ANNALS OF RESEARCH IN SPORT AND PHYSICAL ACTIVITY

Effects of exercise training on kynurenines, metabolism, and mental health

Autor(es): Ruas, Jorge Lira

Publicado por: Imprensa da Universidade de Coimbra

URL persistente: URI:<http://hdl.handle.net/10316.2/44080>

DOI: DOI:https://doi.org/10.14195/2182-7087_ex2018_17

Accessed : 26-Apr-2023 12:55:46

A navegação consulta e descarregamento dos títulos inseridos nas Bibliotecas Digitais UC Digitalis, UC Pombalina e UC Impactum, pressupõem a aceitação plena e sem reservas dos Termos e Condições de Uso destas Bibliotecas Digitais, disponíveis em <https://digitalis.uc.pt/pt-pt/termos>.

Conforme exposto nos referidos Termos e Condições de Uso, o descarregamento de títulos de acesso restrito requer uma licença válida de autorização devendo o utilizador aceder ao(s) documento(s) a partir de um endereço de IP da instituição detentora da supramencionada licença.

Ao utilizador é apenas permitido o descarregamento para uso pessoal, pelo que o emprego do(s) título(s) descarregado(s) para outro fim, designadamente comercial, carece de autorização do respetivo autor ou editor da obra.

Na medida em que todas as obras da UC Digitalis se encontram protegidas pelo Código do Direito de Autor e Direitos Conexos e demais legislação aplicável, toda a cópia, parcial ou total, deste documento, nos casos em que é legalmente admitida, deverá conter ou fazer-se acompanhar por este aviso.

ANNALS OF
**RESEARCH IN SPORT
AND
PHYSICAL ACTIVITY**

EFFECTS OF EXERCISE TRAINING ON KYNURENINES, METABOLISM, AND MENTAL HEALTH.

Jorge Lira Ruas¹

KEYWORDS: Skeletal Muscle, PGC-1alpha, coactivators, isoforms, exercise, depression.

Skeletal muscle condition and physical exercise play a clear role in the prevention and treatment of several diseases such as diabetes, obesity, sarcopenia (age-related loss of muscle mass and strength), and even neurodegenerative diseases and cancer. Skeletal muscle is an extremely plastic tissue that can use energy to generate work, generate energy by breaking down proteins into amino acids, undergo atrophy, hypertrophy, and even change its metabolism when stimulated by distinct challenges (i.e. endurance versus resistance training). Accordingly, different exercise programs can be used to ameliorate different conditions. Endurance training increases muscle energy efficiency, oxidative capacity, resistance to fatigue as well as cardiovascular function, whereas resistance training leads to muscle hypertrophy and can be used to treat sarcopenia.

Although our understanding of the mechanisms that regulate skeletal muscle adaptation to different exercise challenges is still incomplete, proteins of the peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha) family of transcriptional coactivators have been shown to play important roles in these processes. PGC-1alpha coactivators are expressed in energy-demanding tissues like fat, muscle, liver and brain. Interestingly, one single gene can be differently regulated by alternative promoter usage and alternative splicing to generate discrete PGC-1alpha variants with different biological activities. PGC-1alpha1 (the founding member of the family) is activated by aerobic exercise and regulates genes involved in mitochondrial biogenesis, adaptive thermogenesis, lipid and glucose homeostasis, fiber-type switching, among other. For these reasons, deficiencies in PGC-1alpha1 activity have been suggested to be involved in pathogenic conditions such as obesity, diabetes, sarcopenia, and neurodegeneration. Conversely, it has been shown that overexpression of PGC-1alpha1 in murine skeletal muscle has several beneficial effects. PGC-1alpha4 is induced by resistance exercise training and specifically promotes skeletal

• 79

¹ Dept. of Physiology and Pharmacology; Karolinska Institutet, Sweden

muscle growth and strength. Importantly, transgenic animals with elevated PGC-1 α levels in skeletal muscle show increased exercise performance, and resistance to atrophy and to cancer-induced cachexia.

Until recent years, changing skeletal muscle mass and condition through diverse exercise interventions was seen as a way to improve systemic bioenergetics and metabolic disease. Although this is indeed an efficient strategy to fight diseases such as obesity and diabetes, it is increasingly appreciated that skeletal muscle function can impact systemic physiology by changing the nature and quantity of circulating factors (myokines). These include molecules involved in angiogenesis (VEGF-A), cellular hypertrophy (Myostatin and IGF1), immune cell recruitment (IL-6, 8, and 15), adipocyte-mediated thermogenesis (FGF21, meteorin-like, myostatin, Fndc5), and neuroinflammation (kynurenine), among other.

Of particular interest are the well-known effects of physical exercise on mood, behavior, and cognition. Indeed, physical exercise has often been described as the most underutilized treatment in psychiatric disease. However, the mechanisms that mediate its therapeutic effects are largely unknown. We have recently identified a novel biochemical pathway, activated in exercised muscle, that changes tryptophan-kynurenine metabolism and protects from stress-induced depression. This results from the increased conversion of the tryptophan metabolite kynurenine (KYN) into kynurenic acid (KYNA) in skeletal muscle. Reducing kynurenine levels protects the brain from neuroinflammation and other changes associated with depression, anxiety, and schizophrenia, among other diseases. The master regulator of this detoxification pathway is the transcriptional regulator PGC-1 α , which is itself activated by exercise and mediates many of the effects of exercise training. Muscle PGC-1 α induces the expression of several kynurenine aminotransferases (KATs), which convert KYN to KYNA thus protecting the brain from insults known to be associated with psychiatric disease.

Understanding the molecular mechanisms that regulate how skeletal muscle adapts to different stimuli, and how these pathways can be targeted to harvest some of the beneficial effects of physical exercise can open important therapeutic opportunities.