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5. Histamines metabolism and polyamines

Histamine antilipolytic action in rat adipocytes: comparison with the effect of tyramine

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Introduction

The termination of the multiple actions of histamine is dependent on the inactivation of this signal molecule by amine oxidase or histamine-N-methyl-transferase in the central nervous system and in peripheral tissues. We have recently reported that the oxidation of histamine induces a stimulation of glucose uptake in rat adipocytes [1]. This histamine-stimulated glucose transport is inhibited by inhibitors of monoamine oxidases (MAO) or semicarbazide-sensitive amine oxidases (SSAO) as is the case for benzylamine, tyramine and other MAO/SSAO substrates [2]. The insulin-like effect of these amines was attributed to the hydrogen peroxide generated during oxidative deamination [3]. Since insulin is not only able to stimulate glucose uptake but also to inhibit lipolytic activity of rat adipocytes, we tested whether histamine and tyramine also exhibited such antilipolytic actions.

Materials and methods

Adipocytes were isolated from intra-abdominal white adipose tissues (INWAT) of male Wistar rats (200–250 g) by collagenase digestion and lipolytic activity was measured using enzymatic determination of glycerol release by isolated adipocytes after 90 min incubation with the tested drugs [4]. MAO and SSAO activities were measured using ^{14}C-tyramine oxidation and selective inhibitors of MAO (pargyline) or SSAO (semicarbazide) as previously reported [3].

Results and discussion

Basal lipolysis of rat isolated adipocytes was stimulated up to threefold by 10 nM isoprenaline while histamine and tyramine were without effect, even when tested at concentrations from 10 nM to 1 mM (not shown). The submaximal activation of lipolysis by 10 nM isoprenaline allowed us to detect an inhibitory effect of insulin which was maximal at 100 nM. Under these conditions, tyramine dose-dependently inhibited the lipolytic action of the β-adrenergic agonist, reaching an almost complete blockade at 1 mM while, at the same concentration, histamine was partially, but significantly, antilipolytic (Fig. 1). Benzylamine, a synthetic substrate of SSAO, and methylamine, the proposed endogenous substrate of SSAO, were also partially antilipolytic (Fig. 1). In order to verify whether these antilipolytic effects were dependent on amine oxidation, similar experiments were conducted on animals previously treated by i. p. administration with the MAO-inhibitor pargyline (2.4 mg/kg) or the SSAO inhibitor semicarbazide (3.2 mg/kg). After 9 days of treatment, there was no change in the body mass or in the adiposity of the animals. However, while MAO activity was not affected in the semicarbazide-treated rats, it was significantly decreased in the INWAT of pargyline group: pargyline-sensitive oxidation of 0.5 mM ^{14}C-tyramine was 0.17 ± 0.02, 0.19 ± 0.03 and 0.09 ± 0.01 nmol/mg protein/min in the control, semicarbazide- and pargyline-treated groups, respectively. In contrast, SSAO–dependent oxidation of tyramine was reduced by semicarbazide treatment (not shown). Figure 2 shows that the antilipolytic effect of tyramine did not remain significant in the pargyline-treated group, while the antilipolytic response to benzylamine was altered in semicarbazide-treated rats. No histamine-induced antilipolysis was found on adipocytes from semicarbazide- or pargyline-treated rats, indicating that the adipocyte SSAO and MAO activities were implicated in the mechanism of the antilipolytic action of histamine.

Although known as a lipolytic agent via H_2-receptor activation in dog [5] and rat [6], but not human, adipocytes [7] histamine exhibits multiple effects on adipocytes, several of them being apparently dependent on its oxidative deamination. Our results confirm that histamine, known to be oxidized by diamine oxidase, behaves in rat fat cells as an MAO/SSAO substrate as already reported [6]. They also indicate that deaminative oxidation of histamine or tyramine induces inhibition of lipolysis.

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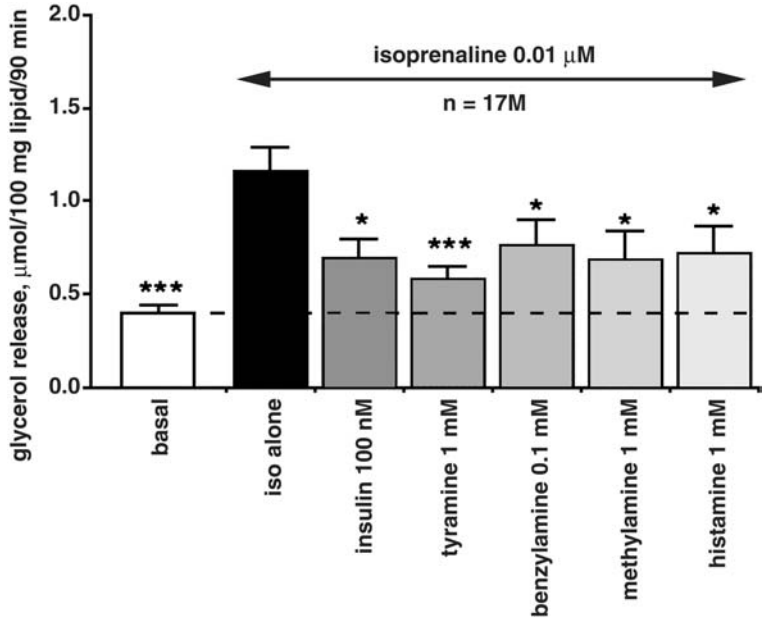

Fig. 1. Effect of insulin, histamine and diverse amines on isoprenaline-stimulated lipolysis. Rat adipocytes were incubated for 90 min with isoprenaline alone (10 nM-black column) or in combination with the indicated concentrations of the tested compounds. Different from isoprenaline alone at: *$p < 0.05$, ***$p < 0.001$.

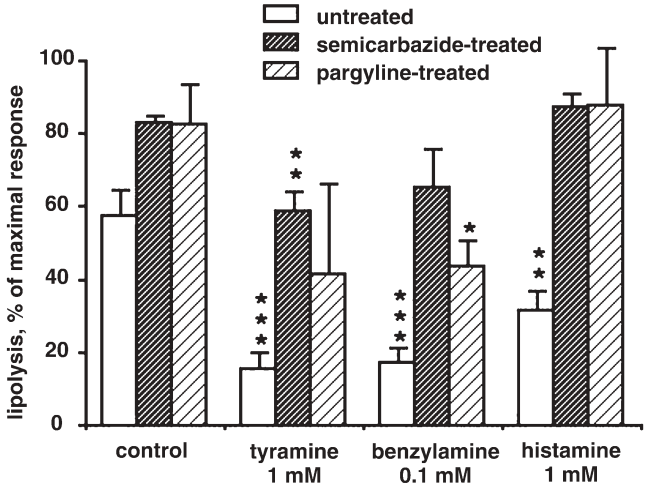

Fig. 2. Inhibition of the antilipolytic effects of tyramine, benzylamine and histamine by semicarbazide or pargyline treatment. The inhibitory action of the tested amines was measured on lipolysis stimulated by isoprenaline (10 nM) plus vanadate (0.1 mM). Results are expressed as percentage of maximal lipolytic response to 10 μM isoprenaline which reached 1.8 ± 0.2, 2.4 ± 0.2 and 2.5 ± 0.2 μmol glycerol/100 mg lipid/90 min in untreated, semicarbazide- or pargyline-treated rats. Different from the corresponding isoprenaline + vanadate control at: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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