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FNDC5/irisin, a molecular target for boosting reward-related learning and motivation

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ABSTRACT

Interventions focusing on the prevention and treatment of chronic non-communicable diseases are on rise. In the current article, we propose that dysfunction of the mesocortico-limbic reward system contributes to the emergence of the WHO-identified risk behaviors (tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol), behaviors that underlie the evolution of major non-communicable diseases (e.g. cardiovascular diseases, cancer, diabetes and chronic respiratory diseases). Given that dopaminergic neurons of the mesocortico-limbic system are tightly associated with reward-related processes and motivation, their dysfunction may fundamentally influence behavior. While nicotine and alcohol alter dopamine neuron function by influencing some receptors, mesocortico-limbic system dysfunction was associated with elevation of metabolic set-point leading to hedonic over-eating. Although there is some empirical evidence, precise molecular mechanism for linking physical inactivity and mesocortico-limbic dysfunction *per se* seems to be missing; identification of which may contribute to higher success rates for interventions targeting lifestyle changes pertaining to physical activity.

In the current article, we compile evidence in support of a link between exercise and the mesocortico-limbic system by elucidating interactions on the axis of muscle – irisin – brain derived neurotrophic factor (BDNF) – and dopaminergic function of the midbrain. Irisin is a contraction-regulated myokine formed primarily in skeletal muscle but also in the brain. Irisin stirred considerable interest, when its ability to induce browning of white adipose tissue parallel to increasing thermogenesis was discovered. Furthermore, it may also play a role in the regulation of behavior given it readily enters the central nervous system, where it induces BDNF expression in several brain areas linked to reward processing, e.g. the ventral tegmental area and the hippocampus. BDNF is a neurotropic factor that increases neuronal dopamine content, modulates dopamine release relevant for neuronal plasticity and increased neuronal survival as well as learning and memory. Further linking BDNF to dopaminergic function is BDNF's ability to activate tropomyosin-related kinase B receptor that shares signalization with presynaptic dopamine-3 receptors in the ventral tegmental area.

Summarizing, we propose that the skeletal muscle derived irisin may be the link between physical activity and reward-related processes and motivation. Moreover alteration of this axis may contribute to sedentary lifestyle and subsequent non-communicable diseases. Preclinical and clinical experimental models to test this hypothesis are also proposed.

General background

Physical inactivity, unhealthy diet, tobacco use and harmful use of alcohol are identified by the World Health Organization (WHO) as key risk factors for major chronic non-communicable diseases (NCDs) primarily responsible for premature death worldwide, e.g. cardiovascular diseases, cancer, diabetes and chronic inflammatory lung disease [1,2].

It is clear that combating NCDs is one of the greatest pressing challenges high-income countries must face, a challenge articulated in and reflected by several international policies, such as the Global Action Plan for the Prevention and Control of NCDs 2013–2020 resolution [1]. This Global Action Plan posits a paradigm shift by providing a road map and a menu of policy options that if implemented collectively could halt the rise in diabetes and obesity, lead to a 25% relative reduction in risk of premature

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mortality from cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases.

Furthermore, a relative reduction in the prevalence of risk factors such as insufficient physical activity and tobacco use in persons aged 15+ years, and harmful use of alcohol, is anticipated by 10%, 30% and 10%, respectively [1]. Nonetheless rather than risk factors, all of them could be viewed as risk behaviors, with lifestyle changes or behavioral modifications being amongst the most effective means for preventing or slowing the progression of NCDs.

In our current work, we put forward the hypothesis that the common denominator of risk behaviors underlying the most burdening NCDs may be the dysfunction (or untoward function) of the mesocortico-limbic system. Furthermore we propose that the irisin – brain derived neurotrophic factor (BDNF) pathway forms a significant the link between physical inactivity and the mesocortico-limbic system.

A common denominator for change of behavior is motivation and allied reward-related processes driving change of said behavior. Motivation and reward processing are tightly linked to mesocortico-limbic dopaminergic activation, as laid out by the two major theoretical frameworks, the reward-prediction error and the incentive salience hypothesis [3–5].

According to the reward prediction error hypothesis phasic dopamine response signals the discrepancy between expected and actual reward value of a cue governing future goal-directed activity [5,6]. Placing this concept into the reinforcement learning paradigm, the reward prediction error signal emitted by dopamine neurons is the neural correlate of model-free reinforcement learning's prediction error and is used to compute the value of state without any attempt to build a model. This model-free system interacts with the model-based system [7] that uses a model, possibly utilizing the continuous function of the brain's default network, incorporating structures such as the hippocampus and the orbitofrontal cortex [8].

On the other hand, Berridge and colleagues posit that reward associated processes are conceptualized using three psychological components, e.g. liking (the hedonic value of a cue), reward learning by means of associative learning and incentive salience that is 'wanting' (motivational incentive of a cue) [9]. Accordingly, it attributes incentive (motivational) value to a cue making it more (or alternatively less) 'wanted' (4). This theoretical framework offers a different interpretation of the role attributed to mesocortico-limbic dopaminergic activation as it pointed to dopamine's causal involvement in incentive salience as opposed to prior beliefs linking dopamine to hedonic attribute of cues [4,10]. Summarizing, incentive salience is the Pavlovian-guided attribution of motivational value to a previously reward-related neutral representation of a cue (conditioned stimulus (CS)) that results in a more attractive and 'wanted' cue/stimulus. Accordingly, the incentive salience value of a cue is the net of associative-learning derived prior knowledge concerning the relationship between the cue and the reward (unconditioned stimulus (UCS)) [11].

Either way, the central role of the dopaminergic mesocortico-limbic system has to be acknowledged (Fig. 1).

Substantial evidence may be retrieved tying the influence of alcohol and nicotine to the mesocortico-limbic reward structures in the contemporary literature of addiction (for review see [12,13]). There are also elaborate reviews focusing on the 'hedonic control of eating' [14–16], moreover recently the term 'hedonic obesity' was coined to describe a form of obesity, in which the metabolic set-point is elevated due to hedonic over-eating linked to mesocortico-limbic system dysfunction [17]. Nonetheless, there seems to be missing a link between physical inactivity and mesocortico-limbic dysfunction *per se*, identification of which may contribute to higher success rates for interventions targeting lifestyle changes pertaining to physical activity. In the following section we will compile evidence in support of the link between exercise and the mesocortico-limbic system by elucidating interactions on the axis of skeletal muscle – irisin – BDNF – and dopaminergic function of the midbrain (Fig. 2).

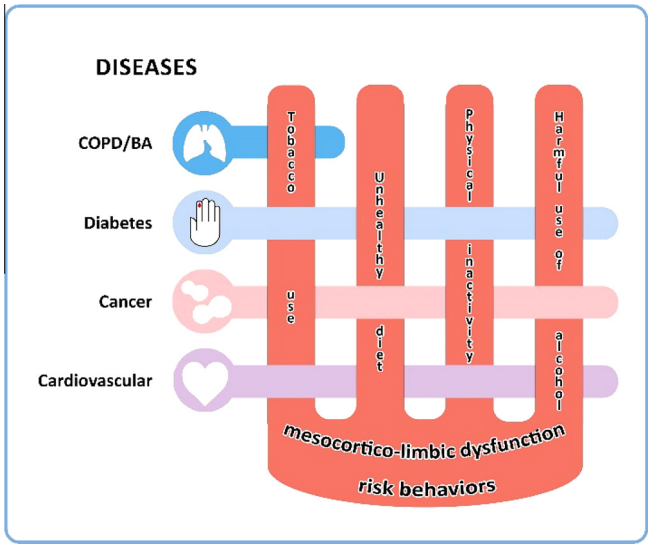

Fig. 1. Dysfunction (or untoward function) of the mesocortico-limbic system may be a causative factor in development of risk behaviors leading to the evolution of major NCDs. Risk behaviors and NCDs are indicated as conceptualized by the WHO for the purpose of Global Action Plan for the Prevention and Control of NCDs 2013–2020 (1). Abbreviations: COPD: chronic obstructive pulmonary disease, BA: bronchial asthma.

Emergence of skeletal muscle as an endocrine organ

The identification of several muscle-derived cytokines and peptides termed myokines has led to the re-conceptualization of skeletal muscle as an endocrine organ [20,21]. Myokines, by definition, are produced, expressed, and released by muscle fibers and exert local or remote effects in an autocrine/paracrine or endocrine fashion, respectively. Myokines may be clustered based on their postulated function e.g. their contribution to metabolism, angiogenesis and myogenesis [22]. One subset of myokines, contraction-regulated myokines, has raised considerable interest recently, based on its potential to account for the beneficial effects of exercise, given that it allegedly assumes a fundamental role for the interplay between skeletal muscle, adipose tissue and brain [21].

One aspect of muscle-fat-brain crosstalk relevant for exercise-related beneficial effects of myokines concerns the browning of white adipose tissue [23]. Conventionally, white adipose tissue (WAT) and brown adipose tissue (BAT) are differentiated based on their developmental origin and the role they assume in energy homeostasis. While WAT serves as the primary energy storing organ enabling prolonged survival in the absence of meals, BAT is responsible for energy dissipation in the form of non-shivering thermogenesis. In line with this, expression of mitochondrial uncoupling protein UCP1, a key protein underlying thermogenic activity of BAT, is low in WAT and high in BAT [24]. Nonetheless, recently an intermediate form of adipocytes was identified called beige or brite (brown in white) adipocytes [25,26]. These cells originate from cell lines resembling that of WAT and are consistently found at anatomical locations typical for WAT. At baseline, they have low expression of UCP1. Nevertheless, if activated these beige adipocytes have the capability to switch from energy storing to energy dissipating mode, by changing from a baseline expression to increased expression of UCP1, parallel to phenotypic alterations