MOBILIZATION OF NONESTERIFIED FATTY ACIDS DURING OVERSTIMULATION OF ANIMALS AFTER EXHAUSTION OF THE TISSUE CATECHOLAMINE DEPOTS BY RESERPINE

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To study the role of catecholamines (CA) in the mobilization of nonesterified fatty acids (NEFA) produced by overstimulation of rats, the drug reserpine, which reduces the CA reserves in many tissues, including the fat depots, was used. If reserpine was injected in doses of 1, 3, and 10 mg/kg 18 h before stimulation the degree of increase in the NEFA level in the serum and adipose tissues remained the same as in the control. These results indicate that mobilization of NEFA produced by overstimulation of rats can take place despite marked exhaustion of the tissue CA depots by reserpine. The experiments also showed that reserpine itself, if injected into intact animals, has a lipid-mobilizing action which is intensified if the dose of the drug is increased.

Catcholamines (CA) are known to activate adenyl cyclase, the enzyme converting ATP into cyclic 3,5-AMP. Accumulation of this latter compound is accompanied by activation of the hormone-sensitive lipase which acts on triglycerides [4, 5, 13, 16]. In the modern view adenyl cyclase is acted upon not only by CA, but also by other hormones stimulating lipolysis, such as ACTH, glucagon, growth hormone, etc. [14]. It is important to note in this connection that the mobilization of nonesterified fatty acids (NEFA) develops in response both to injection of exogenous CA and ACTH and to many other factors (trauma, emotional excitation, cooling, immobilization, etc.).

The object of the present investigation was to study the role of CA in NEFA mobilization produced by overstimulation of animals. Reserpine, which exhausts depots of CA and other biogenic amines in adipose tissues [12, 15, 17], was used for this purpose. The NEFA content was determined not only in the blood, but also in the "white" (epididymal and retrospinal) adipose tissues, for it has been shown that the NEFA level in these tissues rises during overstimulation of rats [1, 11].

EXPERIMENTAL

Experiments were carried out on 100 satiated male rats weighing 200-300 g. The rats were fixed to a frame and stimulated by an electric current of threshold strength for 2 h through electrodes inserted beneath the skin of the forelimbs. A solution of reserpine phosphate in a dose of 1, 3, and 10 mg/kg, acidified with acetic acid, was injected intraperitoneally 18 h before stimulation. Control animals received an equal volume of acetic acid solution. Intact animals receiving either reserpine or acetic acid solution were investigated at the same times as the rats subjected to immobilization and electrical stimulation. The animals were decapitated and their blood was kept in a refrigerator at 4°C before centrifugation. The adipose tissues were quickly removed and placed on ice; 100 mg tissue was triturated with Dole's mixture. NEFA were analyzed by Dole's method [7]. The degree to which the pituitary-adrenal system was involved in the response to stimulation was characterized by determining the cholesterol content in the adrenals by Bloor's method.

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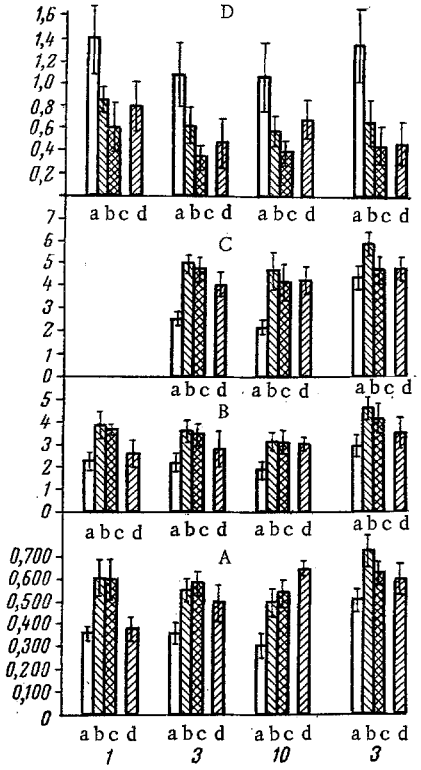

Fig. 1. Effect of reserpine on NEFA content in blood serum and adipose tissues and also on cholesterol content in adrenals of intact rats and animals exposed to overstimulation. Abscissa, dose of reserpine injected (mg/kg); A) NEFA content in blood serum; ordinate – μeq/ml; B) NEFA content in epididymal adipose tissue; C) NEFA content in retrospinal adipose tissue; ordinate – μeq/g fresh tissue; D) cholesterol content in adrenals; ordinate – mg/100 g fresh weight of gland. a) Intact rats; b) rats exposed to immobilization and electrical stimulation; c) ditto + reserpine; d) intact rats receiving reserpine. Last group of columns in each row represents experiment on starving rats. Confidence limits of mean values shown.

EXPERIMENTAL RESULTS AND DISCUSSION

After electrical stimulation of immobilized rats for 2 h there was a marked increase in the NEFA level both in the blood serum and in the adipose tissues (Fig. 1).

If reserpine was injected into doses of 1, 3, and 10 mg/kg 18 h before overstimulation, the consequent degree of NEFA mobilization was virtually unchanged.

Overstimulation of the animals was accompanied by a marked decrease in the cholesterol content in the adrenals. In the animals receiving reserpine the cholesterol content in the adrenals was reduced by a lesser degree after overstimulation.

Injection of reserpine into intact animals itself caused an increase in the NEFA level in the blood serum and adipose tissues, as other workers have found [10, 18]. The animals developed ptosis and gastro-intestinal disorders, the severity of which increased with an increase in the dose of reserpine. In connection with their general inhibition the reserpinized animals took no food, and this could have been an additional stimulus for the activation of lipolysis. Special experiments on animals deprived of food for 20 h showed that the effect of reserpinization itself on NEFA metabolism could depend to some extent on this factor.

The cholesterol content in the adrenals of animals receiving reserpine but not exposed to stimulation fell, indirect evidence of stimulation of the pituitary-adrenal system.

Injection of reserpine in doses of 1, 3, and 10 mg/kg 18 h before the beginning of stimulation of the animals thus had no significant effect on their response to the stimulus. This was shown by the approximately equal degree of increase in the NEFA level in the blood serum and adipose tissues of the control and reserpinized animals exposed to stimulation, despite the fact that reserpine in these doses leads to a marked decrease in the CA content in adipose tissue [6, 12, 15]. In other words, NEFA mobilization produced by overstimulation of rats can take place even if the tissue CA depots have first been exhausted by reserpine. Stimulation of lipolysis during exposure to overstimulation when the CA reserves in the tissues are sharply reduced presumably takes place on account of an increased secretion of pituitary hormones, especially of ACTH. Reserpine has been shown to activate the pituitary-adrenal system [3, 10]. In these experiments evidence of such activation was given by a decrease in the cholesterol content of the adrenals in the reserpinized animals, whether intact or stimulated. The lipolytic action of ACTH is not inhibited by reserpine [8, 9]. It is interesting to note that in guinea pigs reserpine not only does not prevent NEFA mobilization during overstimulation, but actually potentiates it, while simultaneously activating the pituitary-adrenocortical system [2].

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