THE MOBILIZATION OF PLASMA LIPIDS BY HISTAMINE IN DOGS

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Abstract—The aim of the present work was to study the mechanism of the mobilization of plasma lipids produced by histamine in the dog, in vivo. The increase of plasma lipids by histamine in vivo was suppressed by cimetidine, but not by diphenhydramine. Although, histamine increased the level of plasma adrenaline, adrenaline does not appear to contribute to the lipolysis stimulated by histamine, because propranolol and alprenolol, β-adrenergic blocking agents, did not affect the lipolysis stimulated by histamine. From these data it is concluded that the increase of plasma lipids in vivo is not attributable to the release of adrenaline from adrenal glands by histamine, but is produced by the stimulation through H2-receptors in fat cells.

Histamine may be an agent that stimulates lipolysis in dogs (1–4). Fredholm et al. (1) reported that lipolysis was stimulated in inguinal fat pads perfused with histamine in a dose as low as 2 μg. Grund et al. (3, 4) reported that histamine promoted the release of free fatty acids (FFA) from dog subcutaneous adipose tissue and stimulated it through H2-receptors in fat cells, in vitro. However, little is known of the effects of histamine on lipolysis in vivo.

We assessed the effects of histamine on plasma triglycerides (TG), glycerol and FFA in dogs, and the action mechanism of histamine in vivo. Our findings are reported herein.

MATERIALS AND METHODS

Mongrel dogs (weighing 10–15 kg, both sexes) were used. Eighteen hr prior to the experiment the animals were deprived of food; water was allowed ad libitum. The dogs were anesthetized with sodium thiopental (25 mg/kg, i.v.) and the depth of anesthesia was maintained by giving supplementary doses. Histamine dissolved in saline solution was constantly injected through the apparatus consisting of the roller pump (Furue Science Co., RP-N1), via the cephalic vein of dog. When the plasma lipids was determined, samples of venous blood (2–4 ml) were drawn from the external jugular vein each time, and when both plasma lipids and catecholamines were determined, samples (7 ml) were drawn. In order to supplement the loss of blood, the saline solution (40 ml/hr) containing histamine was injected.

Plasma FFA was measured by the colorimetric method (5). Glycerol in the plasma was measured according to the method of Garland and Randle (6). Plasma TG was measured according to an enzymatic method (7). Adrenaline and noradrenaline in the plasma were estimated by the fluorimetric technique using the tryhydroxy indole method (8). The following agents were used...
in the experiments: histamine (Wako Pure Chemical Industries, Ltd), sodium thiopental (Tanabe Pharmaceutical Co., Ltd), propranolol (Sumitomo Kagaku Kogyo Co., Ltd), alprenolol (Fujisawa Co., Ltd), diphenhydramine (Kowa Co., Ltd) and cimetidine (Smith Kline and French Labo., Ltd). All the other chemicals were of reagent grade.

RESULTS

The results of Fig. 1 clearly show that the level of plasma lipids increased by the injection of histamine. When a low concentration of histamine (0.1 \(\mu g/kg/min\)) was injected, there was little increase in plasma lipids. However, when the histamine concentration was increased to 2.0 or 18 \(\mu g/kg/min\), the level of plasma lipids increased remarkably. During the injection 18 \(\mu g/kg/min\) of histamine, the level of plasma lipids increased to the maximum at about 60 min. At 60 min after the end of the injection (120 min after the beginning of the injection), plasma FFA and glycerol levels remained highly elevated. In addition, the injection of saline solution did not produce any significant change in the plasma lipids.

In view of the fact that histamine has stimulatory effects on the adrenal glands (9), propranolol and alprenolol, \(\beta\)-adrenergic blocking agents, were tested for their ability to inhibit the mobilization of plasma lipids by histamine. Propranolol and alprenolol were injected at 20 min before the injection of histamine. These drugs (each 1 mg/kg) only slightly blocked the increase in the level of plasma lipids and adrenaline induced by histamine (data not shown).

The effect of diphenhydramine, a \(H_1\)-receptor antagonist, on the increase of plasma lipids induced by histamine was investigated. As illustrated in Fig. 2, diphenhydramine was without effect.

The influence of cimetidine, a \(H_2\)-receptor antagonist.

![Fig. 1. Effect of histamine on plasma lipids. Each point represents the mean±S.E. for seven experiments.](image1)

![Fig. 2. Effect of diphenhydramine on the change of plasma lipids induced by histamine. Each point represents the mean±S.E. for seven experiments.](image2)
antagonist, on plasma lipids and catecholamines was also examined and the results are shown in Fig. 3. The increase of plasma lipids was not inhibited by a low dose of cimetidine (1 mg/kg), (data not shown), but was significantly inhibited by the injection of 10 mg/kg cimetidine. However, plasma adrenaline and noradrenaline were not significantly affected by cimetidine.

DISCUSSION

Shaw and Ramwell (10) and Nakano and Oliver (11) found that histamine in vitro has no effect as a lipolytic substance in rat. We also found that histamine has no the lipolytic effect in rat epididymal adipose tissue (12). Grund et al. (3) showed that histamine may be an important lipolytic agent in dog, in vitro.

Fredholm et al. (1) showed that intraarterial injections of histamine and compound 48/80 to subcutaneous adipose tissue in dog led to an increase in the release of FFA and glycerol. We found that histamine cuased an increase in the plasma lipids. The increase was highest at the injection of 18 μg/kg/min of histamine and the elevated levels only slowly returned to the basal levels. These findings suggest that histamine stimulates lipolysis in vivo as well as in vitro.

In the present experiment, although the sampling of blood was repeated several times, the basal levels of plasma lipids did not change in the case of the injection of saline solution. In addition, we observed that the eucrasia of dog was well after experiments. These observations indicate that the effect of hyphemia on the plasma lipids did not occur.

The lipolysis by catecholamines is evoked through the stimulation of β-receptors in fat cells. Since histamine stimulates the adrenal glands (9), the possibility that the increase of plasma lipids may occur through the intermediary of adrenaline release has to be considered. We confirmed that histamine increased the level of plasma adrenaline. If the increase of plasma lipids was caused by adrenaline released by histamine injection, this response should be blocked by β-adrenergic blocking agents. The results obtained in the current study indicate that the increase of plasma lipids caused by histamine injection was not inhibited by the injection of propranolol or alprenolol.

Histamine receptors are currently classified as H1- and H2-receptors, based on the selective antagonism to various histamine response caused by specific histamine receptor blockers (13, 14). Diphenhydramine used in this experiment is referred to as a H1-receptor antagonist (15) and cimetidine is a H2-receptor antagonist (16). Grund et al. (4) showed that burimamide, a H2-receptor antagonist, apparently inhibited histamine-stimulated lipolysis in isolated canine fat cells in vitro and that histamine-stimulated lipolysis was not blocked by tripelennamine, a H1-receptor antagonist. In the present experiment, the mobilization of plasma lipids by histamine was blocked by cimetidine, but not by diphenhydramine, and the increase of plasma adrenaline was not blocked by cimetidine.

Thus, the increase in plasma lipids caused
by histamine is not based on the release of adrenaline, but rather on the stimulation of H₂-receptors by histamine in adipose tissue, at least in this preparation.

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