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Invited talk: Exercise: Understanding physiology and molecular mechanisms — A pathway to therapies

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There is convincing epidemiological evidence that regular physical activity, including structured exercise, is associated with improved health outcomes. This appears to be partly related to the total exercise energy expenditure. Over the years, many physiologists have examined the integrative biology of exercise to better understand physiological responses to homeostatic challenges. These insights have often been used to identify the physiological limits of, and the optimal strategies to enhance, athletic performance. Increasingly, studies in exercise biology provide new ideas on the mechanisms by which exercise exerts its beneficial effects on health. With increased application of emerging techniques in molecular and cell biology, there is now even greater understanding of the molecular mechanisms underpinning the adaptive responses to acute and chronic exercise. This information has the potential to optimise exercise interventions and to identify novel therapeutic strategies, including potential ''exercise mimetics'', although whether full recapitulation of exercise effects can be achieved by one, or several, pharmacological agents is debated. Another prospect emerging from the 'omics' era is greater understanding of the physiological and molecular bases of individual variation in responses to exercise. Although the technology remains ahead of the biology, analysis of the large data sets being generated from exercise studies may one day result in precision ''exercise medicine'' and a really personalised trainer.

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Invited talk: Mapping complex molecular networks underlying exercise using global phosphoproteomics

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Exercise is essential in regulating energy metabolism and remains the most promising therapy for obesity and type 2 diabetes. However, the intricate cellular signalling networks underlying tissue responses to exercise-stimulated metabolic and mechanical stress are not fully understood. Global, unbiased discovery approaches are warranted to map these complex, interconnected molecular networks that promote the systemic health benefits of exercise.

Protein phosphorylation is central to a range of exercise-induced tissue adaptations including regulation of skeletal muscle metabolism and contraction. Therefore, we previously undertook a global mass spectrometry-based phosphoproteomic analysis comparing human skeletal muscle biopsies before and after a high-intensity exercise bout [1]. This revealed over 1000 exercise-regulated phosphorylation sites on over 500 proteins, including a majority of kinases and phosphosites never previously implicated in exercise signalling. Furthermore, novel exercise-regulated substrates of the energy-sensing AMP-activated protein kinase (AMPK) were uncovered using this global approach. Ongoing studies will be discussed that are aimed at determining how components of the acute exercise signalling network are impacted by skeletal muscle contraction and nutrient availability.

Collectively, multidisciplinary global phosphoproteomics and targeted physiological approaches have led to the discovery of exercise biological targets and new roles for kinases such as AMPK. This rapidly expanding frontier in understanding the molecular underpinnings of exercise will aid development of therapeutic strategies to improve human health and target obesity-related pathophysiology.

Reference

[1] Hoffman NJ, Parker BL, et al. Cell Metab 2015;22(5):922—35.

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Invited talk: Use of a potent calorie restriction mimetic to selectively recover POMC activity, thereby reversing dietary induced weight gain

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17α-E2 significantly extends lifespan in male mice following late-life administration. We previously showed that this non-feminising, naturally occurring enantiomer of 17β-estradiol (17β-E2) mimics the beneficial effects of calorie restriction, reversing multimorbidity in aged male mice1. Given that 17α-E2 reduced food intake, it was proposed that 17α-E2 might promote weight loss in obese mice through suppressing appetite.

We first assessed the effect of dietary-17α-E2 treatment on body mass, body composition, food intake, activity and energy expenditure in male mice maintained on an obesogenic high fat diet. 17α-E2 initiated weight loss soon following treatment, resulting in an overall reduction in body mass regardless of continued high fat feeding. Reduced body mass was attributed to a loss in total, epigonadal and subcutaneous fat mass and not fat free mass. This was matched by improved glucose clearance and insulin sensitivity. Dietary supplementation with 17α-E2 selectively reduced food intake, without altering physical activity or metabolic rate. We previously proposed that 17α-E2 might selectively modify food intake, acting via hypothalamic proopiomelanocortin (POMC)-expressing neurons. POMC-expressing neurons, located within the arcuate nucleus (ARC) of the hypothalamus, are widely recognised for their capacity to regulate energy homeostasis, and represent the largest and most dominant anorexigenic node of central appetite regulation. Ancillary experiments in mice with selective deletion of ARC POMC neurons found complete loss of 17α-E2 treatment effects on food intake, confirming that 17α-E2 promotes satiety by enhancing the function of anorexigenic feeding circuitry [1].

Collectively, our data show that 17α-E2 acts via hypothalamic POMC-expressing neurons to inhibit food intake. We propose that 17α-E2 may serve as a potent calorie restriction mimetic by enhancing calorie sensing of POMC neurons.

Reference

[1] Stout MB, Steyn FJ, Jurczak MJ, Camporez JG, Zhu Y, Hawse JR, et al. 17α-Estradiol alleviates age-related metabolic and inflammatory dysfunction in male mice without inducing feminization. J Gerontol A Biol Sci Med Sci 2016;24(January), glv309.

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