In the present experiments we investigated the effect of histamine, 5-HT, and heparin, as well as compound 48/80, on the release of free fatty acids (FFA) and glycerol from canine subcutaneous adipose tissue. Heparin is known to increase lipoprotein lipase (LPL) activity, and this enzyme was also assayed. Moreover the vascular effects of these substances were studied.

Subcutaneous adipose tissue located in the inguinal region of the female dog was isolated and, when metabolic effects were studied, perfused with the dog's own blood at a constant rate from a reservoir (Rosell, 1966). The venous outflow was collected and later analysed for FFA, glycerol content, and LPL activity. Circulatory effects were studied with a plethysmographic technique (Mellander, 1960) permitting the study of series coupled vascular sections.

Compound 48/80 (25–250 μg I.A.) failed to produce a significant LPL release but invariably increased the release of FFA and glycerol. On repeated administration the response decreased. Lower doses of compound 48/80 failed to produce any changes in the above mentioned parameters.

Histamine produced a dose-dependent increase in FFA and glycerol release; thus amounts lower than 0.5 μg had no discernible effect but, with amounts from 0.5 to 150 μg, increasing effects on FFA and glycerol release were seen. Histamine apparently had no effect on LPL activity.

Heparin (0.5–500 μg. I.A.) caused a dose-dependent increase in plasma LPL activity, the response gradually decreasing on repetition of the injection. Heparin had no effect on the release of FFA and glycerol.

Compound 48/80 produced a transient vasodilatation, the response decreasing on repeated administration. Histamine and 5-HT both caused a dose-dependent vasodilatation and an increase in the capillary filtration coefficient indicating an augumented capillary exchange function.

In conclusion, the experiments have shown that histamine and compound 48/80 induce a marked increase in the rate of FFA mobilization from canine subcutaneous adipose tissue and circulatory adjustments favouring capillary exchange.

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Cyclic AMP as a mediator of hormonal metabolic effects in brown adipose tissue

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Noradrenaline in a concentration of 5×10^{-6} g/ml. (Beviz & Mohme-Lundholm, 1967), 5-hydroxytryptamine (2.3×10^{-6} g/ml.) and ACTH (0.34 i.u./ml.) was found to stimulate the oxygen consumption, the production of lactate and glycerol and release of free fatty acids (FFA) maximally in brown adipose tissue of the rat. The maximal calorigenic action of 5-hydroxytryptamine was stronger than that of noradrenaline whereas the action

of noradrenaline on glycerol production was the strongest. All hormones reduced the ATP and creatinine phosphate (CrP) content of the tissue. Noradrenaline and 5-hydroxytryptamine also reduced glucose-6-phosphate content. A β-receptor blocking agent MJ 1999 (6.8×10^{-3} g/ml.) completely blocked the metabolic actions of noradrenaline, 5-hydroxytryptamine and ACTH. Nicotinic acid (2.3×10^{-3} g/ml.) blocked totally the FFA-releasing action of the hormones but only partially inhibited their action on the oxygen consumption and glycerol production.

The lipolytic action of these hormones in white adipose tissue is probably mediated via formation of cyclic AMP (Sutherland, Robinson & Butcher, 1968). We have tried to determine if the metabolic actions of the hormones in brown adipose tissue is mediated by cyclic AMP.

Noradrenaline (5×10^{-6} g/ml.) significantly increased the concentration of cyclic AMP in brown adipose tissue and the concentration of basal cyclic AMP was doubled.

Addition of cyclic AMP (4.5×10^{-3} g/ml.) to the suspension solution increased the oxygen consumption and glycerol, lactate and FFA release. The effect of this amount of cyclic AMP was equivalent to that of noradrenaline at a concentration of 5×10^{-8} g/ml. Cyclic AMP increased the 5'-AMP content of the tissue probably after being hydrolysed by phosphodiesterase. In contrast to noradrenaline, cyclic AMP also increased the ATP content. Dibutyryl cyclic AMP in a ten times lower concentration (4.5×10^{-4} g/ml.) had the same metabolic action as cyclic AMP on oxygen consumption and FFA-release. The lipolytic effect of cyclic AMP and dibutyryl cyclic AMP was blocked by nicotinic acid but the calorigenic actions of the nucleotides was only slightly reduced. MJ 1999 also blocked the FFA-releasing action of dibutyryl cyclic AMP but not its calorigenic action.

Theophylline (4.5×10^{-3} g/ml.) which inhibits phosphodiesterase and the enzymatic hydrolysis of cyclic AMP, blocked the rise of the AMP level produced by cyclic AMP in the tissue. Theophylline stimulated oxygen consumption, glycerol, lactate and FFA-release of brown adipose tissue. The lipolytic effect of theophylline was blocked by nicotinic acid and the calorigenic response reduced. MJ 1999 had no significant influence on the calorigenic or glycerol producing effects of theophylline.

Theophylline and cyclic AMP in combination had a potentiated action on oxygen consumption and an additive effect on lactate and glycerol production. In combination they reduced the ATP and glucose-6-phosphate content of the tissue. The magnitude of the metabolic effects was equivalent to the maximal effect of noradrenaline (5×10^{-6} g/ml.).

The related facts seem to indicate that most of the metabolic actions of noradrenaline as well as those of 5-hydroxytryptamine and ACTH can be explained as a consequence of a stimulation of the adenyl cyclase–cyclic AMP system in the tissue. There are, however, some discrepancies between the metabolic actions of the different hormones which probably cannot only be explained as a consequence of differences in the relative potency of these hormones to stimulate adenyl cyclase. Thus the relative potency of noradrenaline and 5-hydroxytryptamine to stimulate oxygen consumption and glycerol production was different.

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