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Short communication

The serotonin precursor 5-hydroxytryptophan elevates serum leptin levels in mice

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Abstract

The effects of a serotonin (5-HT) precursor 5-hydroxytryptophan (5-HTP) on serum leptin levels were investigated in mice. 5-HTP dose dependently increased serum leptin levels in mice. Pretreatment of the peripheral aromatic amino acid decarboxylase inhibitor carbidopa suppressed 5-HTP-induced hyperleptinemia. These results suggest that the secretion of leptin may be modified by serotonergic mechanisms. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Leptin; 5-Hydroxytryptophan (5-HTP); 5-HT (5-hydroxytryptamine, serotonin); Carbidopa; (Mouse)

1. Introduction

It is recognized that serotonin (5-HT) is involved in the regulation of food intake (Curzon, 1990; Dourish, 1995). 5-HT-releasing drugs or selective 5-HT reuptake inhibitors such as fenfluramine or fluoxetine can inhibit appetite in humans and animals (Curzon, 1990; Dourish, 1995). A 5-HT precursor 5-hydroxytryptophan (5-HTP) also decreases food intake (Fletcher and Burton, 1986). 5-HT inhibits appetite by stimulation of central 5-HT receptors. Central 5-HT_{1B} or 5-HT_{2C} receptors are present in the hypothalamus and are related to the appetite-suppressant effects of 5-HT, since agonists of these receptors induce anorexia in animals (Dourish, 1995). Moreover, peripheral 5-HT receptor agonists elicits anorexia, which is in part mediated by peripheral 5-HT_{2A} receptors (Simansky, 1996; Sugimoto et al., 1996).

Leptin is the product of the obese gene and plays an important role in the regulation of body weight and food intake(Flier, 1997). Leptin is released from adipocytes and its administration induces decreases food intake in both lean and obese animals (Schwartz et al., 1996; Flier, 1997; Pelleymounter et al., 1998). Therefore, leptin is an important factor controlling appetite and energy expenditure. Recent findings suggest that leptin acts on hypothalamic areas, where leptin receptors are located, to induce hypophagia (Schwartz et al., 1996; Flier, 1997; Fruhbeck et al., 1998). It has been reported that the hypophagic effects of leptin are associated with neuropeptide Y and melanin-concentrating hormone, which are orexigenic substances (Schwartz et al., 1996; Sahu, 1998). It has been reported that leptin release from adipocytes into the blood is regulated by several factors. Glucocorticoids or insulin stimulate leptin release, while catecholamine inhibits it (Fruhbeck et al., 1998). Although both leptin and 5-HT are metabolic signals for hypophagia, little is known about whether there is an interaction between 5-HT and leptin or whether 5-HT modifies leptin levels in the blood. In this paper, we examined the effects of a 5-HT precursor, 5-HTP, on serum leptin levels of 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 7:00 a.m. to 7:00

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p.m.), with a room temperature of 23 ± 1°C and humidity of 55 ± 5%.

2.2. Drug treatment

5-Hydroxytryptophan(5-HTP) was obtained from Wako (Japan) and dissolved in saline. Carbidopa was purchased from RBI (USA) and suspended in 1% carboxylmethylcellulose–Na (CMC–Na). Drugs were given i.p. in a volume of 0.1 ml/10 g.

2.3. Determination of serum leptin levels

Mice were decapitated and blood was collected in plastic tubes. Serum leptin was measured using a commercially available ELISA kit (Morinaga mouse leptin kit, Japan).

2.4. Statistics

Dose-related effects of 5-HTP on serum leptin levels were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test. Effects of carbidopa on 5-HTP-elicited hyperleptinemia were analyzed by two-way ANOVA followed by Tukey's test.

3. Results

Fig. 1 shows the time course of changes in serum leptin levels following the administration of 5-HTP. 5-HTP significantly increased serum leptin levels in mice, and its effects reached a maximum 30 min after the injection. Fig. 2 shows the effects of the peripheral aromatic amino acid decarboxylase inhibitor carbidopa on 5-HTP-induced hyperleptinemia. The pretreatment with carbidopa significantly reduced the increase in leptin levels elicited by 5-HTP.

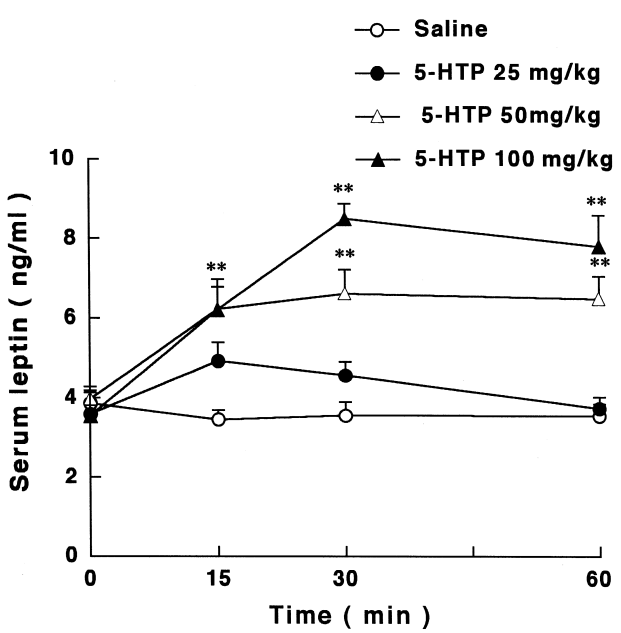

Fig. 1. Effects of 5-HTP on the serum leptin levels in mice. Results are shown as means ± S.E. ($N = 5–9$). 5-HTP was given i.p. $^{**}P < 0.01$.

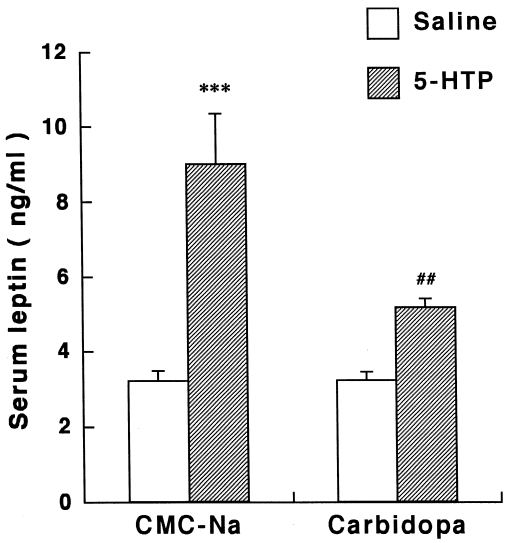

Fig. 2. Effects of carbidopa on 5-HTP-elicited hyperleptinemia in mice. Results are shown as means ± S.E. ($N = 5–7$). 5-HTP was injected i.p. at 100 mg/kg. Carbidopa at 50 mg/kg was given i.p. 30 min before the injection of 5-HTP. Serum leptin levels were determined 30 min after the injection of 5-HTP. $^{***}P < 0.001$ vs. saline of respective group. $^{\#\#}P < 0.01$ vs. saline + 5-HTP-treated group.

4. Discussion

Interest in leptin has been focused on its anoretic and anti-obese effects (Pelleymounter et al. , 1995). 5-HT also reduces appetite, and drugs that enhance serotonergic neurotransmission are used for the treatment of obesity (Curzon, 1990; Dourish, 1995). However, it is still unclear whether the serotonergic system affects serum leptin levels or anorexia induced by leptin. Our results demonstrate that a 5-HT precursor, 5-HTP, increased serum leptin levels of mice dose dependently. The effects of 5-HTP appeared rapidly and lasted for at least 60 min. Our results show, for the first time, that the serotonergic drug 5-HTP elicits hyperleptinemia. The doses of 5-HTP used in this study are similar to those used in other tests. 5-HTP at 10–50 mg/kg decreases food intake or facilitates the release of several hormones such as corticosterone or prolactin (Fletcher and Burton, 1986; Van de Kar, 1991).

Systemically administered 5-HTP is rapidly converted to 5-HT by aromatic amino acid decarboxylase. To clarify the involvement of 5-HT, we investigated the effect of the peripheral aromatic amino acid decarboxylase inhibitor carbidopa on 5-HTP-induced hyperleptinemia in mice. As shown in the results, carbidopa significantly inhibited the elevation of serum leptin levels induced by 5-HTP. This

suggests that the hyperleptinemia induced by 5-HTP is elicited by 5-HT and not by 5-HTP itself. Carbidopa inhibits the decarboxylase in peripheral organs but not in the central nervous system. Therefore, 5-HT formed in the peripheral system may be associated with the hyperleptinemia induced by 5-HTP.

Previous reports demonstrate that the administration of 5-HTP decreases food intake in rats (Fletcher and Burton, 1986). Our results show that the hypophagic effects of 5-HTP may be related to the elevation of circulating leptin levels. Since leptin is secreted from adipose tissues, 5-HT may enhance the expression of leptin mRNA in these tissues. Acute administration of 5-HTP causes neuroendocrinological responses in both animals and humans mediated by 5-HT receptors (Van de Kar, 1991). Since 5-HTP increases plasma corticosterone and insulin levels (Furman and Wilson, 1980; Van de Kar, 1991), the hyperleptinemia induced by 5-HTP is mediated by these hormones. The involvement of 5-HT receptor subtypes in 5-HTP-induced hyperleptinemia remains unclear and further studies are required.

In summary, we demonstrated for the first time that a 5-HT precursor, 5-HTP, elevates serum leptin levels in mice. The hyperleptinemia elicited by 5-HTP may be caused by 5-HT formed in the periphery. Our present results suggest that 5-HT has a role in the regulation of leptin secretion and that leptin and 5-HT may interact in the regulation of feeding behavior.

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