Blood Glucose and Free Fatty Acid (FFA) Responses to Catecholamines in Rats Treated Chronically with Noradrenaline or Adrenaline[1] (36099)

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The oxygen consumption response to noradrenaline (NA) (1) and to adrenaline (A) (2) is greatly increased in rats that are treated chronically with noradrenaline. Because of known actions of catecholamines on metabolic processes (3), it seemed likely that this sensitization would be related to changes in lipid and carbohydrate metabolism. The present study was then undertaken to determine the effect of noradrenaline and adrenaline on the levels of free fatty acids, glucose, and lactic acid in the blood of control rats and of rats chronically treated with noradrenaline or adrenaline.

Materials and Methods. Three groups of 24 male Wistar rats with an average initial weight of 200 g were used. The rats of the first group served as control and were injected twice a day with 0.2 ml of olive oil; those of the second group, the NA-treated group, were injected twice a day with 300 μg/kg of noradrenaline base (in the form of hydrochloride) suspended in olive oil, while those of the third group, the A-treated group, were injected twice a day with 300 μg/kg of adrenaline base suspended in olive oil. All injections were given subcutaneously for a period of 28 days.

On the last morning of the experiment, each group was divided into three subgroups: the first of these received no injection (initial values); the second, 300 μg/kg of noradrenaline base (in the form of bitartrate); and the third, 300 μg/kg of adrenaline base (in the form of chloride). Injections of noradrenaline and adrenaline were given subcutaneously in saline. One hour after injection, the animals were decapitated and the collected blood was heparinized and kept on ice for glucose, free fatty acid (FFA), lactic acid, and pyruvic acid determinations. For blood glucose determinations, 0.2 ml of blood were added to 1.8 of H_2O and deproteinized with 1.0 ml of 1.8% $Ba(OH)_2$ and 1.0 ml of 2.0% $ZnSO_4$. The mixture kept on ice was then centrifuged at 4° and the filtrates were frozen for later glucose determinations (Glucostat, Worthington Biochemical Corp. NJ). The blood lactic acid (4) and pyruvic acid (5) determinations were also carried out on blood filtrates: 0.4 ml of blood were added to 1.6 ml of H_2O and then deproteinized, centrifuged, and frozen as for glucose determination. The rest of the blood was centrifuged at 4° to obtain plasma which was kept refrigerated approximately 2 hr before the FFA determinations were done (6). The statistical analysis for each parameter studied was carried out using the Duncan multiple-range test (7) on all nine subgroups simultaneously.

Results. Figure 1 represents the responses of the plasma FFA to noradrenaline and adrenaline in the control group, the NA-treated group and the A-treated group. In the control group, both amines increase FFA levels but the response is greater with noradrenaline than with adrenaline. In the NA-treated group, only noradrenaline produces a response significantly higher than the initial values; whereas, in the A-treated group, a response is observed only with adrenaline. Chronic treatment with noradrenaline or adrenaline does not affect initial plasma FFA values.

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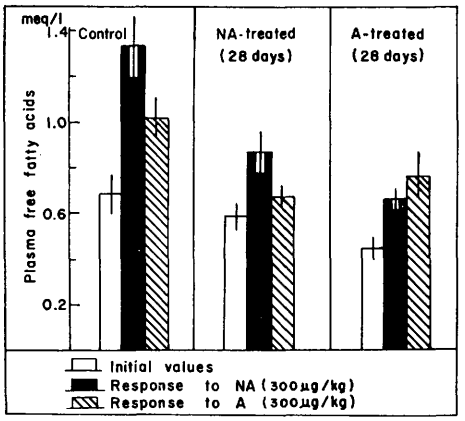

FIG. 1. Plasma free fatty acid responses 1 hr after noradrenaline (NA) or adrenaline (A) injections in control rats and in rats treated chronically with noradrenaline or adrenaline for 28 days.

The responses of blood glucose to noradrenaline and adrenaline are illustrated in Fig. 2. In the control group, both amines increase blood glucose levels but the response is greater with adrenaline than with noradrenaline. In the NA-treated group, only adrenaline produces a highly significant response, in the A-treated group a significant response is also observed only with adrenaline. Figure 2 shows that chronic treatment with noradrenaline or adrenaline does not modify blood glucose initial values.

Figure 3 represents the responses of the blood lactic acid. In the control group, only adrenaline produces a very highly significant response. In the NA-treated group, the response to adrenaline is also highly significant, the response to noradrenaline is moderately elevated and significantly higher than the initial values. In the A-treated group the response to noradrenaline or adrenaline is not significant but the initial values are significantly different from those of either the control or the NA-treated groups; the initial values of the latter two groups being comparable. There is no significant differences between the blood pyruvic acid concentrations of the nine subgroups. The values range from 0.42 ± 0.06 to 0.55 ± 0.06 mg/100 ml.

Discussion. To facilitate the discussion, we have summarized our results in Fig. 4. The results obtained in the control rats are in accord with those of other authors (3). Both noradrenaline and adrenaline produce increased plasma FFA concentrations, and this effect is greater with noradrenaline. The results obtained on blood glucose and lactic acid show that noradrenaline has weaker hyperglycemic action than adrenaline, confirming observations made in man (8) and in the rat (9, 10).

In the NA- or A-treated rats, the effects of noradrenaline or adrenaline on blood glucose, lactic acid, and on plasma FFA levels are, on the whole, smaller than those observed in the control rats. This could indicate either a decreased mobilization or an enhanced utilization in animals injected chronically with catecholamines. Studies by LeBlanc and Pouliot (1), by LeBlanc and Villemaire (11) and by Villemaire (2), have shown that rats injected chronically with noradrenaline (similar studies with adrenaline have not been reported) become more sensitive to the calorigenic action of both noradrenaline and adrenaline. Consequently, it seems that chronic treatment with noradrenaline leads to an increased utilization of substrate in response to either noradrenaline or adrenaline. The point then is to ask whether glucose or FFA are preferentially utilized. One aspect which would argue against an enhanced utilization of glucose is the fact that adrenaline (12) and noradrenaline (13) inhibit insulin secretion in man. Adrenaline was shown to have a similar effect in the rat (14). In

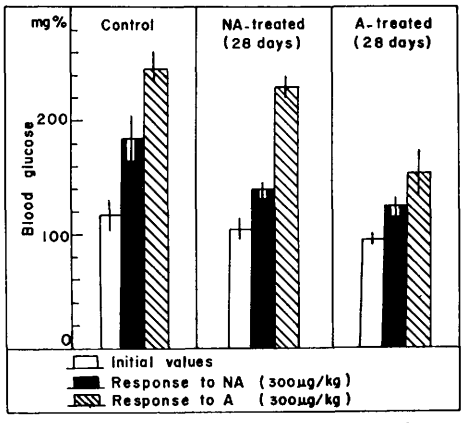

FIG. 2. Blood glucose responses 1 hr after noradrenaline (NA) or adrenaline (A) injections in control rats and in rats treated chronically with noradrenaline or adrenaline for 28 days.

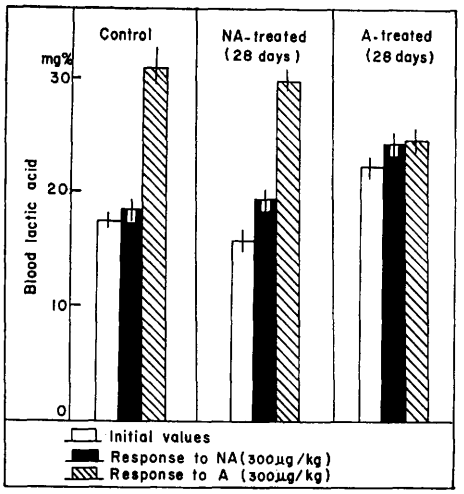

FIG. 3. Blood lactic acid responses 1 hr after noradrenaline (NA) or adrenaline (A) injections in control rats and in rats treated chronically with noradrenaline or adrenaline for 28 days.

addition, adrenaline infusion, while it increases plasma glucose concentration, does not increase glucose uptake in the dog (15). In our experiment, we observe reduced levels of blood glucose in response to noradrenaline in either NA- or A-treated rats and to adrenaline in A-treated rats. In view of the effects of catecholamines on insulin secretion reported by Altszuler *et al.* (15), our results could be explained by reduced glucose mobilization due to depletion of the glycogen reserves or to alterations in glycogenolysis. Similarly a depletion of muscle glycogen due to the chronic treatment could explain why plasma lactic acid failed to increase following adrenaline in the A-treated rats. Nevertheless the participation of carbohydrate metabolism cannot be altogether discarded in the observed metabolic sensitization to catecholamines induced by repeated injections; the importance of alterations in insulin secretion in our experiment is not known, specially with regard to noradrenaline, which has been found less active in that respect (13).

Looking now at the possible participation of lipids in catecholamine sensitization, it is seen first that FFA levels do not increase as much in the NA- or A-treated rats as in the control rats in response to noradrenaline. The FFA response to adrenaline, on the other hand, is reduced in the NA-treated rats and comparable to that of the control rats in the A-treated rats. These results, on the whole, would favor the hypothesis of an enhancement by catecholamines of FFA utilization specially in the NA-treated rats.

The oxygen consumption increase in response to noradrenaline (1, 11) and adrenaline (2) following chronic NA-treatment, has also been observed in cold-adapted rats (16–18), which secrete larger quantities of catecholamines (19, 20). The plasma FFA response to noradrenaline is diminished in cold adaptation (21), as it is in the present study after chronic treatment with noradrenaline or adrenaline. In conclusion it may be said that exposure to increased amounts of catecholamines by either exogenous supply, as in noradrenaline treatment, or by endogenous source as in cold adaptation, leads to increased sensitization to the metabolic effects of noradrenaline and adrenaline and this is possibly due to a preferential enhance-

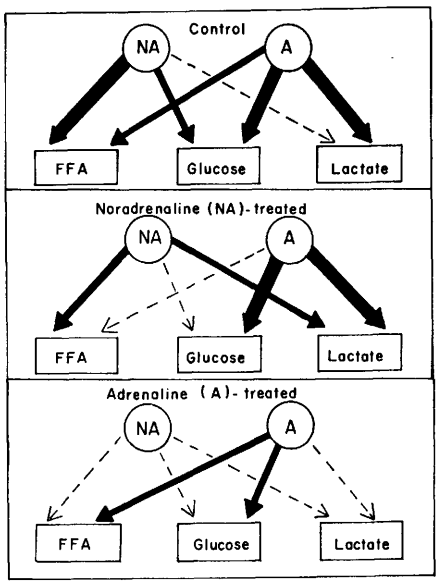

FIG. 4. Responses of plasma free fatty acids (FFA), blood glucose, and lactic acid 1 hr after noradrenaline (NA) or adrenaline (A) injections in control rats and in rats treated chronically with noradrenaline or adrenaline for 28 days: (broken arrows) show that the initial levels are not changed by NA or A; (thin arrows) a moderate response; and (thick arrows) a response greater than a moderate response for any given parameter.

ment of the utilization of lipids rather than of glucose.

Summary. Control rats and rats injected subcutaneously twice a day with a dose of 300 μg/kg of noradrenaline or adrenaline suspended in olive oil were used. After 28 days of treatment, blood glucose, lactic acid, and plasma free fatty acid (FFA) levels were measured in response to noradrenaline or adrenaline (300 μg/kg in saline). In the control rats, it was found that the effect of noradrenaline is more pronounced on FFA levels, while the effect of adrenaline is greater on glucose and lactic acid levels. These responses on the whole, were diminished in animals treated chronically with either noradrenaline or adrenaline. In view of the enhanced oxygen consumption response to noradrenaline or adrenaline in noradrenaline-treated rats which was previously reported, it seems that the lower levels of FFA and glucose obtained, following the same treatment, could indicate an enhanced utilization of those substrates. It is also possible, since catecholamines are known to inhibit insulin liberation, that chronic treatment with catecholamines produces a preferentially enhanced lipid rather than glucose utilization in response to noradrenaline or adrenaline.

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