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Letter

Tanycytes and hypothalamic FGF21: New players in the metabolic game

Sarah Geller[1,3,*] and Luc Pellerin[2,3,4,*]
[1]Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland
[2]Inserm U1313 IRMETIST, Université de Poitiers et CHU de Poitiers, Poitiers, France
[3]These authors contributed equally
[4]Lead contact
*Correspondence: sarah.geller@unil.ch (S.G.), luc.pellerin@univ-poitiers.fr (L.P.)
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The actual obesity and diabetes pandemics require new approaches to stop their progression. Recent findings converged on the therapeutic potential of fibroblast growth factor 21 (FGF21) in these metabolic diseases. FGF21 is a master regulator of metabolism by acting not only directly on peripheral tissues but also through the brain. The central nervous system seems to be a target for the beneficial effects of FGF21 in the treatment of diabetes (in particular, insulin resistance) as well as obesity, highlighting the importance of investigating its central mechanisms of action. The source of this messenger and its target cells in the brain are debated topics that currently raise great interest in the field of metabolism. Under physiological conditions, the liver is the major source of circulating Fgf21. Fgf21 protein can cross the blood-brain barrier by simple diffusion[1] but also reach part of the brain via fenestrated vessels in the hypothalamus.[2] Recently, Zhou et al. reported in this journal a central production of neuronal Fgf21 in the thalamus and the retrosplenial cortex.[3] This neuronal production of Fgf21 seems to be involved in the enhancement of spatial memory but does not regulate energy homeostasis or sugar intake. More surprisingly, in contrast to several recent studies, they did not detect Fgf21 production in the hypothalamus using a new transgenic mouse model. Over the past three years, several studies from independent groups with various experimental conditions reported *Fgf21* mRNA expression by the hypothalamus in mouse,[4–7] rat,[4,8,9] and pig[10] by using, among other techniques, PCR and *in situ* hybridization (such as the novel RNAscope technology). Moreover, three of these studies described an *Fgf21* mRNA synthesis by glial cells including tanycytes,[6,7,9] peculiar ependymal cells of the hypothalamus. The recent challenge by Zhou et al.[3] of a specific tanycytic Fgf21 production created a controversial issue on whether the protein detected in tanycytes is produced locally or comes from the bloodstream. Interestingly, a parallel study confirmed a mixed origin of Fgf21 protein detected in tanycytes.[9] This study validated that rat tanycytes synthesize *Fgf21* mRNA but also demonstrated that they transport peripheral Fgf21 protein into the hypothalamus. Indeed, hepatic Fgf21 reaches deeper hypothalamic structures through active transport by tanycytes, a mechanism shown to be necessary to observe a beneficial effect on systemic metabolism in animals that underwent delayed weaning and were exposed to a high-fat diet later in life.[9] Intriguingly, hepatic and hypothalamic *Fgf21* mRNA expression seem to be either similarly or differentially regulated according to the type of nutrients. Although a first study showed that fasting and fatty acids (such as palmitate) stimulate both hepatic and tanycytic *Fgf21* mRNA expression,[6] delayed weaning or protein deficiency induced an opposite effect on *Fgf21* mRNA expression from both tissues.[8,9] These observations confirm a complex regulation of Fgf21 production according to the tissue and nutritional status. The mechanisms responsible for these specific regulations need to be identified and described. Moreover, the opposite effects of nutrients on hypothalamic and hepatic *Fgf21* mRNA expression raise the question about the existence of a counter-regulation or compensation system that must be coordinated somehow between both structures. Furthermore, one may wonder, *in fine*, what is the benefit of parallel tanycytic Fgf21 production and active transport of hepatic Fgf21 by tanycytes? It is clear that the physiological functions of such a glial Fgf21 production need to be further explored and more firmly established, although specific roles in systemic lipid and glucose homeostasis have been unraveled in lean rodents.[6,7] Undoubtedly, tanycytes have joined the Fgf21 team, but we need more time to read their game if we want to win against obesity and diabetes.

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