Inflaming Hypothalamic Neurons Raises Blood Pressure

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Obesity and hypertension are strongly associated, and neural dysfunction has been implicated in both. The hypothalamus integrates signals regulating blood pressure and energy homeostasis. A recent paper in *Nature Medicine* (Purkayastha et al., 2011) suggests that obesity and hypertension are caused by inflammation in distinct hypothalamic neuronal populations.

The rising prevalence of obesity is a serious public health problem, particularly in the U.S. Excess fat mass is associated with increased cardiovascular morbidity and mortality in part because it induces hypertension (Esler et al., 2006). Moreover, obesity is a major risk factor for resistant hypertension, defined as patients who have uncontrolled blood pressure despite use of three or more antihypertensive medications (Persell, 2011). Although the mechanisms involved in the pathogenesis of obesity-associated hypertension are not completely understood, it is increasingly clear that central neural mechanisms via activation of the sympathetic nervous system play a pivotal role (Rahmouni et al., 2005; Esler et al., 2006). There is also increasing epidemiological, clinical, and experimental evidence that inflammation is causally linked to both obesity (Gregor and Hotamisligil, 2011) and hypertension (Zubcevic et al., 2011), and the transcription factor nuclear factor kappa B (NF-κB) and its upstream regulator kappa B kinase beta (IKKβ) have emerged as key players (Figure 1). The fundamental importance of the IKKβ/NF-κB axis in the pathogenesis of obesity is well documented, particularly in peripheral tissues (Gregor and Hotamisligil, 2011; Lumeng and Saltiel, 2011). Recently, activation of the IKKβ/NF-κB axis in a subpopulation of hypothalamic neurons has been shown to play a key role in energy homeostasis and obesity (Zhang et al., 2008).

The importance of the central nervous system, particularly the hypothalamus, in blood pressure regulation, along with the established links between obesity and hypertension, raises the question of whether hypothalamic IKKβ/NF-κB signaling is involved in blood pressure regulation. Cai and colleagues (Purkayastha et al., 2011) address this question using a series of elegant gain- and loss-of-function experiments. Their data suggest that activity of IKKβ/NF-κB in hypothalamic neurons does indeed regulate arterial pressure. Virally or pharmacologically mediated upregulation of IKKβ/NF-κB activity in the mediobasal hypothalamus causes a significant elevation in arterial pressure in mice. Conversely, blockade of mediobasal hypothalamic IKKβ/NF-κB activity with a virus expressing a dominant-negative mutant of $I_\kappa B\alpha$ prevents the hypertension caused by diet-induced obesity, a condition associated with upregulation of hypothalamic NF-κB activity (Zhang et al., 2008). This viral treatment has no effect on basal arterial pressure in lean mice.

One of the most intriguing observations of the study is that the effects on arterial pressure resulting from modulating hypothalamic IKKβ/NF-κB activity appear unrelated to changes in body weight and adiposity, suggesting a dissociation between the hypothalamic mechanisms controlling energy homeostasis and arterial pressure in obesity. In the authors' previous study, alterations in hypothalamic IKKβ/NF-κB signaling caused dramatic changes in body weight in obese mice (Zhang et al., 2008). Importantly, those studies were performed over a period of several weeks. In contrast, the protocols employed in the *Nature Medicine* study were short-term, thus resulting in insignificant changes in food intake and body weight. This provided the opportunity to examine effects on cardiovascular endpoints without confounding changes in body weight. The activity of the sympathetic nervous system was identified as a key mediator of the effect of hypothalamic IKKβ/NF-κB signaling on arterial pressure. This is based on several observations, including spectral analysis of radiotelemetry recordings of arterial pressure and heart rate, changes in plasma catecholamine levels, and the efficacy of pharmacological blockade of α-adrenergic receptors to prevent the arterial pressure elevation induced by upregulation of hypothalamic IKKβ/NF-κB activity. These findings are in line with the emerging role of the mediobasal hypothalamus in sympathetic nerve regulation (Harlan et al., 2011). Furthermore, these findings are consistent with the well-established importance of neurogenic mechanisms in the pathophysiology of obesity-associated hypertension (Esler et al., 2006).

The investigators next delineated the specific neuronal population within the mediobasal hypothalamus responsible for modulating the arterial pressure effect of IKKβ/NF-κB. In so doing, they focused on two neuronal populations located in the arcuate nucleus that receive and integrate signals from the periphery, including leptin and insulin, i.e., neurons expressing pro-opiomelanocortin (POMC) and neurons

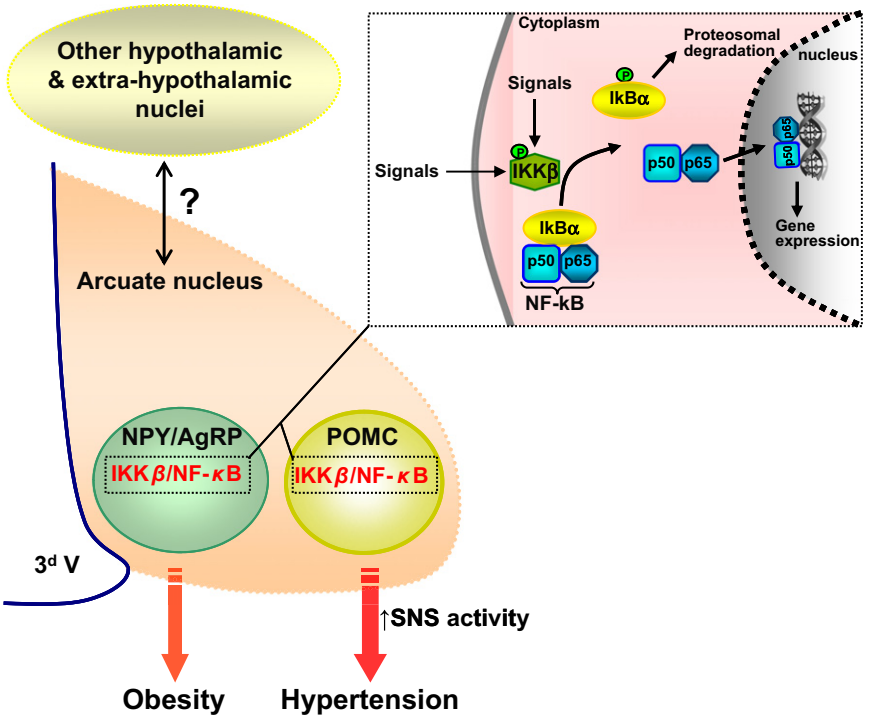

Figure 1. Differential Involvement of IKKβ/NF-κB Signaling in Neurons of the Hypothalamic Arcuate Nucleus in the Pathogenesis of Obesity and Hypertension

There are two key neuronal populations in the arcuate nucleus: the pro-opiomelanocortin (POMC) neurons and the neuropeptide Y (NPY) neurons, which also express agouti-related protein (AgRP). IKKβ/NF-κB axis in the orexigenic NPY/AgRP neurons is required for the development of diet-induced obesity. On the other hand, IKKβ/NF-κB axis in the POMC neurons mediates the obesity-associated hypertension via activation of the sympathetic nervous system (SNS). The inset shows the pathway for IKKβ/NF-κB signaling that leads to the modulation of gene expression. Under basal conditions, inactive NF-κB resides in the cytoplasm bound to the inhibitory protein $I_KB\alpha$. Phosphorylation of $I_KB\alpha$ causes it to be released from NF-κB, ubiquitinated, and degraded in the proteasome. The phosphorylation of $I_KB\alpha$ is facilitated by the IκB kinase IKKβ, which is itself activated via serine phosphorylation in response to activation of cell surface receptors such as IL-1β, TNFα, or the toll-like receptors or in response to reactive oxygen species. Free of I_KB, NF-κB can then translocate to the nucleus, where it modulates the transcription of its target genes.

expressing neuropeptide Y/agouti-related protein (NPY/AgRP) (Figure 1). They first examined the arterial pressure response to acute inflammation caused by intracerebroventricular injection of TNF-α and then assessed the response to high-fat diet. Interestingly, Cre-LoxP-mediated ablation of IKKβ in POMC neurons, but not NPY/AgRP neurons, resulted in a blunting of the pressor effects caused by acute activation of the IKKβ/NF-κB axis by TNF-α. Moreover, while ablation of IKKβ from POMC neurons did not alter basal arterial pressure levels in lean mice, it was sufficient to prevent the development of hypertension caused by high-fat feeding. These results suggest that activation of the NF-κB pathway in POMC neurons in response to inflammatory stimuli is required to raise arterial pressure. The data also imply that activation of the inflammatory pathway in POMC neurons may mediate the arterial pressure elevation in obesity (Figure 1).

The contribution of IKKβ in NPY/AgRP neurons in obesity-associated hypertension is a question that remains unanswered and deserves further investigation. The authors provide indirect evidence that this signaling pathway in NPY/AgRP neurons may not be required for the blood pressure elevation that accompanies obesity. This is based on their finding that selective ablation of IKKβ from POMC neurons completely reversed obesity-induced hypertension despite the preservation of IKKβ in NPY/AgRP neurons. Obtaining direct evidence for the contribution of IKKβ/NF-κB signaling in NPY/AgRP neurons to obesity-associated hypertension is challenging because mice bearing a targeted deletion of IKKβ from NPY/AgRP neurons are resistant to obesity induced by high-fat diet (Zhang et al., 2008).

The study by Cai and colleagues highlights the importance of arcuate nucleus IKKβ/NF-κB signaling in arterial pressure regulation and in obesity-associated hypertension. Important next steps will include determining the upstream signals driving activity of the hypothalamic IKKβ/NF-κB axis, the involvement of NF-κB target genes and pathways, and the neural circuits through which they act. For instance, how do other hypothalamic and extra-hypothalamic cardioregulatory nuclei interface with IKKβ/NF-κB pathways in POMC neurons in obesity-associated hypertension? This is critical because POMC neurons form complex circuits with other energy homeostasis and cardioregulatory centers of the brain (Ghamari-Langroudi et al., 2011). Finally, it will be important to determine whether the involvement of the IKKβ/NF-κB axis in POMC neurons is limited to obesity-associated hypertension or applies to other forms of hypertension.

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