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Changes in the Concentrations of Glucose, Free Fatty Acids, Insulin and Ketone Bodies in the Blood during Sodium β-Hydroxybutyrate Infusions in Man

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Summary. Sodium β-hydroxybutyrate was infused for 1.5 h in 8 normal subjects, at a constant rate of 5 mmoles/kg/h. Equimolar amounts of sodium chloride were infused in 5 control subjects. — The induced hyperketonaemia provoked the following changes in peripheral blood: a fall in glycaemia (15 mg/100 ml) and in plasma NEFA concentration (50%) without concomitant modifications of insulin concentrations. These results indicate that the glucose and NEFA changes observed are not mediated by a pancreatic stimulation.

Modifications des concentrations de glucose, d'acides gras libres, d'insuline et de corps cétoniques dans le sang pendant des perfusions de β-hydroxybutyrate de sodium chez l'homme

Résumé. Les auteurs ont étudié chez 8 sujets normaux les effets d'une perfusion de β-hydroxy-butyrate de sodium (5 m mol/kg/h pendant 1.5 h) sur la concentration sanguine en glucose, en acides gras libres, en corps cétoniques et en insuline dans le sang veineux périphérique. Cinq sujets témoins ont été perfusés à l'aide de solution équimolaires de NaCl. — L'hypercétonémie provoque une chute de la glycémie d'environ 15 mg/100 ml, une chute des NEFA atteignant 50%, sans modifications concommitantes de l'insulinémie. Ces résultats plaident contre l'intervention d'une stimulation pancréatique dans la chute de la glycémie et des NEFA.

Änderungen der Glucose-, FFS-, Insulin- und Ketokörper-Konzentrationen unter einer Natrium-β-hydroxybutyrat-Infusion beim Menschen

Zusammenfassung. Natrium-β-hydroxy-butyrat wurde 8 Normalpersonen während 1.5 Std bei konstanter Geschwindigkeit von 5 mMol/kg/Std infundiert. 5 Kontrollpersonen erhielten äquimolekulare Mengen einer Kochsalzlösung. — Die so bewirkte Erhöhung der Ketokörper-Spiegel führte im peripheren Blut zu folgenden Veränderungen: Absinken des Blutzuckers um 15 mg %, Abfall der Plasma-FFS auf die Hälfte ohne gleichzeitige Änderung der Insulinspiegel. Diese Ergebnisse sprechen dafür, daß die Änderung der Glucose- und FFS-Konzentrationen nicht durch eine Stimulierung des Pankreas ausgelöst wird.

Key-words: Glucose, free fatty acids, insulin, ketone bodies, sodium-β-hydroxybutyrate.

Introduction

In a recent work performed on dogs [1], we observed that sodium β-hydroxybutyrate (Na β-OH-B) infusions provoke a decrease in blood sugar and plasma NEFA concentrations together with a small, transient increase in the insulin concentration of peripheral blood. By the technique of isotope dilution using glucose-1-^{14}C, we showed that hypoglycaemia was only due to a reduction of hepatic glucose output without any modification of the rate of peripheral utilization of glucose. Data available at present regarding the action of insulin on the output of glucose from the liver allowed us to conclude that the observed changes in blood glucose were not mediated by the small changes in blood insulin. Experiments with palmitate-1-^{14}C revealed that the fall of NEFA was the consequence of both an inhibition of their production by adipose tissue and an increase in their peripheral uptake. The role of insulin in these mechanisms was also questionable.

In the present work, which was performed in man, we have reëvaluated the eventual role of insulin in the modifications of blood glucose and NEFA induced by Na β-OH-B.

Materials and Methods

Thirteen normal subjects of both sexes, aged 14—50 (mean: 34 years) were examined.

An aqueous solution of Na DL-β-OH-B was infused into eight of these through a peripheral vein at a rate of 5 mmoles/kg/h for 1.5 h. The total volume infused was 500 ml in every case.

Blood samples for estimation of glucose, NEFA, insulin, ketones and haematocrit were withdrawn from an antecubital vein on the opposite side. In 2 subjects, measurements of arterial pH were performed. The bladder was emptied before the tests and urine was collected at the end of the infusions for determination of the urinary ketone excretion. The solutions were sterilized prior to administration by filtration through a Millipore filter (diam. 0.45 μ). Their pH varied according to the concentration; for example, the pH of a solution prepared for a subject weighing 70 kg (66 g Na β-OH-B/500 ml) was 8.35.

Five subjects taken as controls were infused in the same experimental conditions with equimolar amounts of NaCl; in these experiments, blood analyses were limited to glycaemia, NEFA concentration and haematocrit.

Some patients from both the treated and the control groups complained of slight headache; all were thirsty during and after the infusion as a consequence of the hypertonicity of the injected solutions; they were allowed to drink water *ad libitum* during the tests.

Chemical determinations. Total blood glucose: HOFFMAN's method [7], adapted to the Technicon autoanalyser; plasma NEFA: TROUT's modification [16] of DOLE's technique [3], this procedure reducing the interference caused by Na β-OH-B [14]; plasma insulin (I.R.I.): method of MORGAN and LAZAROW [12]; total ketones bodies: estimation both in urine (after a 1:10 dilution) and in plasma according to a modification [8] of MICHAELS' method [11], the results being expressed as equivalents of acetone.

Results

1. Na β-OH-B treated subjects. The amount of Na β-OH-B lost in urine during the test reached 4.5 to 9.2% (mean 6.4%) of the injected dose.

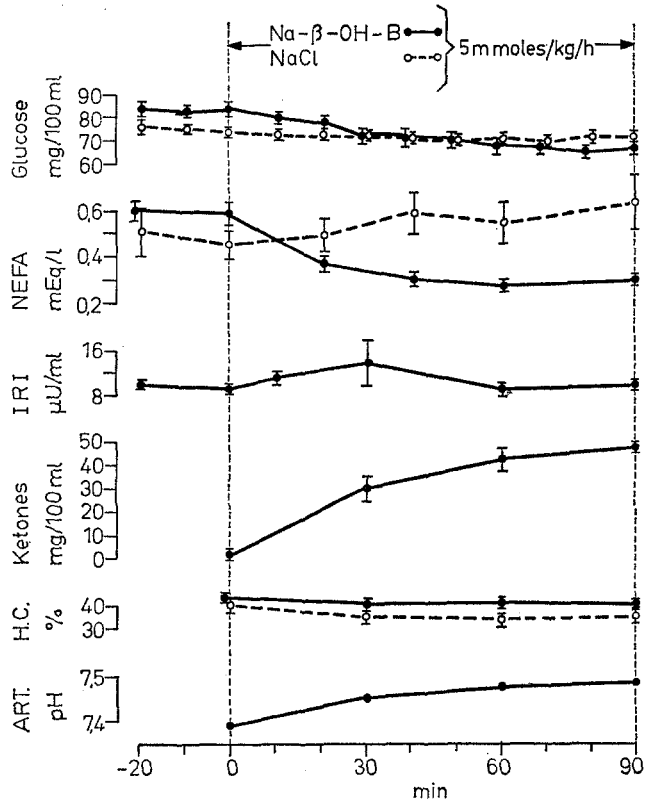

Fig. 1. Modifications induced by Na β-OH-B infusions in man
●——● mean results for 8 subjects ± S.E.M.
o- — -o Mean results for 5 control subjects ± S.E.M.

The other results are represented in the figure: the infusion of Na β-OH-B provoked the following changes (mean values):

a) an important increase in ketonaemia up to 47.6 mg/100 ml; b) a slight alkalosis, arterial pH rising from 7.39 to 7.48; c) a small decrease in haematocrit from 43% to 40%; d) a fall in blood sugar from 84 mg/100 ml during the control period to 69 mg/100 ml during the last 30 min of the infusion; using Student's *t* test, statistical significance has been checked at 30, 60 and 90 min and found to be at 1 percent level; e) a 50% fall in plasma NEFA whose concentration decreased from 0.59 mEq/l during the control period to 0.28 mEq/l at the end of the infusion (significant at 1% percent level); f) a lack of change in insulin concentration in peripheral blood.

2. Control subjects. As shown in the figure, no significant changes occured in either the blood sugar or the plasma NEFA concentrations. A slight decrease in haematocrit was noted for Na β-OH-B infusions.

Discussion

The observed hypoglycaemia is consistent with data obtained in man by FAJANS et al. with acetoacetate infusions [4]; similar findings were made in dogs by NEPTUNE et al. [13], MEBANE et al. [10], FELTS et al. [5], and BALASSE et al. [1].

MADISON et al. [9] noticed that Na β-OH-B infusions in dogs produced an important and prolonged increase in insulin concentration in pancreatic vein. In our experience, during infusions at a rate of 5 mmoles/kg/h, an insulinic response was hardly detectable in peripheral blood of dogs [1], and not at all in man, as is shown by the present results. This is in agreement with data from FAJANS et al. [4]. These observations might of course be interpreted as if the extra insulin secreted by the pancreas was completely trapped by the liver. But even this hypothesis cannot explain the observed hypoglycaemia. We have shown, indeed, [1] that the hypoglycaemic action of Na β-OH-B in dogs is due only to a reduction in liver glucose output, and it has been proved that during insulin hypoglycaemia, the inhibitory influence of insulin on the output of glucose by the liver is always overwhelmed by the stimulating effect of peripheral hypoglycaemia [6, 15]. Therefore, a direct inhibitory action of Na β-OH-B on the output of glucose by the liver must be considered.

The present observation of a decrease in NEFA concentration induced by Na β-OH-B in man is in agreement with similar results obtained in dogs [10]. Our data do not support the hypothesis of an insulinic effect, as proposed by MADISON et al. [9], since no modification of insulin concentration occured in peripheral blood. The decrease in NEFA concentration observed can reasonably be related to a direct inhibitory effect of Na β-OH-B on lipolysis at the level of adipose tissue, as it has been proved *in vitro* (2).

In our experiments using ketone infusions, the ketone levels obtained were close to those observed during prolonged starvation: the mean plasma ketone levels estimated in 5 starved patients, who were moderately obese, reached 34 mg/100 ml and 37 mg/100 ml after 8 and 12 days respectively of fasting.

MADISON et al. [9] have suggested some interesting implications of the metabolic influence of ketone bodies during fasting. Hyperketonaemia might be a factor responsible for the hypoglycaemia observed during fasting, which, together with a reduction of

peripheral glucose utilization, could contribute to the sparing of glucose for use by the brain. Moreover, the high ketone levels could prevent an excessive elevation of the NEFA, and thereby prevent fatal ketoacidosis during prolonged starvation.

Our data provide further information supporting these views but suggest that these control mechanisms are not mediated through a pancreatic stimulation.

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