Acute stimulation of fatty acid oxidation does not alter energy expenditure

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There is great interest in developing drugs that stimulate fat oxidation pathways as potential treatments for obesity and insulin resistance. However, it is unclear whether elevating fat oxidation will result in weight loss, unless there is also an associated increase in energy expenditure. To investigate this we examined whole-body energy metabolism in rats treated with compounds that stimulate fat oxidation *via* activation of the AMP-activated protein kinase pathway.

Energy expenditure (VO_2) and substrate oxidation (indicated by the respiratory exchange ratio [RER]) were measured using an Oxymax indirect calorimetry system. Rats were acclimatised overnight and at 10 am dosed with either vehicle (saline, $n = 12$), metformin (500 mg/kg, $n = 10$), AICAR (250 mg/kg, $n = 11$) or the mitochondrial uncoupler, dinitrophenol (DNP; 30 mg/kg, $n = 10$). In the 8 hour period following dosing, animals treated with metformin, AICAR and DNP all displayed increased fat oxidation compared with vehicle-treated animals, as evidenced by a reduction in RER (0.87-0.89 *vs* 0.92, $p < 0.001$). However during this time only DNP increased VO_2 (1957 ± 22 ml/kg/h, $p < 0.001$) compared with vehicle-treated animals (1633 ± 17 ml/kg/h), with no difference observed for metformin (1682 ± 18 ml/kg/h) or AICAR (1627 ± 16 ml/kg/h). As there was no change in energy expenditure with metformin and AICAR, our results suggested that the increase in fat oxidation was associated with a decrease in the oxidation of other substrates. To test this possibility, EDL muscles isolated from rats (anaesthetised with 60 mg/kg sodium pentobarbital i.p.) were treated with either AICAR (2 mM) or DNP (0.5 mM) and *ex vivo* palmitate and glucose oxidation was measured. Consistent with its effect to elevate energy expenditure, DNP treatment caused a significant increase in the oxidation of both palmitate (+41%, $p < 0.01$) and glucose (+77%, $p < 0.01$). In contrast, AICAR robustly increased palmitate oxidation (+45%, $p < 0.001$), but decreased glucose oxidation by 28% ($p < 0.01$).

These results suggest that in the absence of any change in energy demand, acute increases in fat oxidation are accompanied by a concomitant decrease in the oxidation of other substrates, and subsequently no change in energy expenditure.