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Mini Review

組織・神経解剖学ハイライト

No. 1

肥満・老化制御中枢としての視床下部：免疫-神経内分泌クロストークと視床下部神経新生

Hypothalamus as a controlling centre for obesity and ageing : Immune-neuroendocrine crosstalk and adult hypothalamic neurogenesis

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Hypothalamus is an autonomic centre for body homeostasis. Despite its physiological function in food intake, energy balance and so on, it remained obscure how hypothalamus controls ageing and its related diseases such as obesity/pre-diabetes. Recent studies showed that neural stem cells reside in adult hypothalamus, and that adult hypothalamic neurogenesis seems to be a response to environmental conditions, implying its physiological role in homeostatic responses.

Cai's group extended the view and further explored the molecular basis of adult neurogenesis in the hypothalamus[1]. They have suggested that chronic high fat diet (HFD) induces IKKβ/NF-κB activation in microglia, and that positive feed-forward activation of IKKβ/NF-κB and TNFα is involved in microglia-neuron cross talk. Accordingly, the microglial IKKβ/NF-κB activation results in the apoptosis of adult hypothalamic neural stem cells (NSCs) (Fig. 1). Neuronal differentiation of proopiomelanocortin (POMC) neurons in the hypothalamus was also impaired in HFD mice, due to the activation of Notch signalling (Fig. 1). Conversely, a dominant-negative IκBα that inhibits NF-κB rather promoted neuronal differentiation of adult hypothalamic NSCs. Importantly, constitutive activation of IKKβ/NF-κB led to obesity and pre-diabetes of adult mice. Together, IKKβ/NF-κB overactivation mediates an inflammatory response of hypothalamus and impairs adult hypothalamic neurogenesis of POMC-expressing anorexigenic neurons, leading to obesity and pre-diabetes.

Based on these findings, they further tested whether microglia-neuron cross talk in the hypothalamus also control systemic ageing[2]. They first showed that NF-κB activation occurs in an ageing-dependent manner. Using genetically engineered mice with either activation or inhibition of NF-κB, they next showed that NF-κB activation shortens the lifespan of mice, whereas its inhibition rather extended the lifespan. This NF-κB activation is attributed to the increase of activated microglia. Brain-specific knockout of IKKβ, an activator of NF-κB retarded ageing. Moreover, they discovered that ageing-dependent increase of NF-κB activation via Fos/Jun and protein kinase C (PKC) leads to the decline of GnRH expression in the hypothalamus. In contrast, a daily GnRH therapy counteracted ageing-dependent declines in adult neurogenesis, cognition, and muscle endurance (Fig. 2). Together, their studies highlight the impor-

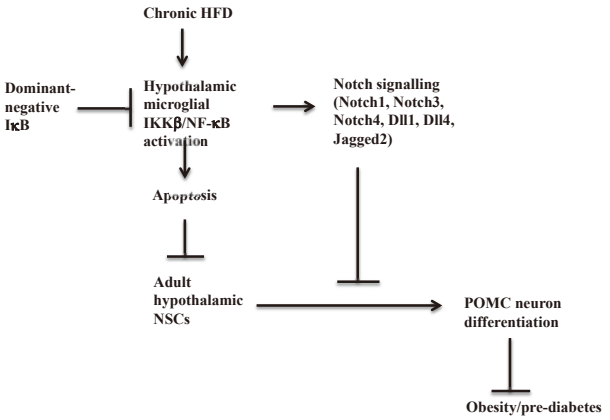

Fig. 1 Hypothalamic microglial IKKβ/NF-κB activation disrupts adult hypothalamic NSC, resulting in obesity/pre-diabetes (1)

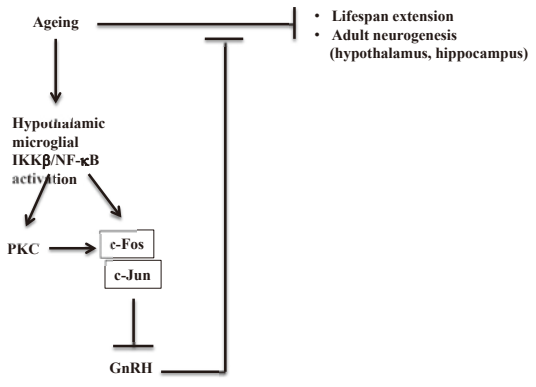

Fig. 2 Hypothalamic microglial IKKβ/NF-κB activation controls systemic ageing through the regulation of GnRH (2)

tance of hypothalamic inflammatory response for both ageing and obesity/pre-diabetes. Recent study also showed that Sirtuin1 (SIRT1), a key regulator for longevity and metabolism deacetylates NF-κB p65[3]. It is therefore possible that ageing-dependent decline of sirtuins might explain how NF-κB activation takes place in old animals.

Another line of evidence identified pSmad3 as a key regulator for obesity[4]. A blockade of TGFβ-pSmad3 signalling protects against obesity with reduced inflammatory response[4)5)]. Interestingly, SIRT1 deacetylates Smad4, thereby inhibiting TGFβ signalling[6]. However, in contrast with GnRH-treated mice discussed above, Smad3-null mice are less reproductive and smaller in body size. Further, at 4-6 months of age, they develop gastric tumors[7]. These studies clearly indicate that an ambient level of Smad3 signalling is necessary for lifespan extension. Future study will need to carefully examine the cross talk of sirtuins, NF-κB, and Smad3 not only in ageing and obesity but also in tissue homeostasis of other organs such as gonads and intestines.

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