A WAY OF PREVENTING THE FREE FATTY ACID CONCENTRATION IN THE SERUM OF RABBITS FROM RISING

I. V. Kryukova and V. I. Kandror

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A scheme of administration of nicotinic acid by mouth is suggested in order to prevent any increase in the free fatty acid concentration in the serum after intravenous injection of heparin or triiodothyronine, prolonged starvation, and thyroid feeding.
KEY WORDS: free fatty acids; nicotinic acid; lipolysis block; starvation; thyroid hormones.

The pathogenic role of an increase in the supply of free fatty acids (FFA) for oxidative tissue metabolism in many diseases has been actively discussed in the literature [2, 3, 14-17]. Meanwhile the increase in the blood FFA level might be purely an associated feature and not a factor concerned with the pathogenesis of the principal manifestations of these states. The experimental simulation of these diseases under conditions in which a rise in the blood FFA level is prevented would obviously make a major contribution toward the solution of this problem.

Among existing metabolic blocking agents of lipolysis in adipose tissue considerable attention has recently been paid to nicotinic acid, the mechanism of action of which is not yet completely understood [1, 5, 8, 10, 13]. However, the essential fact is that nicotinic acid, both in animals and in man, prevents the increase in the blood FFA level normally observed in certain acute hormonal disturbances [4, 6, 12]usually accompanied by activation of lipolysis in adipose tissue.

A method of using nicotinic acid to prevent the increase in the FFA concentration in the serum in certain acute and chronic conditions in rabbits is described below.

Experiments were carried out on male chinchilla rabbits weighing 2.5-3.2 kg. Considering the importance of the feeding program during determination of the blood FFA level, the experiments were carried out in accordance with the following scheme. The animals received food (the ordinary diet of the animal house) twice a day: at 9-10 a.m. and 5-6 p.m. During the intervals the feeding bowls were removed from the cages. Water was given ad lib. Blood for analysis was taken from the marginal vein of the ear in the morning before feeding. Nicotinic acid was given by mouth twice a day before feeding in a dose of 0.5 g per animal, in gelatin capsules.

The lipolytic effect of intravenous injection of 700 i.u./kg heparin (1 h after injection), 150 μg/kg of 3,5,3'-L-triiodothyronine (3 and 5 h after administration), and also of prolonged starvation (8-10 days) and administration of thyroid extract for 12-14 days was tested in animals receiving and not receiving nicotinic acid [2].

In these experiments the serum FFA concentration of the fasting rabbits, determined by Duncombe's method [11], averaged 0.383 ± 0.09 μeq/ml ($n=45$). In the experiments with heparin and triiodothyronine these substances were injected intravenously 2 h after the morning dose of nicotinic acid. The animals were fed after the end of the experiments.

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TABLE 1. Dynamics of FFA Concentration (in μeq/ml) in Serum of Rabbits during Starvation Accompanied by Nicotinic Acid Administration (M ± m)

Experimental conditions	Before starvation	After beginning of starvation		
		4 days	6 days	10 days
Without nicotinic acid	0,355±0,04 (6)	0,500±0,05 (5) $P<0,05$	0,554±0,02 (5) $P<0,05$	0,639±0,1 (5) $P<0,05$
Preceded (for 3 days) and accompanied by administration of nicotinic acid	0,371±0,04(11)	0,208±0,008 (6) $P>0,05$	0,165±0,02 (5) $P<0,05$	0,112±0,04 (4) $P<0,05$

Notes. 1) Here and in Table 2 number of animals given in parentheses; 2) P is the criterion of significance of differences between initial values and those after the beginning of treatment.

TABLE 2. Dynamics of FFA Concentration (in μeq/ml) during Thyrotoxicosis Accompanied by Nicotinic Acid Administration (M ± m)

Experimental conditions	Before administration of thyroid extract	After beginning of administration of thyroid extract		
		2—4-day	5—9-day	10—14-day
Without nicotinic acid	0,300±0,02 (39)	0,452±0,04 (32) $0,05<P<0,1$	0,600±0,07 (10) $P<0,01$	0,610±0,05 (30) $P<0,01$
Preceded (for 3 days) and accompanied by administration of nicotinic acid	0,371±0,04 (11)	0,310±0,04 (6) $P>0,1$	0,448±0,05 (8) $P>0,1$	0,276±0,06 (7) $P>0,1$

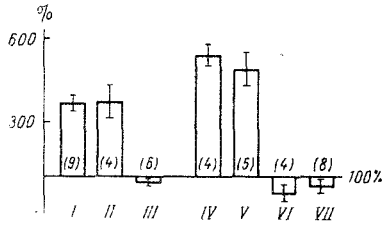

Fig. 1. Action of nicotinic acid on effects of intravenous injection of heparin and triiodothyronine: I) 1 h after injection of heparin; II) the same, after preliminary (for 1 day) administration of nicotinic acid; III) the same after preliminary (for 3 days) administration of nicotinic acid (in the morning no nicotinic acid was given before the heparin); IV, V) 3 and 5 h respectively after injection of triiodothyronine; VI, VII) the same, after preliminary (for 3 days) administration of nicotinic acid. Initial level of serum FFA concentration taken as 100%. Number of animals in each experiment given in parentheses. Values given are M ± m (%).

The information given in Fig. 1 shows that 1 h after injection of heparin into the control animals their serum FFA had risen by more than 150% ($P<0.001$). If the nicotinic acid was given 3 times (twice on the day before the experiment, and the last time 2 h before injection of heparin) before the injection of heparin no prevention of lipolysis could be found. If, however, the animals received nicotinic acid for 3 days (twice a day) before the experiment, a subsequent injection of heparin caused no increase in the serum FFA regardless of whether they had received nicotinic acid in the morning on the day of the experiment or not ($P > 0.6$). These results indicate that, first, the lipolytic effect of heparin can be blocked only by a sufficiently prolonged preceding saturation with nicotinic acid and, second, that this block lasts at least 16-18 h.

Similar results were obtained in experiments in which a single injection of triiodothyronine was given. Whereas in the control animals the serum FFA level 3 and 5 h after injection of the hormone was about 300% higher than initially ($P<0.001$), if nicotinic acid was given for 3 days beforehand, the serum FFA level after injection of the hormone was actually a little below its initial value.

The results of the administration of nicotinic acid in chronic experiments are evidently of the greatest interest.

Starvation and experimental thyrotoxicosis were chosen as models of states characterized by a high serum FFA level. On

the basis of the data given above the animals began a long period of starvation or of thyroid administration 3 days after the beginning of receiving nicotinic acid. The rabbits continued to receive nicotinic acid throughout the experiment.

The results given in Table 1 show that the serum FFA concentration in the fasting animals at all times of the investigation was higher than initially. Meanwhile starvation, accompanied by nicotinic acid administration, did not cause any increase in the serum FFA level. At all times of the investigation the corresponding valves were actually lower than initially.

The above program of nicotinic acid administration also prevented the serum FFA level from rising in rabbits with thyrotoxicosis (Table 2). Whereas in animals receiving thyroid extract the serum FFA concentration at certain times of the experiment was twice as high as initially, in none of the rabbits receiving precisely the same dose of thyroid extract in conjunction with nicotinic acid was there any significant increase in the serum FFA concentration.

Administration of nicotinic acid by the suggested scheme thus provides a method of simulating certain pathological states from which one symptom (elevation of the serum FFA level), regarded by some workers [9, 14, 15] as playing a causative role in the genesis of other manifestations, is eliminated. In other words, the use of nicotinic acid can prove an effective method of studying the role of FFA in the pathogenesis of certain diseases.

In conclusion it must be stated that, according to the writers' observations, prolonged administration of nicotinic acid by mouth does not change the serum FFA concentration, by contrast with the effect of a single intravenous injection of the compound [7, 8].

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