

## Invited Speaker Plenary 3: Gene-Nutrient Interactions

### Dietary regulation of skeletal muscle metabolic genes

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**Background** - Skeletal muscle is the largest component of fat-free mass in humans. Skeletal muscle is also a dynamic tissue which undergoes marked metabolic and structural adaptation in response to altered nutrient availability and exercise patterns. A significant component of this cellular adaptation is the coordinated expression of mRNA species that encode the desired proteins. However, relatively little is known of the gene responses that take place within human skeletal muscle following either altered macronutrient availability or the interaction between macronutrient supply and exercise.

The major macronutrients, carbohydrates and lipids, are the predominant oxidative substrates used by muscle. In addition to being a source of energy, both glucose and fatty acids (FA) communicate directly to the nucleus or via a range of transcription factors which regulate the expression of coordinated groups of genes. Our laboratory has focused on the regulation of genes essential for the oxidative metabolism of fatty acids, as an impaired capacity to oxidize lipids is a hallmark of insulin resistant states, including obesity, diabetes and advanced age.

**Aims** -Our experimental studies aim to evaluate the impact of FA and exercise on the control of genes that regulate lipid metabolism within human skeletal muscle.

**Human clinical trials** - Initial studies demonstrated that short periods of high fat feeding (48 hours to 4 days) increased the expression a range of genes important in FA metabolism, including; the FA transporter, Fatty acid translocase (FAT/CD36), the  $\beta$ -oxidative enzyme,  $\beta$ -hydroxyacyl-CoA dehydrogenase ( $\beta$ -HAD) and the negative regulator of glucose oxidation, pyruvate dehydrogenase kinase 4 (PDK4). Similar responses in gene expression were demonstrated with endurance exercise training, a condition in which oxidative capacity is enhanced.

To determine whether these effects are mediated rapidly via changes in fatty acid supply or sustained alterations in hormonal status, 7 healthy male subjects were infused with a sterile intravenous lipid emulsion (Intralipid) for 5 hours. Plasma FA concentrations and oxidation were increased. In response to this rapid perturbation in FA supply, expression of PDK4 was increased 15 fold. This same gene was shown to be increased by short-term fasting, with increased expression evident after 15 and 40 hours without food, consistent with an increased use of FA as the predominant fuel source of the muscle. Thus, these studies provide evidence that the PDK4 gene is sensitive to FA supply. Endurance exercise also results in increased plasma FA concentrations. To separate out the actions of muscular contraction, per se, rather than the increased plasma FA supply on the gene expression of PDK4, endurance cycling exercise was performed in the presence or absence of the lipolysis inhibitor, Acipimox. In this study, exercise increased PDK4 gene abundance, irrespective of the changes in plasma FA. Thus exercise and FA-supply may operate via independent pathways to elicit the expression of some genes.

**Human muscle cell culture** - Whether these gene changes are influenced by the type of FA studies have been undertaken using primary cultured human muscle cells. The exposure of muscle cells with the saturated FA, palmitate and the monounsaturated FA, oleate, both at a concentration of 250 $\mu$ M increased PDK4 gene expression markedly. This action was dampened by the addition of a long chain omega-3 polyunsaturated FA, eicosapentaenoic acid (EPA). These data suggest that the actions of FA on gene expression differ depending upon the species of FA, with EPA, antagonizing the actions of other FA.

**Conclusions** - Fatty acids are potent regulators of skeletal muscle gene expression. These actions are mediated rapidly in response to increased FA supply. Thus muscle genes are regulated by the supply and type of FA present in the blood supply. On-going analysis is aimed at determine if the ability of FA to activate skeletal muscle genes is preserved or abnormally regulated in obese and diabetic states.