NEURODEGENERATIVE DISEASE

Hooking FSH as a potential target for Alzheimer disease

The incidence of Alzheimer disease (AD), speed of progression and burden of symptoms is much higher in women after the menopause than in men. Oestrogen deficiency has been suggested as a possible cause, but its role remains controversial, as restoring oestrogen levels has often no effect or can even worsen AD symptoms. A new study has now shown that increased levels of a different hormone, follicle-stimulating hormone (FSH), accelerate deposition of amyloid-β (Aβ) peptides and tau proteins and impair cognition via the neuronal CCAAT/enhancer binding protein β/asparagine endopeptidase (C/EBβ/AEP) pathway in mouse models of AD. Blocking FSH with antibodies ameliorates AD symptoms and prevents them from developing.

Pituitary gonadotropins, including FSH, can directly regulate bodily systems beyond traditional endocrine targets. Indeed, increased FSH levels in the years before the onset of menopause are associated with rapid bone loss, visceral adiposity, impaired energy balance and cognitive decline.

The team led by Keqiang Ye, one of the lead authors of the study, has been studying the role of the C/EBPβ/AEP signalling pathway in neurodegenerative diseases, including AD. AEP is a δ-secretase that cleaves amyloid precursor protein (APP) and tau, promoting the formation of Aβ and tau aggregates. In previous work they had observed that FSH selectively stimulates C/EBPβ/AEP signalling and that administration of FSH into a young male AD mouse model triggers earlier AD onset.

In turn, the team lead by Mone Zaidi, another lead author of the study, had previously described how blocking FSH action with a targeted antibody (FSH-Ab) reduced osteoporosis, prevented fat gain, and increased thermogenesis in mice.

In this collaborative study, the authors sought to further clarify the mechanism by which FSH may drive AD, and to assess whether blocking FSH with FSH-Ab could specifically block this effect.

First, the authors evaluated the effect of FSH-Ab in 3xTg-AD mice, a mouse model of AD. These mice display features of AD that are exacerbated after ovariectomy. Treatment of ovariectomized 3xTg-AD mice with FSH-Ab (200 μg per mouse, every 2 days, intraperitoneally) for 8 weeks inhibited plaque and neurofibrillary tangle formation. Treatment also inhibited increases in expression and activation of the C/EBPβ/AEP pathway induced by ovariectomy, APP and tau cleavage, and tau phosphorylation, which is a hallmark of AD. It also reversed ovariectomy-induced spatial learning and memory retrieval deficits. These results were replicated in *APP/PS1* mice, a different AD mouse model.

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Further experiments showed mRNA expression of FSH receptor (*FSHR*) in human cortex, human neuroblastoma SH-SY5Y cells, mouse cortex and hippocampus, and in rat cortical neurons. This confirms the ubiquity of pituitary hormone action, previously thought to act only on endocrine targets.

In SH-SY5Y cells, treatment with FSH increased C/EBPβ and AEP activity and APP and tau cleavage. These results were confirmed in vivo, in female 3xTg mice (aged 2.5 months) injected with recombinant human FSH. C/EBPβ haploinsufficiency in *Cebpb*$^{+/-}$ 3xTg mutant mice resulted in lower AEP activation and APP and tau cleavage at baseline and in response to FSH, corroborating the essential role of C/EBPβ in mediating the AD pathology induced by FSH.

Mechanistically, FSH activates AKT that phosphorylates SRPK2, which leads to the activation of the C/EBPβ/AEP axis and to the subsequent proteolytic cleavage of APP and tau.

“From the mechanistic point of view, this finding once again validates our theory that C/EBPβ/AEP signalling is a core driver for neurodegenerative diseases,” says Ye. “From the pharmacological intervention angle, neutralizing FSH, blockade of FSHR or inhibition of AEP may all provide promising therapeutic targets,” he adds. Ye points out that FSHR is a GPCR, which is easy to target. The team has also identified an AEP inhibitor, currently under IND-enabling study for AD and osteoporosis.

Zaidi’s team has now developed a humanized monoclonal antibody against FSH that they intend to test in people in early clinical studies within the next two years. “Our ambitious goal is to treat three diseases of public health magnitude — osteoporosis, obesity and AD — with a single agent,” he concludes.

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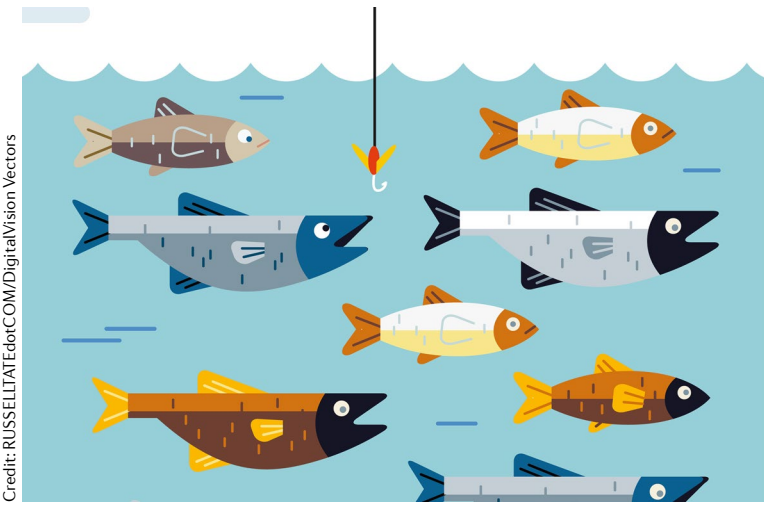

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