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Perspective

Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits

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The beneficial effects of physical activity (PA) are well documented, yet the mechanisms by which PA prevents disease and improves health outcomes are poorly understood. To identify major gaps in knowledge and potential strategies for catalyzing progress in the field, the NIH convened a workshop in late October 2014 entitled "Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits." Presentations and discussions emphasized the challenges imposed by the integrative and intermittent nature of PA, the tremendous discovery potential of applying "-omics" technologies to understand interorgan crosstalk and biological networking systems during PA, and the need to establish an infrastructure of clinical trial sites with sufficient expertise to incorporate mechanistic outcome measures into adequately sized human PA trials. Identification of the mechanisms that underlie the link between PA and improved health holds extraordinary promise for discovery of novel therapeutic targets and development of personalized exercise medicine.

Introduction

Physical activity (PA), defined as bodily movement produced by skeletal muscles that requires energy expenditure, is an integral part of human life that influences development and overall health across the lifespan (Bamman et al., 2014; Bouchard et al., 1995; Colpani et al., 2013; Juonala et al., 2013; Whellan et al., 2007). Evolutionarily, the ability of man to perform PA was essential to survival, and therefore adaptive biological responses to both acute and repeated episodes of PA have played a critical role in shaping and defining "normal" human physiology. Whereas physical work associated with gathering food, building shelter, and evading predators was an absolute requirement of daily life for our ancestors, the advent of modern technology has now relegated PA from a necessity of human existence to a

choice of human lifestyle. As a result, physical inactivity has been identified as the fourth leading risk factor for global mortality (WHO, 2009).

Considering that the human species evolved to perform and endure habitual PA, it is not surprising that its absence can lead to devastating physiological and clinical consequences. Conversely, the impact of PA on human health is profound and unequivocal. PA helps to build muscle mass during development and preserve musculoskeletal function during aging (Christianson and Shen, 2013). PA promotes cardiometabolic wellness, improves cognitive performance, and effectively aids in the prevention and treatment of a variety of health conditions, including cardiovascular disease, diabetes and other disorders of metabolism, neurological diseases, sarcopenia, osteoporosis, and cancer (U.S. Department of Health and Human Services, 2008; Bouchard et al., 1990; Garber et al., 2011; Pate et al., 1995; Stranahan and Mattson, 2012). Additionally, tailored exercise programs, while all too often ignored, are essential for optimizing health in people with a wide variety of disabilities (Peterson et al., 2012).

Despite indisputable evidence of the myriad physiological benefits conferred by regular PA, the exact molecular mechanisms by which PA promotes human health remain poorly understood. In fact, epidemiological evidence suggests that the protective effects of PA on cardiovascular disease are nearly double that which would be predicted based on changes in traditional risk factors (Joyner and Green, 2009). In other words, ~50% of the protection afforded by PA remains unexplained. This knowledge gap was the focus of a recent NIH workshop "Understanding the Cellular and Molecular Mechanisms of PA-induced Health Benefits" on October 30–31, 2014 in Bethesda, MD. Attendees were asked to identify the major gaps in current knowledge regarding the molecular mechanisms underlying the health benefits of PA, obstacles to obtaining that knowledge, and possible solutions that would potentiate major progress in the field. Five working groups prepared sessions on (1) tools to facilitate clinical research to elucidate the mechanisms of PA, (2) integrative physiological mechanisms by which PA benefits multiple tissues and organ systems, (3) role of tissue stress in the benefits of PA, (4) role of mitochondria in the mechanisms underlying the benefits of PA, and (5) discovery tools to identify circulating and tissue signals that mediate the effects of PA. Progress toward a clearer mechanistic understanding of the extraordinary link between PA and health outcomes could lead to transformative biomedical discoveries that (1) reveal potential novel molecular and cellular therapeutic targets for disease prevention/treatment and (2) support development of personalized approaches for optimizing health outcomes in response to specific interventions, including the best combination of therapies (i.e., PA alone or plus drug, nutrient, diet, etc.). In response to the recommendations emanating from this workshop, the NIH will initiate a program through the Common Fund to catalog molecular transducers of physical activity in humans and to begin to explore their functions.

Gaps in Knowledge Regarding the Health Benefits of PA

Constructing a Network Model that Guides and Informs PA Research

The sophistication and capacity of modern technology has shifted the landscape of basic life sciences research from that of traditional biological reductionism to a much more integrative, holistic systems approach. Rapid technical progress has led to the growing recognition that living organisms are not merely the sum of their parts, but rather that interactions among cellular components and their environment are ultimately responsible for organismal form, function, and phenotype. Implicit in this philosophy is that the failure of biological networks to maintain homeostasis gives rise to pathophysiology and the development of complex diseases, whereas biological adaptations that enhance network flexibility and build functional reserve confer stress resistance and promote health.

As an energetic and physical challenge that broadly impacts the complex physiologic and metabolic networks of a multi-system organism, PA provides a paradigm through which a deeper and more sophisticated understanding of those networks can be developed. Because PA affects all cells and tissues in the body in numerous ways that vary with the type and intensity of activity, as well as the fitness, developmental, and disease state(s) of the individual, a two-tiered conceptual framework is proposed to capture the integrative and hierarchical nature of network control in response to PA (Figure 1) (Walz, 2005). The first tier encompasses the various vertical levels at which hierarchical control is exerted, as well as the molecular mechanisms that mediate crosstalk between systems to maintain homeostasis in the healthy state. A comprehensive understanding of the integrated regulatory mechanisms that operate within (i.e., horizontal) and between (i.e., vertical) levels informs a model from which hypotheses can be formed and experimentally tested. The second tier considers factors contributing to inherent (genetic, sex, height, etc.) and acquired (age, environment, fitness level, disease state, etc.) variability among individuals that in turn influence network dynamics in the first tier. Construction and application of this model serves the ultimate goal of biomedical science, which is to integrate knowledge of innate regulatory architecture with that of well-defined adaptive, homeostatic mechanisms to effectively forestall, predict, treat, and manage human disease on an individualized basis.

PA challenges homeostasis in virtually every organ system and activates acute and long-term compensatory mechanisms to preserve and/or re-establish homeostasis (see the recent review by Hawley et al., 2014). With a two-tiered approach in mind, the following sections raise several outstanding questions and pinpoint key knowledge gaps regarding the mechanisms by which hierarchical control is integrated within and between levels in response to PA, and the inherent/acquired mitigating factors that influence the response to PA and thereby determine the resulting health benefits.

How Do All Cells/Tissues Respond to Exercise?

Deciphering the molecular mechanisms underlying PA-induced health benefits begins with defining the extent and magnitude to which PA disrupts homeostasis in different cell types, and how various cells react to meet those challenges. Still unknown is whether PA-induced alterations in homeostasis are common or unique among different cell types, and to what degree the mode of exercise influences the responses. For example, does endurance exercise increase energy turnover rate in cell types other than skeletal muscle and heart? How do physical forces (strain, concentric, eccentric, gravitational, etc.) influence metabolism and energetics in cells that do not perform contractile