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【Keynote lecture I】

Interelukin-6 System and Exercise

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Interleukin-6 (IL-6) is a pleiotropic cytokine that has an anti-inflammatory and metabolic response to acute exercise. It increases with exercise in an duration- and intensity-dependent manner (For review Pedersen, 2007). This contrasts with chronic elevation of this and the pro-inflammatory cytokines, termed chronic low grade inflammation, which is known to be associated with chronic conditions such as obesity and insulin resistance (Bruunsgaard, 2005).

For IL-6 to become active and initiate cellular signalling, it must bind with two receptors forming a membrane-bound IL-6/IL-R/gp130 complex, consisting of 2 IL-6, 2 IL-6R and 2 gp130 molecules. Although gp130 is an ubiquitously distributed membrane-bound receptor, some tissues are deficient in membrane-bound IL-6R, or have low levels, such as in skeletal muscle. The soluble form of this receptor sIL-6R plays an important role in initiating signalling in skeletal muscle. IL-6 combines with IL-6R to form an IL-6/IL-6 complex which increases the biological activity and half life of IL-6 through a process called trans-signalling. Once active, IL-6 initiates the release of anti-inflammatory cytokines, gene transcription and metabolism (For review Pedersen & Febrraio, 2008 & Glund & Krook, 2008).

Exercise

Our research group has conducted a number of studies to investigate the response of plasma sIL-6, sIL-6R and sgp130. Gray *et al.*, (2008) was the first study to demonstrate the soluble receptor response to fatiguing sub-maximal exercise in humans, where twelve participants performed an exercise bout (96+6% lactate threshold) to volitional exhaustion. It was established that immediately after exercise, IL-6 increased significantly (P<0.01) from rest. The two soluble receptors sIL-6R and sgp130 also increased significantly (P<0.05) A subsequent study also demonstrated that in nine healthy males, cycling for 1hour at 90% lactate threshold sIL-6R increased significantly post-exercise, which coincided with a 2.1-fold elevation (P<0.05) in the soluble IL-6/IL-6R complex (Gray et al., 2009a).

Glucose Uptake

IL-6 is also involved in metabolic regulation, stimulating glucose transport and fatty acid oxidation (For review Pedersen, 2009). Research by our group investigated the influence of *in vitro* combination of IL-6 and IL-6R on type-I mouse *soleus* muscle fibres. The combination of cytokine and receptor resulted in a significant (P<0.05) (1.4-fold increase) in glucose uptake at physiological levels and 2-fold increase (P<0.05) at supra-physiological concentrations (Gray *et al.*, 2009b). This study demonstrated that while IL-6 does not enhance insulin-stimulated glucose uptake nor does IL-6 alone stimulate glucose transport in mouse *soleus*, when sIL6R is combined with IL-6, glucose transport is directly up-regulated.

Insulin is well-known as the predominant signalling mechanism that controls the uptake of cellular glucose. Under the control of insulin, binding to the insulin receptor, triggers a signalling cascade via PKB/Akt signals for the translocation of GLUT-4 to allow for the cellular uptake of glucose. In our mouse study, the 2 fold increase in glucose uptake was not matched by any changes in the phosphorylation of PKB/Akt suggesting that the glucose mediated uptake was independent of insulin. At supraphysiological levels however an increase of AMPK was demonstrated, however it only accounted for 70% of the increased glucose uptake and there was no increase at physiological doses. This would suggest that there is an additional pathway involved. As yet this remains undefined.

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