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NEUROENDOCRINOLOGY

FGF21—central pathways of action unravelled

Two new studies published in *Nature Medicine* implicate the central nervous system in the mechanisms of action by which fibroblast growth factor 21 (FGF21) exerts its effects on metabolism and growth in mice. Furthermore, the data reveal hitherto unknown actions of centrally acting FGF21: the induction of glucocorticoid levels, the inhibition of female ovulation, and the alteration of circadian behaviour.

The hepatokine FGF21 has important roles in energy metabolism. For example, FGF21 is well-known to induce metabolic processes in response to starvation, such as increased ketogenesis and inhibition of growth. Direct effects of FGF21 on peripheral target tissues, such as white adipose tissue, have previously been reported. In addition, evidence of an indirect mode of action of FGF21 via the central nervous system has steadily increased; for example, administration of exogenous FGF21 directly into the ventricular system of obese rodent brains increased energy expenditure and insulin sensitivity. However, the distinct site of central action and the mechanistic pathways linking to the periphery have remained elusive.

Researchers from the University of Texas Southwestern Medical Center used laser-capture microdissection coupled with quantitative PCR to map the mRNA for β-klotho—an essential protein component of the FGF receptor—to two small regions of the brain: the suprachiasmatic nucleus (SCN) in the hypothalamus and the dorsal–vagal complex (DVC) in the hindbrain. "This finding was very exciting, as these regions regulate not only female reproduction but also metabolism and, in the case of the SCN, circadian rhythm," recalls Steven A. Kliewer, who led the studies together with David J. Mangelsdorf.

Next, the investigators used genetically engineered mouse models, such as *Fgf21*-overexpressing and conditional *Klb* knockout mice (in which the gene encoding β-klotho was selectively eliminated in the SCN and DVC but not in other tissues), to study the biological consequences of chronic FGF21 exposure or of eliminating central FGF21 action, respectively.

To examine the effects of FGF21 on circadian rhythm, Kliewer and colleagues performed wheel-running experiments. "These experiments were the logical next step once we found β-klotho in the SCN, the master regulator of circadian rhythm," explains Kliewer.

The studies showed that "many if not most of FGF21's biological actions require it to act on the brain," as Kliewer describes it. Previously established effects of FGF21—that is, the induction of metabolic processes such as increased fatty acid oxidation, reduced insulin levels and suppression of whole-body growth in response to starvation—required expression of β-klotho in the brain. In addition to these effects, centrally acting FGF21 altered circadian behaviour and increased systemic corticosterone levels, a known characteristic of fasting and starvation. "Importantly, both pharmacological and physiological concentrations of FGF21 acted on the brain to modulate energy metabolism," says Nobuyuki Itoh (Kyoto University Graduate School of Pharmaceutical Sciences), who was not affiliated with the studies.

Another physiology that is affected by starvation is reproduction; fertility is markedly reduced as a result. As reported in a second study, the teams led by Kliewer and Mangelsdorf found that mice chronically exposed to FGF21 (via transgenic overexpression) were infertile and exhibited signs of hypothalamic hypogonadism. The effects of FGF21 on glucocorticoids and female reproduction were probably mediated by suppressing expression of the neuropeptide vasopressin in the SCN.

Taken together, the findings suggest a unifying explanation for the actions of FGF21 during starvation. "In response to long-term fasting, FGF21 is released from the liver and circulates to the brain, where it acts to regulate diverse aspects of the adaptive starvation response in other tissues," comments Kliewer. "These effects include increasing fatty acid oxidation and glucocorticoid concentrations, inhibiting growth and female reproduction, and changing circadian behaviour so as to optimize food-seeking behaviour."

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Pharmacologically, FGF21 causes weight loss and improves insulin sensitivity and lipid parameters in rodent and monkey models of obesity and insulin resistance. Using the tissue-specific *Klb* knockout mice, Kliewer and co-workers are currently testing whether these actions require centrally acting FGF21 in obese mice.

"The pharmaceutical interest in FGF21 for treating metabolic disease is tremendous, and several companies have FGF21 in clinical trials," states Kliewer. "If the effects of FGF21 on glucocorticoids and female fertility translate to humans, these factors are likely to be major liabilities." However, whether these concerns are justified, remains to be determined.

Linda Koch

Original articles Bookout, A. L. *et al.* FGF21 regulates metabolism and circadian behavior by acting on the nervous system. *Nat. Med.* doi:10.1038/nm.3249 | Owen, B. M. *et al.* FGF21 contributes to neuroendocrine control of female reproduction. *Nat. Med.* doi:10.1038/nm.3250