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Endogenous histamine reduces plasma insulin-like growth factor I via H_1 receptor-mediated pathway in the rat

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Abstract

Endotoxin has been recently shown to reduce plasma insulin-like growth factor I. As it was reported that histamine can induce gut-derived endotoxemia, we wanted to determine whether histamine has a similar effect on plasma insulin-like growth factor I. Compound 48/80 (a histamine releaser) was injected subcutaneously into rats, then blood was taken for plasma insulin-like growth factor I assay and the livers were assayed for insulin-like growth factor I mRNA. Like endotoxin, injection of compound 48/80 significantly reduced plasma insulin-like growth factor I. Six hours post-injection, plasma insulin-like growth factor I was reduced by 61% ($P < 0.001$), and 24 h post-injection, it was still lower (by 35% $P < 0.001$) than in the control group. Hepatic insulin-like growth factor I mRNA was not reduced by this treatment. The effect of compound 48/80 on plasma insulin-like growth factor I was significantly attenuated by oral administration of the histamine H_1 receptor antagonist (chlorpheniramine), but not by the histamine H_2 receptor antagonists (cimetidine and ranitidine). Oral administration of polymyxin B (an antiendotoxin antibiotic) did not attenuate the effect of compound 48/80 on plasma insulin-like growth factor I at all. In conclusion, endogenous histamine reduces plasma insulin-like growth factor I via H_1 receptor-mediated pathway. Our study suggests a novel role of histamine in the regulation of insulin-like growth factor I metabolism in vivo.

Keywords: Histamine; Compound 48/80; Endotoxin; Insulin-like growth factor I

1. Introduction

Histamine is synthesized in mast cells and circulating basophils, and stored within cellular secretory granules. Other cells can also synthesize histamine, but lack the capacity for histamine storage. The action of histamine is initiated by interaction with its specific cell receptors. Three histamine receptor subtypes, H_1, H_2 and H_3, have been identified (Hill, 1990). The histamine H_1 and H_2 receptors are widely distributed in many tissues, whereas the histamine H_3 receptor appears to be confined to the nervous system. It has been well-established that histamine plays important roles in allergic response and secretion of gastric acid and also acts as a neurotransmitter (Hill, 1990). Histamine is also involved in the control of lipoprotein metabolism and in the development of atherosclerosis and coronary heart disease (Harman, 1962; Kasatkina, 1964; Owens and Hollis, 1979; Ginsburg et al., 1981; Forman et al., 1985; Langeler et al., 1989; Atkinson et al., 1994; Kovanen et al., 1995; Liao et al., 1997a).

Insulin-like growth factor I (IGF-I) is an anabolic hormone that is produced in many tissues. The liver appears to be the major source of circulating IGF-I (Schwander et al., 1983). Whereas growth hormone stimulates the synthesis and secretion of IGF-I from various tissues (D'Ercole et al., 1984), IGF-I mediates many effects of growth hormone (Jones and Clemmons, 1995). In addition to its growth-promoting effects, IGF-I also influences various aspects of carbohydrate, lipid and protein metabolism. Endotoxin has recently been shown to reduce plasma IGF-I (Fan et al., 1994). As it was reported that histamine can induce gut-derived endotoxemia (Cuevas and Fine, 1973; Grun et al., 1976), we wanted to determine whether histamine reduces plasma IGF-I. We here demonstrate that

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endogenous histamine reduces plasma IGF-I via a histamine H_1 receptor-mediated pathway in the rat. However, the effect is not likely through gut-derived endotoxemia. Our findings suggest a novel role of histamine in the regulation of IGF-I metabolism in vivo.

2. Materials and methods

2.1. Reagents

Histamine (diphosphate salt; H 7375), compound 48/80 (C 2313), endotoxin from *Escherichia coli* O55B5 (L 2880), polymyxin B sulfate (7730 units/mg; P 1004), (±)-chlorpheniramine (maleate salt; C 3025), cimetidine (C 4522) and ranitidine (hydrochloride; R 0663) were purchased from Sigma (St. Louis, MO). 2-Methylhistamine (dihydrochloride; SKF-91256-A2), 2-thiazolylethylamine (dihydrochloride; SKF-71481-A2), dimaprit (dihydrochloride; SKF-91441-A2) and impromidine (trihydrochloride; SKF-92676-A3) were kindly provided by SmithKline Beecham Pharmaceuticals, England, UK.

2.2. Animals and experimental procedure

Male Sprague–Dawley rats (about 250 g) were maintained under standardized conditions with free access to chow and water. The light cycle hours were between 0600 h to 1800 h. Animals were allowed to adapt to the environment for at least 1 week before starting the experiments. All protocols were approved by the institutional Animal Care and Use Committee.

Altogether, 216 rats were studied in nine separate experiments. In all experiments, each group consisted of six animals. The experiments shown in Figs. 1, 2, Fig. 3B, and Fig. 4B and C have also been designed to study the effects of histamine on lipoprotein metabolism (Liao et al., 1997a). Thus, the blood and liver samples for those experiments were taken from the rats used for our previous studies.

Animals were fasted for about 24 h (started about 1500 h) before blood and liver samples were taken. At 0900 h of the following day (for experiments shown in Fig. 2, Fig. 3B, and Fig. 4B and C) or at indicated time (for experiments shown in Fig. 1, Fig. 3A, and Fig. 4A), rats were injected subcutaneously with compound 48/80 (2 mg/rat, Fig. 1, Fig. 2, and Fig. 3B), or intraperitoneally with endotoxin (5 mg/kg body weight, Fig. 3A), histamine (0.065 or 0.130 mmol/kg body weight; i.e., 20 or 40 mg/kg body weight, Fig. 4A) or histamine receptor agonists (0.065 mmol/kg body weight; i.e., 13 mg for 2-methylhistamine and 2-thiazolylethylamine, 15 mg for dimaprit, 28 mg for impromidine per kilogram body weight; Fig. 4B and C). Sterile saline was used as vehicle; control rats received saline. In all experiments, samples were collected at 1500 h post-injection. Blood was taken into EDTA-containing tubes (VACUTAINER®, Becton Dickinson, France) by puncture of the abdominal aorta and plasma was separated for IGF-I assay; and the liver was removed and immediately frozen in the liquid nitrogen and later stored at −80°C for IGF-I mRNA assay. Polymyxin B, chlorpheniramine, cimetidine and ranitidine were given orally through a stomach tube using saline as vehicle. While the groups of animals were given these drugs orally, other groups of animals received the same volume of saline. Polymyxin B was given at a dose of 4.8 mg (~37000 units)/kg body weight twice, 1 and 13 h before the injection of compound 48/80 (Fig. 3B). Chlorpheniramine (H_1 antagonist), cimetidine and ranitidine (H_2 antagonists) were given 1 h before the injection of compound 48/80 at a dose of 0.6 mmol/kg body weight (233 mg, 150 mg and 209 mg/kg body weight for chlorpheniramine, cimetidine and ranitidine, respectively) (Fig. 2).

2.3. Plasma IGF-I measurement and hepatic IGF-I mRNA assay

Plasma IGF-I was measured by radioimmunoassay as described previously (Liao et al., 1997b). In brief, after acid ethanol extraction of the samples (Daughaday et al., 1980) and subsequent overnight incubation with the antibodies and tracer at room temperature, the immune complex was precipitated with a second antibody in the presence of polyethylene glycol. After centrifugation, the pellet was counted in a gamma counter using recombinant human IGF-I as standard.

The liver IGF-I mRNA was measured as described previously (Möller et al., 1991). Briefly, total nucleic acid was prepared from the liver samples and hybridized in solution to a 160-base ^{35}S UTP-labeled RNA probe complementary to IGF-I mRNA (Mathews et al., 1986). RNase resistant radioactivity was precipitated by trichloroacetic acid and collected on glass fiber filters (Whatman). The radioactivity was counted in a scintillation counter, and signals obtained were compared with a standard curve of known amounts of IGF-I mRNA. The DNA content in the total nucleic acid samples was measured by a fluorometric assay (Labarca and Paigen, 1980) and results are expressed as amol IGF-I mRNA per microgram DNA.

2.4. Statistics

Data are presented as means ± S.E.M. and analysed by using StatView software (Abacus Concepts). One-way analysis of variance was used to evaluate the presence of significant differences between groups, followed by comparisons of the group means according to the method of Scheffe.

3. Results

First, we used compound 48/80 to induce release of endogenous histamine (Koibuchi et al., 1985). Rats were

subcutaneously injected with compound 48/80 (2 mg/rat) 6 and 24 h before sampling. Compound 48/80 at such a dose induces a typical allergic reaction (Grun et al., 1976). In our present study, the animals developed a typical allergic skin reaction after receiving compound 48/80, i.e., marked edema or erythema of snoots, ears and paws, which occurred about 3 h and peaked about 6 h post-injection. No diarrhoea occurred in the compound 48/80-treated animals. Six hours post-injection, plasma IGF-I was reduced by 61% ($P < 0.001$), and 24 h post-injection, it was still significantly lower (by 35%, $P < 0.001$) than in the control group (Fig. 1). However, the hepatic IGF-I mRNA levels were not reduced at all after injection of compound 48/80 (Fig. 1). Our results thus indicate that endogenous histamine reduces plasma IGF-I, an effect which does not involve reduction of hepatic IGF-I mRNA.

To establish which histamine receptor mediates the effect of compound 48/80 on plasma IGF-I, H_1 and H_2 receptor antagonists were used. Chlorpheniramine (an H_1 receptor antagonist) and cimetidine (an H_2 receptor antagonist) were orally administered (0.6 mmol/kg body weight) 1 h before injection of compound 48/80. Our previous study showed that at such a dose, chlorpheniramine blocks the reducing effect of compound 48/80 on plasma high density lipoprotein cholesterol (Liao et al., 1997a). Again, compound 48/80 markedly reduced plasma IGF-I (by 60%, $P < 0.001$, Fig. 2), but did not reduce the liver IGF-I mRNA levels (data not shown), confirming the reducing effect of compound 48/80 on plasma IGF-I. Chlorpheniramine and cimetidine themselves did not significantly reduce plasma IGF-I (15% and 10% reduction, respectively). Chlorpheniramine significantly attenuated, although not completely, the effect of compound 48/80 on plasma IGF-I ($P = 0.001$), whereas cimetidine had no effect (Fig. 2). The lack of full ability to reverse the effect of compound 48/80 by chlorpheniramine is probably attributed to the fact that chlorpheniramine itself reduced plasma IGF-I. Thus, if the reducing effect of chlorpheniramine is taken in consideration, chlorpheniramine almost completely blocked the effect of compound 48/80.

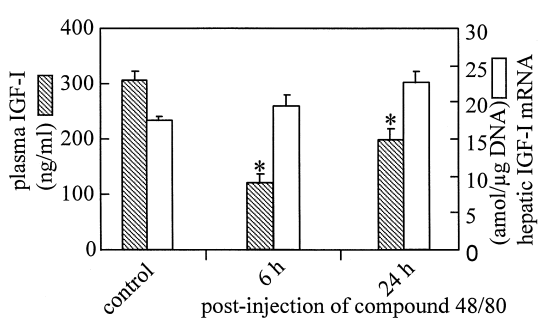

Fig. 1. Effect of compound 48/80 on plasma IGF-I. Groups of rats were injected with compound 48/80 (2 mg/rat) at 6 or 24 h before sampling. Control rats received an equal volume of vehicle 24 h before sampling. Blood was drawn for IGF-I assay and the livers were assayed for IGF-I mRNA. $^*P < 0.001$ vs. control.

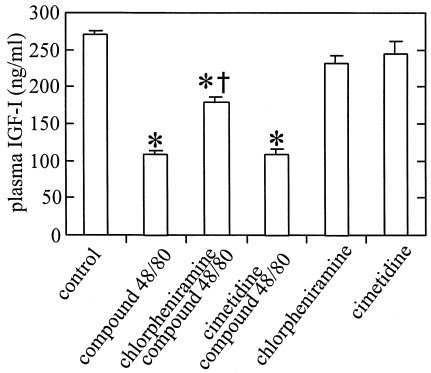

Fig. 2. Influence of histamine receptor antagonists on the effect of compound 48/80 on plasma IGF-I. Chlorpheniramine (H_1 antagonist) or cimetidine (H_2 antagonist) were orally administered at a dose of 0.6 mmol/kg body weight 1 h before the injection of compound 48/80 (2 mg/rat). Six hours after the injection of compound 48/80, blood was drawn for IGF-I assay. $^*P < 0.001$ vs. control; $^\dagger P = 0.001$ vs. compound 48/80.

In a separate experiment, we found that oral administration of ranitidine (0.6 mmol/kg body weight), another potent H_2 receptor antagonist, also did not block the effect

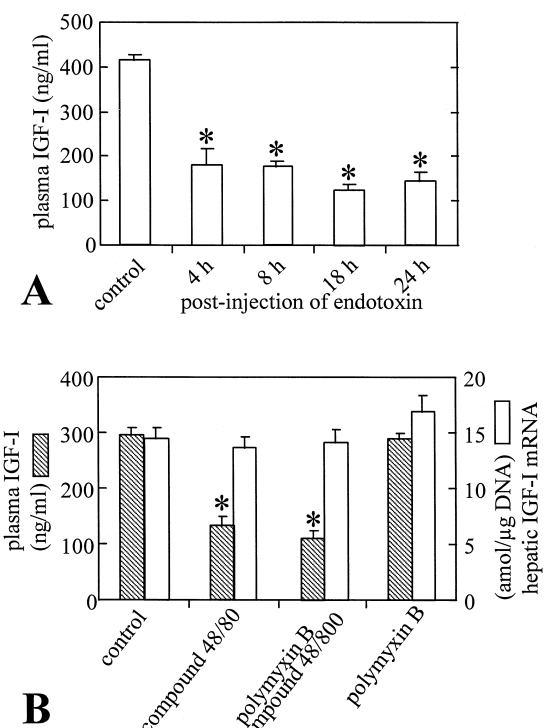

Fig. 3. (Panel A) Effect of endotoxin on plasma IGF-I. Groups of rats were injected with endotoxin (5 mg/kg body weight) at 4, 8, 18 and 24 h before sampling. Control rats received an equal volume of vehicle 24 h before sampling. Blood was drawn for IGF-I assay. $^*P < 0.001$ vs. control. (Panel B) Influence of polymyxin B on the effect of compound 48/80 on plasma IGF-I. Polymyxin B was given twice at a dose of 4.8 mg/kg body weight, 1 and 13 h before the injection of compound 48/80. Six hours after the injection of compound 48/80 (2 mg/rat), blood was drawn for IGF-I assay and the livers were assayed for IGF-I mRNA. $^*P < 0.001$ vs. control.

of compound 48/80 on plasma IGF-I (data not shown), which further excludes the possibility that histamine reduces plasma IGF-I via the H_2 receptor pathway.

We then injected endotoxin to rats to observe its effect on plasma IGF-I. Rats were intraperitoneally injected with endotoxin (5 mg/kg body weight) 4, 8, 18 and 24 h before sampling. Diarrhoea occurred in all endotoxin-treated animals. Endotoxin markedly reduced plasma IGF-I. Four hours after endotoxin injection, plasma IGF-I was reduced by 57% ($P < 0.001$). The reducing effect of endotoxin on plasma IGF-I remained essentially unchanged during 24 h period observation (Fig. 3A). Thus, our findings confirm the reducing effect of endotoxin on plasma IGF-I demonstrated by others (Fan et al., 1994).

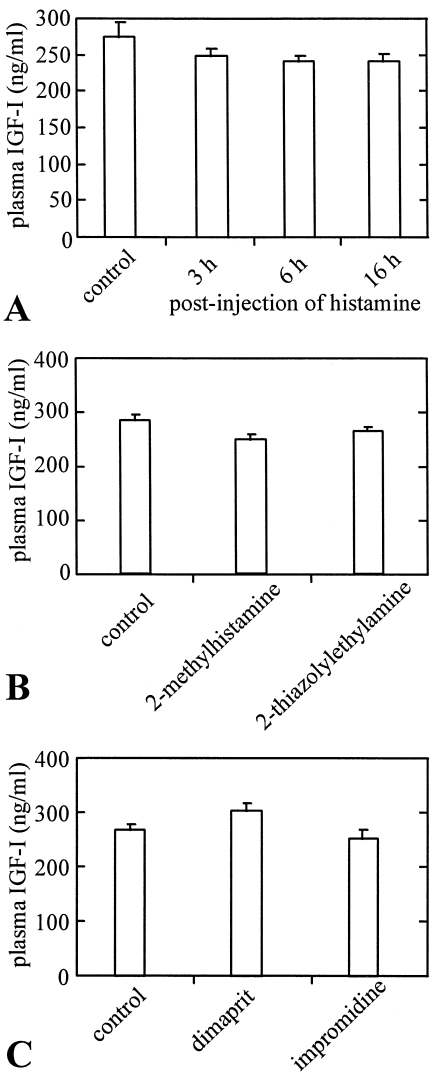

Fig. 4. (Panel A) Effect of histamine on plasma IGF-I. Groups of rats were injected with histamine (0.13 mmol/kg body weight) at 3, 6 or 16 h before sampling. Control rats received an equal volume of vehicle 6 h before sampling. Blood was drawn for IGF-I assay. (Panel B) Effect of H_1 agonists on plasma IGF-I. Groups of rats were injected with H_1 agonists (0.065 mmol/kg body weight), 2-methylhistamine or 2-thiazolylethylamine. Six hours after the injection of H_1 agonists, blood was drawn for IGF-I assay. (Panel C) Effect of H_2 agonists on plasma IGF-I. Groups of rats were injected with H_2 agonists (0.065 mmol/kg body weight), dimaprit or impromidine. Six hours after the injection of H_2 agonists, blood was drawn for IGF-I assay.

It was reported that histamine can induce gut-derived endotoxemia (Cuevas and Fine, 1973; Grun et al., 1976). Thus it is possible that histamine reduced plasma IGF-I through the induction of endotoxemia. To test this, polymyxin B was used in the following experiment. Besides its antimicrobial activity, polymyxin B has antiendotoxin properties (Morrison and Jacobs, 1978), as it binds to the lipid A part of endotoxin. Polymyxin B was administered orally for targeting the intestinal endotoxins and for avoiding the systemic toxicity. Polymyxin B was given twice at a dose of 4.8 mg/kg body weight, 1 and 13 h before the injection of compound 48/80. In this experiment, compound 48/80 again reduced plasma IGF-I by 56% ($P < 0.001$, Fig. 3B), but had no effect on hepatic IGF-I mRNA, further confirming the above findings. Polymyxin B itself had no significant effect on plasma IGF-I, and neither did it attenuate the effects of compound 48/80 on plasma IGF-I (Fig. 3B).

We also studied if exogenous histamine could have an effect similar to compound 48/80. Six hours after intraperitoneal injection of histamine at a dose (0.065 mmol/kg body weight) that induces a maximal gastric acid secretion (Hiramatsu and Okabe, 1994), blood was taken for plasma IGF-I assay. The results showed that plasma IGF-I was not significantly reduced (7% reduction, data not shown). We further tested the effects of exogenous histamine on plasma IGF-I in a time course experiment using the double dose. Again, plasma IGF-I was not significantly reduced after histamine injection (~ 10–13% reduction, Fig. 4A).

Histamine H_1 and H_2 receptor agonists were further used. Like histamine injection, plasma IGF-I was not significantly reduced by H_1 agonists, 2-methylhistamine (13% reduction) and 2-thiazolylethylamine (7.5% reduction) (Fig. 4B). On the other hand, H_2 agonists, dimaprit and impromidine did not significantly alter plasma IGF-I (Fig. 4C).

4. Discussion

To our knowledge, our present study shows for the first time that endogenous histamine induced by compound 48/80 can considerably reduce plasma IGF-I. We further demonstrated that endogenous histamine reduces plasma IGF-I via the histamine H_1 receptor-mediated pathway, because the effect of compound 48/80 on plasma IGF-I is blocked by oral administration of the H_1 receptor antagonist (chlorpheniramine), but not by the H_2 receptor antagonists (cimetidine and ranitidine).

It was reported that histamine can induce gut-derived endotoxemia (Cuevas and Fine, 1973; Grun et al., 1976). Thus it is possible that compound 48/80 reduced plasma

IGF-I through the induction of endotoxemia. However, our study indicates it is not likely that gut-derived endotoxemia mediates the effect of compound 48/80, because oral administration of polymyxin B, an antiendotoxin antibiotic (Morrison and Jacobs, 1978), did not attenuate the effect of compound 48/80 on plasma IGF-I at all. This is consistent with our previous study which demonstrated that oral administration of polymyxin B does not block the effect of compound 48/80 on hepatic low density lipoprotein receptor and plasma high density lipoprotein cholesterol (Liao et al., 1997a). Oral administration of polymyxin B has been shown to rapidly eliminate endotoxemia in patients with liver cirrhosis (Adachi et al., 1982) and sepsis (Endo et al., 1992). Although the dose used in our study is high as compared to those studies, polymyxin B treatment prior to the injection of compound 48/80 did not attenuate its effect on plasma IGF-I. Accordingly, there were no signs of endotoxemia in the animals after receiving compound 48/80; and diarrhoea and hypertriglyceridaemia, the known responses to endotoxin in vivo (Mathan et al., 1988; Feingold et al., 1992; Liao et al., 1996), were not present in these animals (Liao et al., 1997a).

It should be noted that polymyxin B can also induce histamine release (Franzen, 1981; Babe and Serafin, 1996). Our previous study showed that compared to compound 48/80, polymyxin B appears to have similar, but less potent effect on hepatic low density lipoprotein receptor and plasma high density lipoprotein cholesterol (Liao et al., 1997a). In the present study, polymyxin B did not have any effect on plasma IGF-I. The difference may reflect different pharmacokinetics and different administration routes of two drugs. Polymyxin B was given orally, whereas compound 48/80 was injected subcutaneously. After oral administration, little polymyxin B is absorbed from intestine.

Administration of histamine or H_1 receptor agonists seemed to have minimal effect on plasma IGF-I. These results are consistent with the lack of significant effect of histamine and H_1 receptor agonists on plasma high density lipoprotein cholesterol (Liao et al., 1997a). The lack of significant effect of exogenous histamine on plasma IGF-I may reflect a rapid clearance of histamine after injection (Babe and Serafin, 1996).

It was reported that histamine stimulates IGF-I mRNA, but it does not increase IGF-I polypeptide in human glioma cells (Van der Ven et al., 1997). In our present study, endogenous histamine markedly reduces plasma IGF-I, but it does not reduce the hepatic IGF-I mRNA level. These studies thus suggest that histamine may have different effects on IGF-I mRNA and on IGF-I protein levels and that histamine may also have different effects on IGF-I metabolism among its targeting tissues. Further studies are needed to elucidate how histamine reduces plasma IGF-I.

While little is known about the pathophysiologic roles of histamine in the conditions other than allergic response, secretion of gastric acid and being a neurotransmitter (Hill, 1990), the pathophysiologic significance of endogenous histamine-mediated reduction of plasma IGF-I is not clear. Endogenous histamine release may attenuate the effects of IGF-I resulting from its reducing effect on plasma IGF-I. It is well-known that IGF-I play an important role in tissue repair and wound healing (Jones and Clemmons, 1995). Histamine released in response to inflammatory stimuli triggers vasodilatation and increases venous permeability during early stage of the pathophysiologic process of the wound and therefore brings more blood-borne growth factors such as IGF-I to injury sites. Thus histamine may work synergistically with IGF-I in improving wound healing process. In addition, nascent intracellular histamine may also be involved in the tissue repair and wound healing (Hill, 1990). However, in response to traumatic injuries, plasma IGF-I decreases dramatically in the patients with burn and trauma (Abribat et al., 1993; Wojnar et al., 1995; Lang et al., 1996; Gianotti et al., 1998), leading to the impairment of wound healing process. The patients complicated with infection would further impair the wound healing process, because infection also decreases circulating IGF-I (Rodriguez-Arnao et al., 1996; Gianotti et al., 1998; Lang et al., 1998). Therefore, administration of exogenous IGF-I or increasing endogenous IGF-I production would be alternative therapies for such critical patients.

In summary, endogenous histamine reduces plasma IGF-I via a histamine H_1 receptor-mediated pathway. This effect is not likely through gut-derived endotoxemia, and is not due to reduction in hepatic IGF-I mRNA level. Our study suggests a novel role of histamine in the regulation of IGF-I metabolism in vivo, warranting a further investigation of the physiologic relevance of this regulation in humans.

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