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Versatile role of NELL2 in brain

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Commentary

A precise communication between the central nervous system (CNS) and the periphery is fundamental in achieving a fine balance between energy intake and expenditure. When this crosstalk is impaired, obesity, a metabolic state characterized by excess fat accumulation in peripheral tissues, occurs. Obesity is the foundation for several metabolic syndromes, such as type 2 diabetes, stroke, and hypertension, all of which are leading causes of mortality. It is no doubt that multiple regions of the brain participate in the regulation of energy homeostasis. However, the hypothalamus has long been highlighted in metabolism regulation as it forms a coherent whole for direct detection of circulating metabolic signals, integration of metabolic information obtained from periphery and other CNS regions, and production of adequate molecular and behavioral outcomes that preserve whole body energy homeostasis [1-4].

NELL2, a mammalian neural tissue-enriched EGF-Like Like protein 2, is a newly identified secreting molecule from neurons as a neurotransmitter [5,6]. Although NELL2 is broadly distributed throughout the mammalian brain, we previously reported that its expression is brain region-specific and cell type-dependent [5]. Importantly, NELL2 is produced relatively high in the hypothalamus compared to other brain regions [5,7]. In addition, core hypothalamic nuclei known to play a critical role in metabolism regulation, such as the paraventricular nucleus, ventromedial nucleus, and the arcuate nucleus of the hypothalamus (ARC) are also a main site of NELL2 production [5,7]. This anatomical observation allowed us to hypothesize a potential function of NELL2 in whole body metabolism regulation.

Recently, we reported "A Role of Central NELL2 in the Regulation of Feeding Behavior in Rats" [7]. In this work, we demonstrated a role for central NELL2 in rodent feeding behavior and energy homeostasis, using an antisense oligonucleotide-dependent gene blocking system for an acute ablation of NELL2 biosynthesis in adult rodent brain in vivo. Importantly, adult rats with acute hypothalamic NELL2 ablation showed a significant reduction in body weight gain under ad libitum, normal chow feeding conditions when compared to controls. This response was attributed to a reduction in food intake behavior. On the other hand, blockade of NELL2 in the hypothalamus did not affect animal's water intake, nor produced sickness behavior. These behavioral studies have demonstrated a role of hypothalamic NELL2 signaling in feeding behavior. Interestingly, short-term food intake followed by overnight fasting was not differ between experimental and control groups, suggesting that NELL2 signaling in the hypothalamus is specific for ad libitum appetite behavior. We also observed in this study that mRNA level of NELL2 expression in the hypothalamus was elevated during fasting, when compared to a fed state. Therefore, it is likely that central NELL2 is responsible for an orexigenic mechanism in rodents.

Anatomical verification revealed that NELL2 is produced both in neuropeptide Y (NPY) and proopiomelanocortin (POMC) cells in the ARC, both of which are critical in metabolism regulation through functional opposition [7]. Therefore, we also investigated whether NELL2 signaling is associated with gene expression of NPY and POMC. NELL2 did not affect a gene expression of either NPY nor POMC. However, this is not surprising because NELL2 is a neurotransmitter, not a transcription factor, indicating that it works as an extracellular signaling molecule for cells that express the NELL2-specific receptor. In line with this, recent work using a co-culture system in which NELL2 overexpressing cells were co-cultured with rodent CNS tissue explants, identified NELL2 specific receptors in the CNS [8]. Following NELL2 release, axonal projections towards NELL2 positive cells in a CNS tissue explant were disrupted. This chemo-repulsive action of NELL2 was ablated when the CNS tissue was replaced with an explant from a robo3 knock out animal. This clearly demonstrates that robo3 receptor is a counterpart to NELL2 [8]. Our unpublished data also revealed that cells overexpressing NELL2 had prolonged projections, while blockade of NELL2 caused shortening of projections. Therefore, it is reasonable to conclude that NELL2 may play a pivotal role in communication between neuronal cells, and may have dominant projection power over adjacent cells that receive NELL2 signals through the robo3 receptors. With this regard, NELL2 may play a key role in controlling metabolic dependent NPY/POMC neuronal plasticity and activity. Further studies using anatomical and molecular verification are necessary to address this issue.

NELL2 is a highly conserved protein among species with its molecular characteristics common in extracellular molecules [6,9,10]. NELL2 has multiple functional domains, including a thrombospondin-1 like domain, von Willebrand factor C, and several EGF-repeats, all of which are known to impact brain development through regulation of synaptic growth, formation and remodeling [10]. Our group first identified NELL2 as an estrogen receptor-dependent signaling molecule in the rodent brain [11]. Using in vivo and in vitro studies we have shown that production of NELL2 is positively associated with estrogen. More importantly, NELL2 signaling is critical in the postnatal development of the hypothalamic nuclei important in male sexual behavior through mediation of estrogen-dependent intercellular $Ca2^{+}$ signaling [12]. Independent studies have also revealed that NELL2 signaling is necessary for normal onset of female puberty and cyclicity [13]. Taken together, our group has demonstrated a versatile role for NELL2 in postnatal brain development through

modification of neuronal function and fate, including vesicle transport and release, neuronal protection, survival and aggregation [14-19].

Concluding Remark

As mentioned above, our recent report demonstrates a role for hypothalamic NELL2 in metabolism regulation [7]. NELL2 expression in the hypothalamus is affected by metabolic state, and acute ablation of hypothalamic NELL2 production in adult rats attenuates a daily body weight gain under normal chow condition. This occurs independent of changes in NPY and POMC gene expression. Neuronal NELL2 is a secreted extracellular signaling molecule that acts in both an autocrine and/or paracrine manner. With this regard, identification of NELL2-specific metabolic receptors in the hypothalamus is necessary, although robo3 is recently identified as a NELL2 counterpart in the spinal cord. In addition, further studies to uncover central NELL2 function in development and/or protection of high fat diet-induced obesity and metabolic syndromes are in urgent demand. A genetically modified animal model to conditionally or acutely knock down NELL2 expression using the Cre-loxp system is now available and will be beneficial to region-specific and target cell-dependent shut down of NELL2 production in the hypothalamus [8]. This will be a powerful tool in studying central NELL2 function in whole body energy homeostasis.

Conflicting Interests

There is no conflict of interest.

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