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Hypothesis: Irisin is a metabolic trigger for the activation of the neurohormonal axis governing puberty onset

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ABSTRACT

A large body of data suggests that body weight influences puberty onset and adult reproduction. However, the underlying mechanism of how body weight influences puberty onset and fertility is not completely understood. The hypothalamic neuronal circuit regulating reproduction is restrained by inhibitory signals during childhood. At the time of puberty, these inhibitory signals are weakened and supplanted by stimulatory signals that, in turn, stimulate the release of gonadotropin-releasing hormone (GnRH) – a hypothalamic neuropeptide governing reproduction. A number of studies, however, suggest that puberty commencement occurs when body (fat) weight reaches a certain threshold, which is critical for the initiation of puberty and for support of the adult reproductive function. Previously, various signals have been studied which might link body (fat) weight-related information to the hypothalamic neuronal network regulating reproduction. However, the nature of the signal(s) that may link body fat and/or muscle mass with the hypothalamic neuronal network governing reproduction is still unclear. It has been intuitively speculated that augmentation of such signal(s) will cause a restriction of inhibitory input and activation of stimulatory input to GnRH secreting neurons at the time of puberty onset. Therefore, the unveiling of such signal(s) will greatly help in understanding the mechanism of puberty onset. Recently, it has been shown that expression of fibronectin type III domain containing-5 (*FNDC5*) mRNA in central and peripheral tissues upsurges during postnatal development, especially around the time of puberty onset. Moreover, the systemic level of irisin – one of the protein products of the *FNDC5* gene that is secreted as myokine and adipokine – also rises during postnatal development and correlates with the timing of puberty onset. Therefore, we propose here that irisin might serve as a possible signal for linking body fat/muscle mass with the hypothalamic center governing reproductive function. We hypothesize that irisin acts as a trigger for the activation of the hypothalamic neuronal network monitoring the onset of puberty.

Background

Puberty, an important postnatal developmental stage, is characterized by several changes in the body in response to augmentation in sex steroid levels after activation of the reproductive axis [1]. However, the mechanism of puberty onset is still not fully defined. It is a well-established fact that gonadotropin-releasing hormone (GnRH) is the main regulator of the pituitary-gonadal axis [1,2]. GnRH release from the hypothalamic GnRH neurons is regulated directly and/ or indirectly by a plethora of hypothalamic inhibitory and excitatory intercellular signaling systems. Major signaling molecules involved in the regulation of GnRH release are kisspeptin, neurokinin B, excitatory amino acids (EAA), gonadotropin-inhibitory hormone (GnIH), pro-opiomelanocortin (POMC), agouti-related protein (AgRP), neuropeptide Y (NPY), and gamma-aminobutyric acid (GABA) [1,3–5]. Besides other roles, all of these intercellular signaling systems have been implicated in the regulation of puberty onset in mammals [1,4–13]. However, one of the most important unanswered questions is: what triggers the activation of this hypothalamic neurohormonal network at the time of puberty onset? It has been proposed that this hypothalamic neurohormonal network is responsive to many central and peripheral cues, including body energy reserves [3,14,15].

At the time of puberty, the hypothalamic neuronal network, which regulates reproductive function, is activated when body

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(fat) weight reaches a certain threshold level essential for puberty onset [16–20]. When the body reaches this critical fat and/or muscle mass, a metabolic signal(s) communicates this information to the hypothalamic neuronal network governing puberty onset. However, the nature of this metabolic trigger is still not clear. Previously, roles of various metabolic signals, for example, leptin, insulin, ghrelin, insulin-like growth factor, etc., have been investigated in linking body weight/metabolic status-related information with the neuroendocrine reproductive axis [3,9,15,21–23]. Evidence in favor of or against a permissive or an inhibitory role of these factors on puberty onset and the regulation of adult reproduction has been documented [7,9,15,24–26]. However, these are not solely metabolic regulators of puberty and fertility. Therefore, investigation of other potential metabolic signal(s) that may link body fat/muscle mass with the hypothalamic neurohormonal network governing puberty onset and adult reproduction is needed.

Recently, it has been reported that the expression of fibronectin type III domain containing-5 (*FNDC5*) transcripts increases in the brain during different postnatal developmental stages. Moreover, systemic levels of irisin – an important adipokine and myokine encoded by *FNDC5* gene – have been reported to change during various stages of puberty [27,28]. However, it is unknown whether irisin serves as a signal for transferring metabolic reserves-related information from the periphery of the body to the hypothalamic neuronal network monitoring the onset of puberty.

Hypotheses

Here we propose the hypothesis that an increase in *FNDC5* mRNA in peripheral tissues, e.g., adipose tissue, heart, muscle, etc., with the ultimate rise in systemic irisin levels serves as a metabolic trigger for the activation of the neurohormonal network controlling puberty onset in mammals. Moreover, as severely obese children frequently experience an early onset of puberty, irisin might function as a potential signal for premature activation of the neuroendocrine reproductive axis. Additionally, we hypothesize that human subjects and animal models of delayed puberty exhibit a relatively late rise in the expression of *FNDC5* mRNA and the subsequent production of irisin.

Testing of the proposed hypotheses

This hypothesis can be tested in human subjects, animal models or hypothalamic neuronal cell lines via different approaches. Firstly, expression of *FNDC5* transcript and protein levels should be checked in peripheral and central tissues, for example, hypothalamus, pituitary, testis, ovary, muscle, adipose tissues, etc., before and during different stages of puberty. Secondly, irisin systemic and cerebrospinal fluid (CSF) concentration should also be checked. Thirdly, the irisin receptor – which is still unknown – needs to be identified. Subsequently, its expression on KNDy (kisspeptin/neurokinin B/dynorphin), GABA, GnIH, EAA, and NPY containing neurons needs to be tested and the effect of irisin on the synthesis and release of the respective neuropeptides needs to be investigated. Irisin plasma levels should be compared between human subjects with the early onset of puberty with those showing normal and delayed puberty. Administration of irisin to prepubertal animals and monitoring GnRH/LH secretion and other hallmarks of puberty would also illuminate the role of irisin during the onset of puberty.

Besides genetic susceptibility, nutritional and other environmental factors exert influence on pubertal maturation [29–32]. Of note, with improvement in nutrition, infection control, and a number of other factors, the mean age of puberty onset in girls has fallen five years in the last 100 years [30,32]. Therefore, comprehensive studies on the impact of nutritional, immunological, and environmental cues on *FNDC5* mRNA expression and irisin release in animal models and how these relate to puberty onset are also required.

Consequences of the proposed hypothesis and discussion

The mechanism of the onset of puberty has been listed among 100 still incompletely understood questions in science [33]. If our hypothesis proves true, it will greatly help in understanding the mechanism of puberty onset. An expression analysis of *FNDC5* during prepubertal, pubertal and postpubertal stages will give the first clue. Relatively high *FNDC5* mRNA expression during the prepubertal period will indicate a potential inhibitory role of irisin on puberty onset. However, if *FNDC5* mRNA expression heightens during the pubertal stages as compared to the prepubertal period, then this will suggest a stimulatory role in puberty onset. Conversely, no change in *FNDC5* mRNA expression or absence of an irisin application effect on hallmarks of puberty will falsify our hypothesis. Nevertheless, a number of available observations support our proposed hypothesis. These include that *FNDC5* mRNA expression increases not only in peripheral tissues but also in the brain during postnatal development, especially around the time of puberty onset [34]. Moreover, plasma levels of irisin have also been noted to correlate with the time of puberty onset [28].

It is possible or even likely that the still undiscovered receptor of irisin might be expressed on neuronal cells constituting (at least a part of) the hypothalamic neuronal networks that regulate reproductive function. These hypothalamic cells include kisspeptin, NKB, GnIH, GnRH, EAA, GABA, and NPY expressing neurons. Irisin might modulate the expression of *Kiss1*, *RFRP*, *GnRH1*, *TAC1*, and *TAC3* mRNAs and the release of the respective peptide products. It is important to mention here that forced expression of *FNDC5* in cortical neurons or its peripheral application has also been reported to enhance the brain-derived neurotrophic factor expression in hippocampal neurons [34]. *FNDC5* mRNA expression has been reported in several peripheral tissues, including testis, muscle, and adipose tissues [34–36]. However, it is unknown whether its expression changes during different stages of puberty in these tissues. Of note, as mentioned above, *FNDC5* mRNA expression increases in the brain during postnatal development [34]. Importantly, a recent study reported an increase in irisin plasma levels in obese children. This change in systemic irisin levels was associated with puberty onset [28]. It is well known that obese children, especially girls, experience the early onset of puberty [37,38].

Comprehensive scientific investigations on the mechanism of the puberty onset in both animal models and humans have established the basis for the so-called "critical mass of body fat hypothesis" [16–20]. This hypothesis suggests that, in both animals and humans, puberty onset is more related to body weight than chronological age. According to this hypothesis, puberty and reproductive function commence when a certain threshold level of body (fat) weight is achieved. In particular, this hypothesis is applicable to females, where the attainment of adequate energy reserves is essential in order to satisfy the considerable additional energy demand of pregnancy and lactation [15,20,26,39]. Moreover, adverse effects of energy deficiency have been reported regarding puberty onset and adult reproductive function in both sexes [7,9,26]. Taken together, the critical body weight (fat) hypothesis and our hypothesis of augmentation of *FNDC5* mRNA expression and irisin secretion at the time of puberty suggest that puberty is initiated when body weight reaches a certain critical level (Fig. 1). Subsequently, an increase in the expression of *FNDC5* mRNA and a rise in the systemic and central levels of irisin are supposed to occur. An appropriately sensed increase in irisin by the