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PRELIMINARY COMMUNICATIONS

Plasma β-Hydroxybutyric Acid Response to Nicotinic Acid-Induced Plasma Free Fatty Acid Decrease in Man*

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Summary. Nicotinic acid was in acute studies administered to 4 patients with untreated juvenile diabetes and to 4 obese fasting patients. In all cases the plasma level of FFA decreased. This was soon followed by a decrease in plasma β-hydroxybutyric acid. The effects were less prompt and pronounced in the obese fasting subjects. There were lesser changes in the concentration of blood glucose.

Réponse de l'acide β-hydroxybutyrique du plasma à la chute des acides gras libres provoquée par l'acide nicotinique.

Résumé. 4 malades avec diabète juvénile non-traité et 4 personnes obèses à jeun ont reçu de l'acide nicotinique dans une étude aiguë. Dans tous les cas le taux des acides gras libres du plasma descendait, suivi par une chute de l'acide bêta-hydroxybutyrique dans le plasma. Les effets étaient moins prompts et moins prononcés chez les personnes obèses à jeun. Des modifications moindres du glucose sanguin ont été observées.

Verhalten der Plasma β-hydroxy-Buttersäure nach durch Nikotinsäure ausgelöstem Abfall der freien Fettsäure beim Menschen.

Zusammenfassung. 4 Patienten mit unbehandeltem, jugendlichen Diabetes und 4 Adipöse im Hungerzustand erhielten im akuten Versuch Nikotinsäure. Bei allen Versuchspersonen trat ein Abfall der freien Fettsäuren im Plasma ein, an den sich ein Absinken des β-hydroxybuttersäure-Spiegels im Plasma anschloß. Bei den übergewichtigen Personen im Hungerzustand setzten diese Wirkungen langsamer ein und waren schwächer ausgeprägt. Die Blutzuckerspiegel änderten sich in geringerem Ausmaße.

Increased hepatic production of ketone bodies may occur as a result of excessive mobilization of free fatty acids (FFA) from adipose tissue [4, 19, 5]. Thus hyperketonemia is observed in man when the plasma level of FFA is raised by increased mobilization, e.g. in starvation and diabetes mellitus and also acutely by administration of adrenaline [13] and noradrenaline [3]. Recently, it has been shown that hyperketonemia can also develop when the plasma level of FFA is increased by the administration of heparin to the rat fed corn-oil [15].

To study the acute effect of inhibition of FFA mobilization on plasma ketone levels in man we have given nicotinic acid, which rapidly inhibits this mobilization [6, 7, 8], and followed the concentration of FFA and β-hydroxybutyric acid (BHBA).

Materials and Methods

Four untreated juvenile diabetics (mean age 27 years), three obese patients with untreated mild diabetes and one obese non-diabetic person (mean age 41 years) were hospitalized and studied during bed rest in the morning. The four obese subjects were investigated during a prolonged fast, ranging from 5 to 50 days; the other subjects were studied after fasting overnight. Nicotinic acid (Nicangin^{R}, Draco) was administered orally four times in doses of 0.5 g each, 30 minutes apart, beginning immediately after the first blood sampling.

At intervals venous blood samples were drawn into heparinized syringes from an indwelling teflon catheter kept patent with 0.9 per cent sodium chloride. Blood for determination of glucose [14] was pipetted off at once. The remainder of the blood was stored in an ice bath in capped tubes until plasma was separated by centrifugation. FFA in plasma was determined by the DOLE procedure [10] as modified by TROUT et al. [20]. BHBA in plasma was determined enzymatically according to the procedure of WILLIAMSON et al. [21]. Plasma protein analysis was made with the BIURET method and all values of FFA and BHBA were corrected for minor changes in plasma protein concentration.

Results

The plasma concentration of FFA (Fig. 1) and BHBA (Fig. 2) decreased rapidly after the administration of nicotinic acid in all subjects and the fall in FFA preceded that of BHBA. However, the time curve pattern for plasma FFA and plasma BHBA indicates that the response to nicotinic acid administration differed in the juvenile diabetics and in the fasting obese patients. In the four juvenile diabetics the concentration of plasma FFA decreased abruptly, reaching a plateau level of 0.20—0.40 mEq/l (after about 1 hour). The concentration of BHBA in plasma also fell rapidly in these patients and remained at a low level from 1 hour onward. In the obese fasting subjects plasma FFA concentration fell less rapidly and did not go below 0.40 mEq/l. After about 30 minutes the concentration of BHBA in plasma decreased gradually, this decrease also being slower than in the juvenile diabetic patients.

Figure 3 shows that the blood glucose decreased about 20 to 30 per cent in three of the four juvenile type diabetics and remained unchanged in the fourth.

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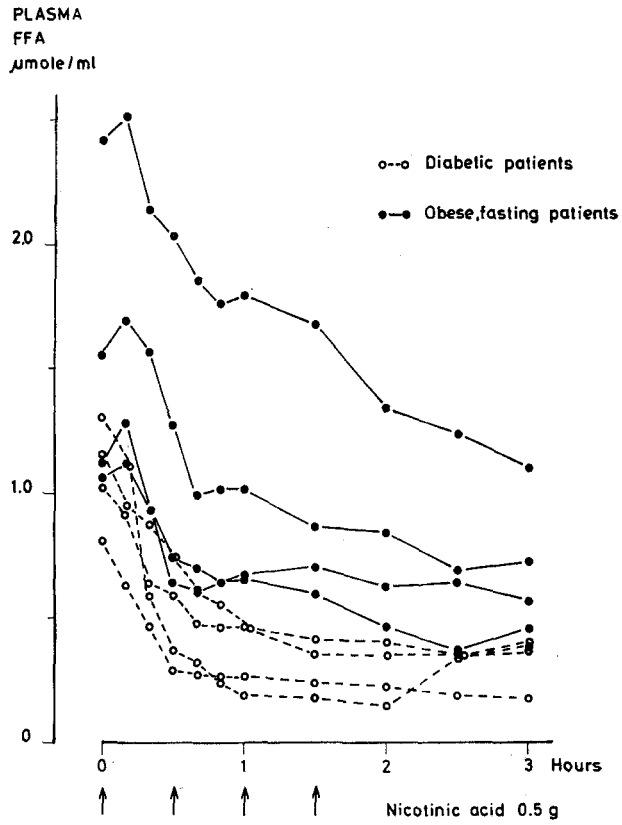

Fig. 1. Effect of nicotinic acid on the concentration of FFA in plasma in 4 insulin dependent diabetic patients and in 4 obese fasting patients

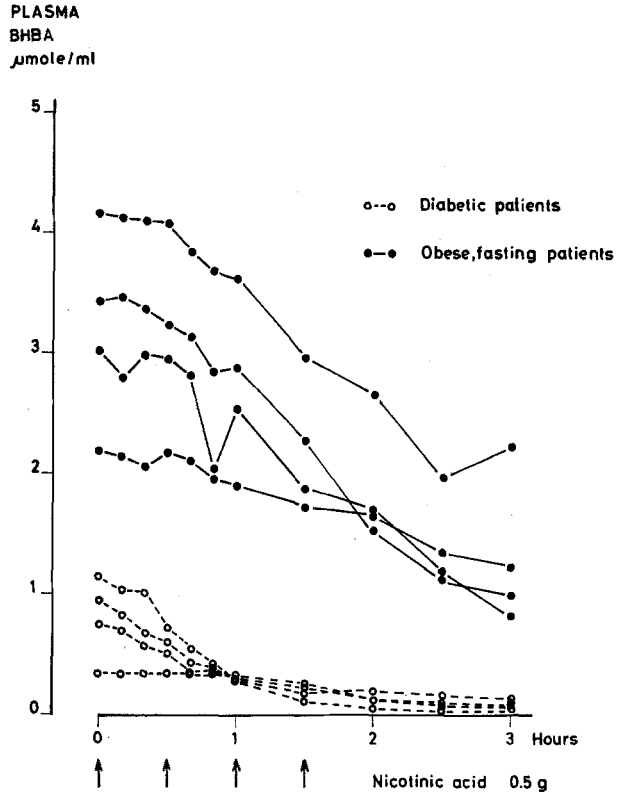

Fig. 2. Effect of nicotinic acid on the concentration of β-hydroxybutyric acid in plasma in 4 insulin dependent diabetic patients and in 4 obese fasting patients

In two of the obese subjects with low fasting blood glucose the concentration rose slowly by about 15 mg/100 ml and remained unchanged in the other two.

Discussion

A most important new finding is that nicotinic acid acutely lowers the BHBA level in plasma. The temporal relationship between the fall of FFA and BHBA clearly is compatible with a causal relationship. Since BHBA constitutes 50 to 75 per cent of plasma ketone bodies [11] there was undoubtedly also a major fall in total ketone level.

The reduction of BHBA concentration may be due to reduced hepatic formation or increased peripheral utilization (or both). The mechanisms by which excessive mobilization of FFA may increase ketone body formation have been discussed elsewhere [5]. Conversely, reduction of FFA mobilization by nicotinic acid will reduce the flow of FFA to the liver and this may lead to a decrease in the availability of acetyl-CoA in the liver for synthesis of ketone bodies. The hepatic production of ketones would then decrease and the plasma level of ketones drop.

That utilization of BHBA increased after nicotinic acid must also be considered. Uptake of substrates such as glucose and pyruvate into the perfused heart has been shown to be regulated by the concentration of

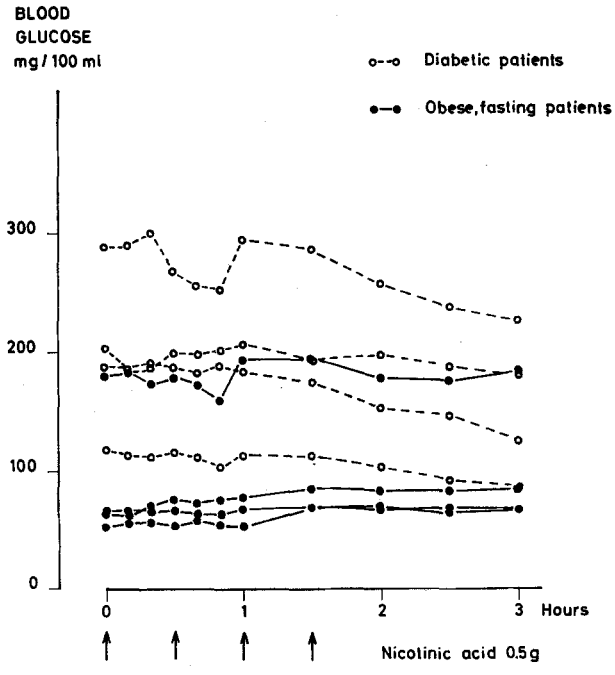

Fig. 3. Effect of nicotinic acid on the concentration of glucose in blood in 4 insulin dependent diabetic patients and in 4 obese fasting patients

other substrates such as ketone bodies and FFA [22, 18, 12]. Whether the level of FFA similarly regulates the peripheral uptake of ketones in such a way that a low FFA level would enhance ketone utilization has, however, not been studied. It may be pertinent that diabetic animals and tissues have a lowered capacity to metabolize ketone bodies [1, 17].

The slight lowering of blood glucose in response to nicotinic acid was somewhat greater than that seen in an earlier study [9] and may be ascribed to a "RANDLE effect" [16].

The reason for the less pronounced FFA response in the obese fasting group is not known. However, *in vitro* there is less inhibition of lipolysis by nicotinic acid in adipose tissue from fasted than from fed rats [2].

The therapeutic value of inhibiting FFA mobilization in diabetic keto-acidosis has to await clinical evaluation, but the prompt effect of nicotinic acid in this context merits its trial.

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