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Acute Metabolic Effects of Nicotinic Acid in Alloxan Diabetic Dogs.* (30312)

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It has been demonstrated that nicotinic acid in high doses for a prolonged time has a cholesterol lowering effect in man(1). The mechanism of this action has not yet been fully elucidated(2). It was further demonstrated that nicotinic acid causes a rapid decrease in the plasma Free Fatty Acids (FFA) concentration and that it inhibits the increase of FFA produced by nor-epinephrine in fasting man(3). Recently it has been shown *in vitro*(4) that nicotinic acid inhibits FFA release from epididymal pads of alloxan diabetic rats and from adipose tissue taken from diabetic human subjects(5). Older reports have suggested that nicotinic acid has a hypoglycemic effect in diabetic patients(6).

The purpose of this paper was to determine if a depression of plasma FFA concentration was obtainable in alloxan-diabetic dogs and what relationship, if any, could be detected between blood sugar and concentration of FFA.

Materials and methods. Six previously alloxanized (90 mg/kg i.v.) diabetic mongrel dogs of both sexes, weighing 9-15 kg were used. They had a daily NPH insulin‡ requirement varying between 15 and 35 U. They were kept in metabolism cages on a regular diet and their daily urinary output, glycosuria and ketonuria were checked. Water was allowed *ad libitum*.

In preparation for each experiment, insulin was withdrawn for 3 days and food withheld for 16 hours. The day of the experiment, all animals showed ketonuria (from traces to mild), in addition to glycosuria (30 to 140 g/24 hr). Two weeks were allowed as an interval between 2 experiments performed in the same dog. The animals were not anesthetized during the tests. Nicotinic acid (50 mg/dog) or isotonic saline was administered in a peripheral vein. Blood samples obtained from another peripheral vein were stored in heparinized tubes kept in an ice bath. Aliquots for blood sugar determinations(7) were removed and the rest of the blood was centrifuged at 4°C. Plasma FFA determinations (8) were carried out immediately after centrifugation. Plasma total cholesterol was measured according to Abell(9).

Results. Results are presented in Table I and Fig. 1. Table I gives the average pre-

TABLE I. Mean Pre-Injection Values in Diabetic Dogs (± S.E.). (12 experiments)

Blood glucose	284 ± 16 mg %
Plasma total cholesterol	232 ± 13 mg %
Plasma FFA	1340 ± 130 μEq/l

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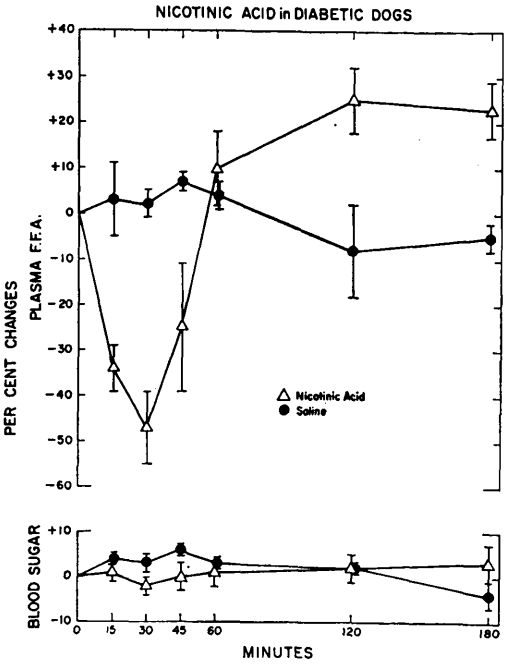

FIG. 1. Changes in blood sugar and plasma FFA following injection of nicotinic acid i.v. (6 exp.) or saline i.v. (6 exp.), ± S.E.

injection values and standard error of the mean of blood sugar, plasma total cholesterol and FFA. Samples for these were taken 60 minutes, 30 minutes, and immediately before injection of nicotinic acid or saline. It can be noted that blood glucose and plasma FFA and total cholesterol were abnormally elevated, as expected in diabetic animals. Fig. 1 represents changes from the average pre-injection values in blood sugar and plasma FFA concentration, after nicotinic acid or saline administration. The results show that nicotinic acid causes a statistically significant fall in plasma FFA concentration lasting about 30 minutes ($P<0.001$). These values return to control levels 60 minutes after the injection and gradually but significantly increase ($P<0.01$) thereafter for the period of observation. Blood sugar concentration is not affected by the injection of nicotinic acid and does not differ from saline controls.

Cholesterol determinations were carried out in all samples described and no significant changes were detected during the period of observation.

Discussion. The present studies show that nicotinic acid depresses the plasma concentration of FFA in alloxan-diabetic dogs, without simultaneous hypoglycemic effects. These animals had glycosuria and ketonuria and presumably little or no insulin in circulation. The lipolysis-arresting effect of nicotinic acid, therefore, could not have been mediated by endogenous insulin, but rather by means of a different pathway.

On the basis of our data, we cannot provide an explanation of the effects described. It is tempting to speculate, however, that we are dealing with some mechanism similar to, or identical with, an adrenergic-blocking effect. This action of nicotinic acid was first suggested by Carlson and Orö(3). Further support for this concept may be derived from the observation that lipolysis is stimulated by catecholamines(8) and/or adrenergic nerve impulses(10), while a depression in lipolysis can be accomplished by adrenergic-blocking agents(11).

The lack of effect of nicotinic acid on plasma total cholesterol in these studies may be explained by the small doses used and by the short duration of the experiments.

Summary. Small doses of nicotinic acid were injected i.v. into alloxan diabetic dogs, causing an initial, rapid, significant decrease of plasma FFA followed by a rebound increase over control values. Blood sugar and total cholesterol were not affected.

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