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In the simulated postprandial state ethanol prevents insulin-dependent stimulation of mitochondrial ATP turnover: NMR study of isolated and perfused rat liver

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In the isolated liver of the fed rat perfusion with 10 mM-ethanol (EtOH), in absence of glucose and insulin (Ins), increases the phosphorylation rate and the yield of oxidative phosphorylation(1). A positive linear glucose-dependent correlation exists between the net fluxes of ATP and glycogen in presence of Ins only, indicating that Ins can control the carbohydrate store via energy metabolism(2). Any change in this relationship could suggest a variation in insulin sensitivity. The effect of EtOH on insulin resistance is controversial, but it has been shown that in presence of Ins the correlation between the net fluxes of ATP and glycogen is 4-fold higher when 10 mM-EtOH is added. It was thus necessary to evaluate the effect of a moderate level of EtOH on mitochondrial ATP turnover in the liver in the presence and absence of Ins perfusion.

Male Wistar rats (100 g) were fed *ad libitum*. The livers were isolated and perfused (5 ml/min per g) with an isotonic buffer (37°C; O_2–CO_2, 95 : 5 (v/v)) containing 0, 6 or 30 mM-glucose with or without Ins (120 mIU/l) and with or without 10 mM-EtOH. The change in the ATP content was followed by ^{31}P NMR (Brucker DPX400, 9.4T; Brucker, Bremen, Germany). Subsequent addition to the perfusate of inhibitors of both glycolytic and mitochondrial ATP synthesis (0.5 mM-iodacetate and 2.5 mM-KCN respectively) enabled calculation of *in situ* liver ATP turnover ($ATP = Aexp^{-kt}$, $R_{(t0)} = -A.k$)(1).

With 30 mM-glucose + Ins (approximating to the portal postprandial state) mitochondrial ATP turnover was 3.61 (SE 0.69) μmol/min per g (n 6) and significantly decreased when EtOH was added in the absence (n 5; $P = 0.026$, t test) or presence of Ins (n 5, $P = 0.018$): 1.48 (SE 0.26) and 1.38 (SE 0.16) μmol/min per g respectively. With 6 mM-glucose (approximating to the interprandial state) ATP turnover remained low in presence of EtOH alone (n 4; 1.39 (SE 0.44) μmol/min per g), but the addition of Ins counteracted the effect of EtOH (n 4; 3.88 (SE 0.91) μmol/min per g; $P = 0.048$). The same pattern was observed for changes in the time constant (k), with a significant decrease in presence of EtOH compared with the absence of EtOH at both 30 mM- and 6 mM-glucose, which was counteracted by the addition of Ins only at 6 mM-glucose.

Ethanol prevents the effect of Ins on ATP turnover in the simulated postprandial state only. The variations in k suggest that the phosphorylating activity of the liver respiratory chain is modulated in a glucose-dependent manner by both Ins and a moderate level of EtOH.

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2. Baillet-Blanco L, Beauvieux MC, Gin H, Rigalleau V & Gallis JL (2005) *Nutr Metab* **2**, 32–41.