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LIPID METABOLISM. CHAIRMAN: M. VAUGHAN

I. INTRODUCTORY REMARKS

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In turning now to a discussion of the effects of catecholamines on lipid metabolism, it is hardly necessary to point out that knowledge of the effects of catecholamines on carbohydrate metabolism antedates by a long time the recognition of their effects on lipid metabolism. This is probably in large part a reflection of the fact that only with the recent development of methodology and new techniques has the study of the lipid metabolism, and especially the metabolism of free fatty acids, come into its own.

Indeed, almost as soon as it was established, about 7 years ago, that adipose tissue lipids were mobilized in the form of free fatty acids, Gordon (1) and White and Engel (8) independently demonstrated that when epinephrine (E) was added to adipose tissue *in vitro*, it stimulated the liberation of free fatty acids (FFA). At that time it was not known by what mechanism the increased FFA release was brought about. Considering the well known effects of E on the phosphorylase systems in liver and muscle, and the observations of Sutherland and Rall (3) concerning the role of cyclic 3′,5′-AMP in these systems, we wondered 1) whether E had any effect on phosphorylase activity in the adipose tissue; and 2) whether an effect of E on phosphorylase activity or on cyclic 3′,5′-AMP accumulation could be in any way causally related to the stimulation of FFA release. It was easy to demonstrate that phosphorylase activity in adipose tissue is increased by the addition of E or norepinephrine (NE) *in vitro* (5). But the second question was more difficult to resolve. Alterations in phosphorylase activity probably do not play a part in the regulation of fatty acid mobilization, but it seems likely that cyclic 3′,5′-AMP does. Dr. Butcher will tell us more about that problem a little later.

It was soon established that the increased fatty acid release produced by E results from an increase in the activity of a specific lipase, referred to as the epinephrine-sensitive or hormone-sensitive lipase. This lipase exists apparently in two forms, active and inactive, which can be rapidly interconverted as with phosphorylase. The presence of E favors the accumulation of the active form of lipase. There are also several other hormones, *e.g.*, glucagon, ACTH and TSH, that produce the same effects. Each of these hormones stimulates the release of FFA from adipose tissue by increasing the amount of active lipase (7). Each is also capable of bringing about an increase in phosphorylase activity in the adipose tissue (5). This latter effect and the effects on lipase activity occur very rapidly. Less than 3 min after the addition of E or one of the other hormones, both the phosphorylase activity and the lipase activity are markedly increased.

As we heard this morning, it has been shown that the effects of these hormones on phosphorylase activity in various other tissues are mediated by cyclic 3′,5-

AMP, and it is most probable that the mechanism is similar in adipose tissue. It has also been demonstrated in Sutherland's laboratory (2) that E causes an accumulation of cyclic 3′,5′-AMP in adipose tissue, but the action of cyclic 3′,5′-AMP in the hormone-induced augmentation of lipase activity has not been defined. Rizack (4) has found that lipase activity in a fraction of homogenized adipose tissue can be increased by the addition of cyclic 3′,5′-AMP plus ATP. In his experiments the concentrations of both nucleotides were critical. Activation was obtained only within a very narrow range of concentrations and under certain conditions both compounds actually inhibited lipase activity.

Although it seems likely that cyclic 3′,5′-AMP is an intermediary in the effects of E on lipase activity, certain observations are difficult at present to fit into any simple scheme. First, serotonin, in concentrations that markedly stimulate phosphorylase activity in isolated adipose tissue, presumably through the cyclic 3′,5′-AMP system, has only a small effect on lipase activity in the same tissues (6). Secondly, it is possible to inhibit differentially the effect of E on phosphorylase and on the lipase. For example, prostaglandin E_1, which Dr. Steinberg will discuss in more detail, blocks almost completely the effects of all of these hormones on lipase activity, while it counteracts only slightly the effects of E on phosphorylase activity. Any proposed scheme for the mechanism of the hormone effects on lipase activation will have to take into account these observations.

One notes a number of parallels, or similarities, between the lipase system in adipose tissue and the phosphorylase systems. It is also striking that the systems for controlling the rate of degradation of stored carbohydrate (glycogen) and of stored lipid (triglyceride are both influenced by catecholamines, at least in the adipose tissue. It seems probable, furthermore, that E-sensitive, or hormone-sensitive lipases exist also in other tissues. It has been shown that E can stimulate the release of glycerol from rat diaphragm and heart *in vitro*, and this fact suggests that lipase activity in these tissues may also be increased by catecholamines. Studies of the E sensitive lipases in other tissues may yield new clues concerning the mechanisms for the regulation of lipase activity, in addition to enlarging our understanding of the multiple actions of catecholamines.

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