

Abstract

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Abolition of the inhibitory effect of ethanol oxidation on gluconeogenesis from lactate by asparagine or low concentrations of ammonia.

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METHODS AND OBJECTIVES: When isolated hepatocytes from fasted rats were incubated with 10 mM lactate, the [lactate]/[pyruvate] ratio measured at the beginning of the incubation was raised above 70:1 but declined to a steady level of about 8:1 within 40 min. The rate of gluconeogenesis from lactate was initially slow but gradually increased over the incubation period becoming maximal by 30 min. The simultaneous addition of lactate and ethanol resulted in an initial [lactate]/[pyruvate] ratio above 250:1 which by 60 min had declined to a new steady-state level of approx. 60:1. The lactate, ethanol combination also brought about a prolongation of the lag phase before glucose synthesis became maximal; however, by 40 min the rate of gluconeogenesis was independent of the presence of ethanol. Thus the inhibitory effect of ethanol on glucose synthesis was manifest only over the early portion of the incubation period.

RESULTS: When asparagine, a precursor of malate/aspartate components, was added to the incubation mixture, the lag before maximal rates of glucose formation from lactate in the absence or presence of ethanol was almost abolished. The presence of asparagine also rapidly lowered the [lactate]/[pyruvate] ratio of hepatocytes incubated with lactate plus ethanol establishing a steady-state level of 15:1 within 10-15 min. Asparagine enhanced the rate of lactate-stimulated ethanol oxidation, particularly during the early part of the incubation. In endeavouring to elucidate which of the products of asparagine catabolism (i.e. ammonia and aspartate) were responsible for these effects, we found that a small and constant level of ammonia, formed by the degradation of urea by urease, almost reproduced the effects of asparagine on the [lactate]/[pyruvate] ratio, glucose synthesis and ethanol oxidation. A bolus addition of 10 mM aspartate or 4 mM ammonia to cells metabolising lactate and ethanol were less effective than a steady-state low ammonia concentration, generated from urea/urease.

CONCLUSIONS: Our studies suggest that asparagine or a low concentration of ammonia, by providing components of the malate/aspartate shuttle, can ameliorate some of the metabolic effects of ethanol on the liver.

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