasma glucose levels following the administration of fluoxetine and fluvoxamine, respectively. Fluoxetine and fluvoxamine elicited significant hyperglycemia in mice and these effects reached a maximum 15 min after injection.

3.2. Effects of fluoxetine and fluvoxamine on serum insulin levels

Table 1 shows serum insulin levels after the injection of fluoxetine and fluvoxamine. However, neither fluoxetine nor fluvoxamine changed the serum insulin levels.

Table 1
Effects of fluoxetine and fluvoxamine on serum insulin levels in mice
Results are shown as the means ± S.E. ($N = 5–8$).
Fluoxetine and fluvoxamine were injected i.p.
Mice were killed 15 min after the injections of fluoxetine and fluvoxamine.

Group	Serum insulin (ng/ml)
Saline	1.4 ± 0.17
Fluoxetine 5 mg/kg	1.3 ± 0.16
Fluoxetine 10 mg/kg	1.5 ± 0.18
Fluoxetine 20 mg/kg	1.5 ± 0.22
Saline	1.5 ± 0.14
Fluvoxamine 5 mg/kg	1.6 ± 0.11
Fluvoxamine 10 mg/kg	1.6 ± 0.12
Fluvoxamine 20 mg/kg	1.7 ± 0.05

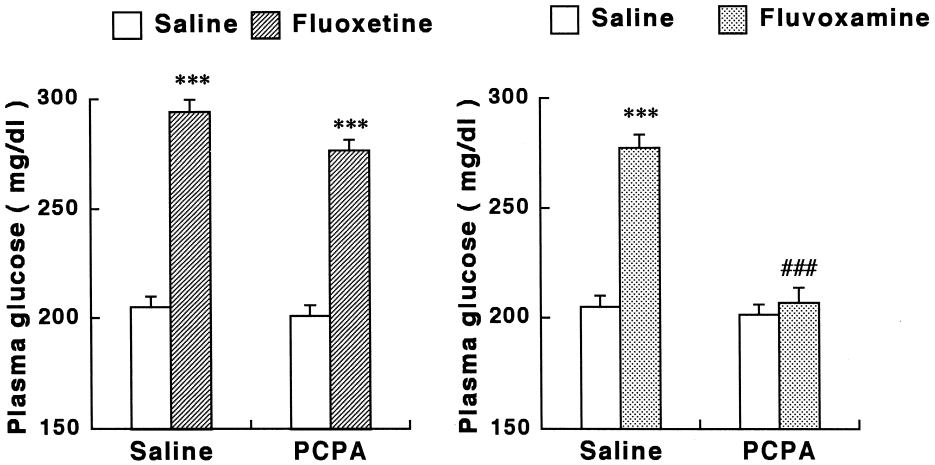

Fig. 3. Effects of *p*CPA on fluoxetine- and fluvoxamine-induced hyperglycemia in mice. Results are shown as means ± S.E. ($N = 5–10$). Fluoxetine and fluvoxamine were injected i.p. at 20 mg/kg. Plasma glucose levels were determined 15 min after the injection of fluoxetine and fluvoxamine. *p*CPA at 400 mg/kg was injected i.p. 5, 3 and 1 days before the administration of fluoxetine and fluvoxamine. $^{***}P < 0.001$ vs. saline of the respective group. $###P < 0.001$ vs. saline + fluvoxamine-treated group.

3.3. Glycemic responses to fluoxetine and fluvoxamine in pCPA-pretreated mice

Fig. 3 shows the effects of the 5-HT depleter *p*CPA on fluoxetine- and fluvoxamine-elicited hyperglycemia. *p*CPA decreased brain levels of 5-HT and its metabolite 5-HIAA (5-HT; saline 598.0 ± 28.7 ng/g, *p*CPA 153.1 ± 12.0 ng/g, $N = 5$, $^{***}P < 0.001$, 5-HIAA; saline 550.5 ± 30.7 ng/g, *p*CPA 73.8 ± 6.9 ng/g, $N = 7$, $^{***}P < 0.001$). *p*CPA strongly reduced fluvoxamine-induced hyperglycemia, although it did not affect fluoxetine-induced hyperglycemic effects.

3.4. Effects of maprotiline on plasma glucose levels of mice

The effects of maprotiline on plasma glucose levels are shown in Fig. 4. Maprotiline at doses of 10 and 20 mg/kg did not affect plasma glucose levels.

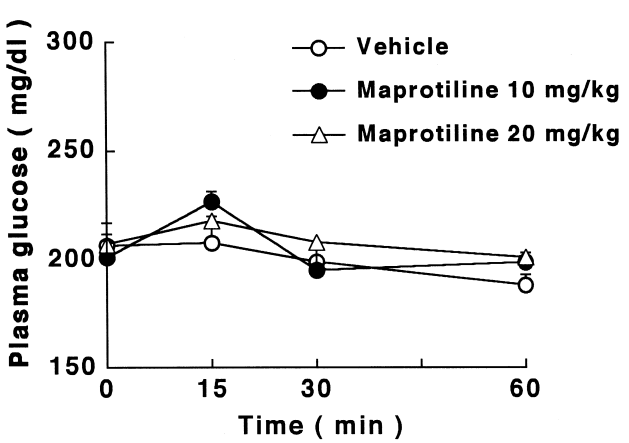

Fig. 4. Effects of maprotiline on the plasma glucose level in mice. Results are shown as means ± S.E. ($N = 5–9$). Maprotiline was given i.p.

4. Discussion

It has been reported that selective serotonin reuptake inhibitors including fluoxetine and fluvoxamine induce several pharmacological effects such as antidepressant, anxiolytic or hypophagic effects by increasing 5-HT availability (Montgomery, 1990). However, little is known regarding their metabolic effects, including their effect on glucose regulation. Our results demonstrate that fluoxetine and fluvoxamine induce hyperglycemic effects in non-fasted mice. The doses of fluoxetine and fluvoxamine that induced hyperglycemia were similar to those that induced antidepressant effects in mice in the forced swimming test (Borsini, 1995; Redrobe et al., 1996). Our results are consistent with those of a study by Jacoby and Bryce (1979) showing that fluoxetine elicits hyperglycemia in fasted rats, but the effect is not dose dependent. Chaouloff et al. (1992) reported that fenfluramine, which releases 5-HT and inhibits 5-HT reuptake at nerve terminals, induced hyperglycemia in rats. Therefore, inhibitory effects on 5-HT reuptake may contribute to fenfluramine-induced hyperglycemia. In mice, Wilson and Furman (1982) showed that, in the fasted condition, fluoxetine 20 mg/kg i.v. did not affect plasma glucose levels but elicited hypoglycemia in mice pretreated with the monoamine oxidase inhibitor nialamide. The discrepancy has not yet been clarified but it may be due to different experimental conditions, fasted or non-fasted conditions, or strains of mice used.

Insulin levels in serum did not change following the administration of fluoxetine and fluvoxamine even though these drugs induced hyperglycemia, indicating that insulin release was suppressed and that insulin is related to these hyperglycemic responses. Both centrally and peripherally acting 5-HT receptor agonists cause hyperglycemia in rats, which is associated with adrenaline release from the adrenal

medulla (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990a, 1990b; Sugimoto et al., 1992, 1996a, 1996b; Yamada et al., 1995). In the rat adrenal medulla, the presence of 5-HT transporter mRNA and [^{3}H]citalopram binding have been reported (Blakely et al., 1994; Wren et al., 1997). The uptake of 5-HT into the adrenal medulla is considered to be inhibited by selective serotonin reuptake inhibitors, suggesting that actions at this site are related to hyperglycemia.

Acute administration of selective serotonin reuptake inhibitors including fluoxetine and fluvoxamine increases 5-HT neurotransmission at nerve terminals and in the cell body (Artigas, 1995). Thus, we investigated the effects of the 5-HT depleter, *p*CPA, which inhibits tryptophan hydroxylase, on fluoxetine- and fluvoxamine-induced hyperglycemia. The dose of *p*CPA used in this study reduced levels of 5-HT and its metabolite 5-HIAA by 74% and 87%, respectively. Pretreatment with *p*CPA completely attenuated fluvoxamine-elicited hyperglycemia, although the hyperglycemia induced by fluoxetine was not affected by *p*CPA. Thus, a clear difference was detected between hyperglycemia elicited by fluoxetine and fluvoxamine.

The result that hyperglycemic effects of fluvoxamine were attenuated by *p*CPA indicates that fluvoxamine-induced hyperglycemia is dependent on increased extracellular 5-HT levels derived from 5-HT reuptake inhibition. Since previous findings demonstrate that stimulation of several 5-HT receptors elicits hyperglycemia (Chaouloff and Jeanrenaud, 1987; Chaouloff et al., 1990a, 1990b; Sugimoto et al., 1992, 1996a, 1996b), fluvoxamine-elicited hyperglycemia may be caused by the activation of these 5-HT receptors after elevation of synaptic 5-HT availability.

In contrast to the hyperglycemia induced by fluvoxamine, that induced by fluoxetine was resistant to 5-HT reduction following *p*CPA administration. Recent studies demonstrated that 5-HT depletion by pretreatment with *p*CPA or 5,7-dihydroxytryptamine (5,7-DHT) did not modify the hypophagic effects of fluoxetine (Grignaschi and Samanin, 1992; Lightowler et al., 1996). Therefore, it has been assumed that hypophagia elicited by fluoxetine is not dependent on the synaptic availability of 5-HT. Our finding that hyperglycemia induced by fluoxetine was not inhibited by *p*CPA is consistent with its effects on fluoxetine-induced hypophagia. In our study, *p*CPA reduced by 74% the brain 5-HT level, suggesting that a small store of 5-HT remains. We found that *p*CPA attenuated fluvoxamine-induced hyperglycemia but not fluoxetine-induced effects. Since small stores of 5-HT remained in *p*CPA-treated mice, the involvement of inhibition of 5-HT reuptake in fluoxetine-induced hyperglycemia cannot be excluded at present. However, the differential effects of *p*CPA on fluoxetine- and fluvoxamine-induced hyperglycemia suggest that another mechanism independent of the inhibition of 5-HT reuptake may be related to the hyperglycemic effects of fluoxetine.

It has been reported that systemic administration of fluoxetine increases extracellular noradrenaline efflux in the rat hypothalamus by microdialysis (Stanford, 1996). In contrast, fluvoxamine did not elevate noradrenaline efflux in the rat frontal cortex (Stanford, 1996), suggesting that activation of the noradrenergic system is related to the hyperglycemic effects of fluoxetine. However, as shown in the results, a selective noradrenaline reuptake inhibitor maprotiline (Richelson and Pfenning, 1984) did not modify plasma glucose levels of mice. Furthermore, it was reported that, in mice, fluoxetine did not change brain noradrenaline turnover (Hall et al., 1995). Thus, it is likely that noradrenaline is not related to the glycemic response to fluoxetine in mice. Fluoxetine is metabolized to the major metabolite norfluoxetine, which has an affinity for 5-HT$_{2C}$ receptors similar to that of fluoxetine (Lightowler et al., 1996). Thus, the possibility that direct actions of fluoxetine or norfluoxetine on 5-HT$_{2C}$ receptors may contribute to hyperglycemia is postulated. As shown in the results, fluoxetine induced significant hyperglycemia 15 min after its injection and its effects declined gradually. It was reported that in rats and mice, after injection of fluoxetine, the metabolite, norfluoxetine, was detected in brain and blood within 15–30 min but at very low levels in the early period; the peak concentration of norfluoxetine was observed 5–10 h after treatment with fluoxetine (Caccia et al., 1990, 1992; Torok-Both et al., 1992; Alvarez et al., 1998). Therefore, the contribution of norfluoxetine to fluoxetine-induced hyperglycemia is probably small, although the effects of norfluoxetine on glycemia have not been clarified.

In summary, our results demonstrated that the selective serotonin reuptake inhibitors fluoxetine and fluvoxamine induced hyperglycemia in mice. These hyperglycemic responses may be related to inhibition of insulin release. The effects of the 5-HT depleter, *p*CPA, on fluoxetine- and fluvoxamine-induced hyperglycemia were different, suggesting that a differential mechanism independent of synaptic 5-HT availability may be related to fluoxetine-induced hyperglycemia.

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