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Commentary and Perspectives

Brain function of the metabolic hormone fibroblast growth factor 21

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How metabolic hormones exert their regulatory functions not only in peripheral organs but also in the brain remains to be fully understood. However, intensive investigations on such hormones have allowed us to recognize the existence of the brain-gut, the brain-liver and other regulatory axes that involve the central nervous system (CNS). Certain metabolic hormones, especially those from gastrointestinal (GI) tract origin including insulin and glucagon-like peptide-1 (GLP-1) are shown to be expressed in the brain as well. Investigations on the brain function of these hormones, either produced in the GI tract or *in situ* in the brain, have advanced our knowledge on hormone function at physiological and pathophysiological settings, as well as on cell signaling in general (Varin et al., 2019; Mehran et al., 2012).

Fibroblast growth factor 21 (FGF21) is a metabolic hormone expressed mainly in the liver. Extra-hepatic expression sites of FGF21 include muscle, white adipose tissue (WAT), brown adipose tissue (BAT), thymus, pancreas and the brain (Nishimura et al., 2000; Fon Tacer et al., 2010; Petryszak et al., 2016; Li et al., 2018). Circulating FGF21 elevation can be induced by nutrient deprivation, fasting, lipid intake, or ketogenic food consumption (Zhang et al., 2015). FGF21 transcription has been shown to be directly activated by the nuclear receptor peroxisome proliferator-activated receptor α (PPARα). FGF21 activation induces hepatic expression of peroxisome proliferator-activated receptor g coactivator 1-α (PGC1α), a transcriptional co-activator that upregulates fatty acid oxidation, tricarboxylic acid cycle, and gluconeogenesis in the liver (Potthoff et al., 2009). Peripherally, FGF21 acts on several extrahepatic tissues, including the browning of white adipose tissue (Fisher et al., 2012). Details outlining the variety of physiological roles of peripheral FGF21 have been described in several informative review articles (Kharitonenkov and DiMarchi, 2015; Fisher and Maratos-Flier, 2016).

Although intensive studies have suggested potential brain functions of FGF21, including the neuroprotection and cognition improvement effect of this metabolic hormone (Makela et al., 2014), our knowledge on the role and mechanism underlying the potential energy homeostatic effect of brain produced FGF21 is very limited. A clinical study by Tan et al. in 2011 revealed that both plasma and cerebrospinal fluid (CSF) FGF21 levels were positively correlated with body mass index (BMI), fat mass, plasma insulin, and homeostasis model assessment of insulin resistance (Tan et al., 2011). A significant negative association, however, was observed between CSF FGF21 levels and Beck Depression Inventory (BDI) scores in Chinese male subjects, indicating the potential role of FGF21 in mood regulation (Liu et al., 2017). These clinical investigations, however, are unable to define the origin of FGF21, which exerts the brain function, as this hormone can penetrate brain-blood barrier (Hsuchou et al., 2007); or provide mechanistic insights on brain FGF21 function.

A very recent study conducted by Geller and colleagues via the utilization of a transgenic mouse model starts to fill this knowledge gap (Geller et al., 2019). In this study, the authors first verified hypothalamic *Fgf*21 mRNA and protein expression, although they did not test the hormone production in mouse CSF. They then characterized the expression and secretion of FGF21 by hypothalamic tanycytes with both *in vivo* and *in vitro* tools. Tanycytes are a subtype of ependymal cells located mainly along the third ventricle of the brain and some lining the floor of the fourth ventricle. These cells extend deep into the hypothalamus, the organ that links the nervous system to the endocrine system via the pituitary gland. Importantly, the investigators demonstrated the regulatory effect of palmitate on tanycyte FGF21 production and function, involving the activation of the reactive oxygen species (ROS)/P-38-MAPK signaling pathway. Finally, they demonstrated that brain tanycyte FGF21 depletion triggers an increase in lipolysis in fat tissue, associated with increased energy expenditure and reduced fat mass accumulation. As stated in the Context and Significance of this study: “These results highlight the complex interplay between the brain and other organs and can inform our decisions in the treatment of metabolic disease”.

Based on this study and related literature information, we can view the function of this novel signaling cascade as a key component of the interplay between brain and peripheral organs during metabolic signaling of FGF21. As shown in Fig. 1, although *Fgf*21 mRNA can be detected in extra-hepatic organs including pancreas, liver, WAT, BAT, muscle, and thymus, circulating FGF21 is mainly produced and secreted from the liver (Fisher et al., 2010). Nutritional stress induces FGF21 elevation as well as the release of free fatty acid (FFA) including palmitate. Both FGF21 and palmitate can pass the blood brain barrier (BBB). Palmitate will stimulate expression of *Fgf*21 mRNA in the brain neurons including tanycytes and the secretion the FGF21 hormone from tanycytes, possibly via the activation of the ROS/P-38-MAPK signaling

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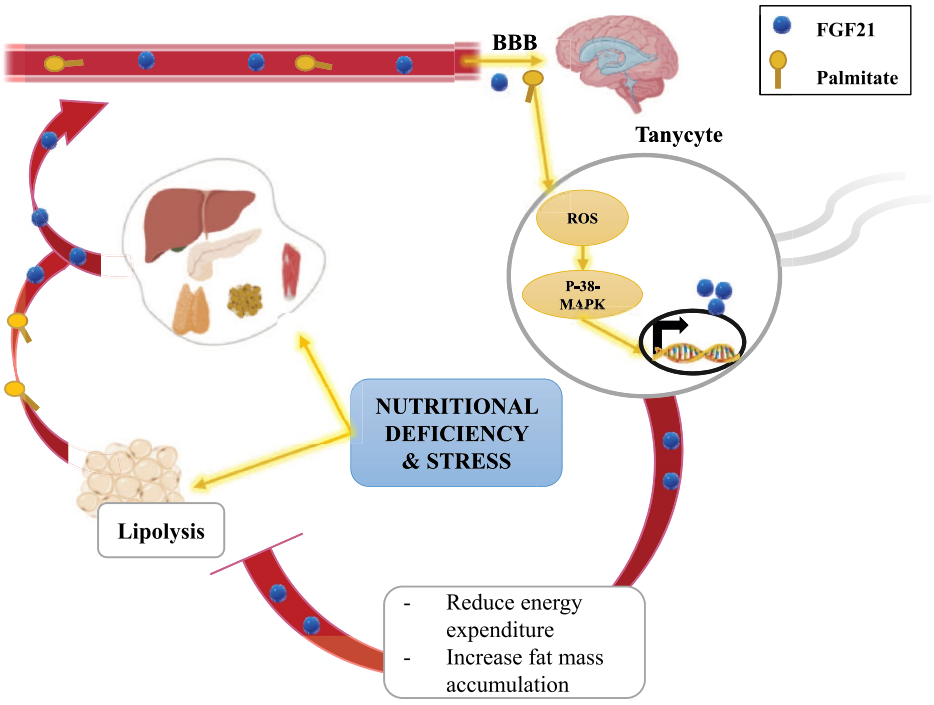

Fig. 1. Brain metabolic function of the hormone fibroblast growth factor 21. Stress-induced circulating FGF21 expressed primarily in liver and other extrahepatic tissue such as pancreas, liver, WAT, BAT, muscle, and thymus can cross the BBB to act on various cells in the brain. Free fatty acid palmitate released in response to fasting causes expression and secretion of FGF21 in tanycytes via the ROS/P-38-MAPK pathway. The downstream effects of tanycytic FGF21 release functions in a negative-feedback loop to preserve energy by reduction of energy expenditure and accumulation of fat mass.

cascade. The downstream effects of tanycytic FGF21 release can function as a negative-feedback loop by attenuating energy expenditure and increasing fat mass accumulation. This way, FGF21 elevation in response to nutritional stress not only provides the alternative energy source for the body in short term but also preserves energy in long run.

Perspectives

Despite prior findings that elucidate the role of neuroendocrine FGF21 signaling in both physiological and pathological conditions, the origin of expression of this hormone has been thus far unclear. Due to the ability of FGF21 to cross the BBB, and its high expression and secretion from the liver, it has been difficult to determine whether downstream signaling of FGF21 in the brain is the result of local or circulating hormone. The implications of FGF21 signaling in control of metabolic homeostasis remain of interest due to potential for development of therapeutic intervention targeting this signaling pathway for metabolic disorders including obesity. Although the knockout approach utilized in this study demonstrated the participation of brain origin FGF21, future studies can explore whether circulating FGF21 is also involved in exerting this negative-feedback loop.

Recently, several investigations, including those conducted by our team have shown that FGF21 is among the targets of dietary polyphenol interventions. Dietary polyphenols including curcumin and resveratrol, as well as betaine, a compound isolated from sugar beets, have all been previously implicated in altering FGF21 expression and improving glucose homeostasis in mice (Song et al., 2016; Zeng et al, 2017a, 2017b; Li et al., 2014; Jin, 2019). Future studies may focus on what the mechanistic pathway is between dietary interventions, FGF21 expression and release, and the interplay involving this neuroendocrine signaling.

Declaration of competing interest

The authors claim that this is no conflict interest on composing this commentary.

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Yasaman Badakhshi
Division of Advanced Diagnostics, Toronto General Research Institute, University Health Network, Canada
Banting & Best Diabetes Centre, Faculty of Medicine, Canada
Department of Physiology, University of Toronto, Toronto, Ontario, Canada

Tianru Jin*
Division of Advanced Diagnostics, Toronto General Research Institute, University Health Network, Canada
Banting & Best Diabetes Centre, Faculty of Medicine, Canada
Department of Physiology, University of Toronto, Toronto, Ontario, Canada
Institute of Medical Science, University of Toronto, Canada
E-mail address: tianru.jin@utoronto.ca.

* Corresponding author. MaRS Centre, Toronto Medical Discovery Tower, Toronto General Research Institute, University Health Network, 101 College Street, 10th Floor, Room 10-354, Toronto, ON, M5G 1L7, Canada.