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LETTER

Comment on: Weickert MO, Pfeiffer AFH (2006) Signalling mechanisms linking hepatic glucose and lipid metabolism. Diabetologia 49:1732–1741

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To the Editor: We read with interest this recent review [1] on an important aspect of glucose and lipid metabolism. It is agreed that there is evidence of metabolic dialogue involving liver, skeletal muscle and adipose tissue within a complex regulatory network. However, we question the assertion that peroxisome proliferator activator receptor α (PPARα) agonists, such as fibrates, increase insulin sensitivity. This assertion was supported by one of the studies quoted [2], which used fenofibrate, ciprofibrate and a high-affinity PPARα agonist, GW9578, in a rat model in vivo. However, due to the doses and model used, the study cannot be directly extrapolated to human subjects. In contrast to the animal model evidence, in vivo studies in man show no consistent effect of PPARα agonists on insulin sensitivity. Using surrogate measures, such as the oral glucose tolerance test [3, 4], fasting insulin [5, 6] and the frequently sampled intravenous glucose tolerance test [7, 8], variable results have been obtained. With the reference-standard method of assessment, the euglycaemic–hyperinsulinaemic clamp, a well-designed study in subjects with type 2 diabetes showed no effect of gemfibrozil compared with placebo [9]. In a further study comparing simvastatin and gemfibrozil in a parallel design, insulin sensitivity decreased in both groups [10]. This parallel effect may relate to lifestyle or other factors not assessed in the trial and thus ascribed to a general trial, rather than pharmacological mechanism.

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As discussed by Weickert and Pfeiffer [1], liver and skeletal muscle fat deposition both seem to cause and be affected by insulin resistance. Agents that improve fatty acid oxidation and disposal would therefore seem likely to affect insulin resistance. However plausible this assertion may be, and despite the fact that animal models suggest an effect, well-designed in vivo studies in human subjects show no significant improvement in insulin sensitivity using PPARα agonists at doses which are currently recommended for therapy in man [9, 10]. As recognised by Guerre-Millo et al. [2], fibrates are low-affinity ligands for PPARα, and agents with higher affinity may be required to elicit a significant effect. Recent reviews such as the detailed, considered article in question [1] should recognise that this effect is not seen with these agents in man.

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