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Editorial: Endocrine Modulators of Neurological Processes: Potential Treatment Targets of Pediatric Neurological Diseases

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Editorial on the Research Topic

Endocrine Modulators of Neurological Processes: Potential Treatment Targets of Pediatric Neurological Diseases

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INTRODUCTION

Over the last decade, significant progress has been made in understanding the effects of neuroendocrine regulators, represented by brain gut peptides, leptin, melatonin, as well as ketogenic diet (KD), on brain development, brain injury repair and early warning. This Research Topic contains 10 articles, contributed by 40 authors, from 17 countries (plus 28 experts participating in the review and editing), focusing on most recent understanding of the effects of neuroendocrine regulators on pediatric neurological diseases, including the predictive value of ghrelin, leptin, and other adipokines in the early diagnosis and intervention on pediatric neuropathy, the progress of basic research and the potential translational medicine value, etc.

Gastrointestinal peptides play important roles by regulating feeding and energy homeostasis. Ghrelin is a multifaceted gut hormone that is famously known as a "hunger hormone," just the opposite of cholecystokinin (CCK), which is referred to as a "satiety factor." Both hormones act *via* the peripheral vagal afferent and interact to modulate feeding regulation (1). The anticonvulsant effects of ghrelin and CCK have been reported (2, 3). Notably, ghrelin is expected to be an effective therapy for lean patients with cachexia caused by chronic heart failure, anorexia nervosa, and

functional dyspepsia (4). In this Research Topic, Marchiò et al. evaluated ghrelin and growth during 1 year of ketogenic diet (KD). They examined a small cohort of six children (two males and four females, age range 3–10.4 years) affected by refractory epilepsy, who received the KD as add-on treatment. The results showed that ghrelin plasma levels are consistently reduced in children with refractory epilepsy and maintained on the KD. This change was associated with low growth indexes in the majority of patients.

Although the mechanism of KD's anti-epileptogenic and neuroprotective effects has been studied in recent years (5, 6), there is still a lack of spectral molecular expression research. Here a proteomics study by Zheng et al. analyzed the effects of KD against lithium chloride/pilocarpine-induced status epilepticus (SE) in rats. Seventy-nine proteins in hippocampus showing a significant change in abundance between SE and control (Ctr) groups were reciprocally regulated in the SE + KD group compared to the SE group (i.e., the seizure-induced change was reversed by KD). Of these, five (dystrobrevin, centromere protein V, oxysterol-binding protein, tetraspanin-2, and progesterone receptor membrane component 2) were verified by parallel reaction monitoring. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis indicated that proteins of the synaptic vesicle cycle pathway were enriched both among proteins differing in abundance between SE and Ctr groups as well as between SE + KD and SE groups.

Chen et al. investigated the effects of different zinc concentrations in the diet on long-term neurobehavioral and seizure thresholds following lithium chloride/pilocarpine-induced developmental seizures. They found that zinc supplementation for 4 weeks significantly improved injury-related changes, and rescued abnormalities in GPR39, ZnT-3, and MBP expression in the hippocampus, which suggests that the role of zinc ions in developmental convulsive brain injury may not be purely excitotoxic as previously thought (7–9), but may play a protective role in the brain as mentioned earlier (10). In a perspective article by Doenyas, a more comprehensive approach termed the "gut-immune-endocrine-brain" axis, is taken, based on which a personalized treatment plan for autism spectrum disorder (ASD) is presented.

Another clinical Cross-Sectional Study by Chen et al. in the present Research Topic investigated the association among plasma adipokines, mainly leptin, visfatin, adiponectin, or IL-6, and the prognosis of febrile seizures (FS). The main findings were that serum adiponectin and IL-6 levels were significantly higher in the FS group than in the FC and HC groups, while there was no statistical difference between the FC and HC groups, indicating that higher plasma levels of IL-6 and adiponectin could serve as an additional biomarker in the early treatment or follow-up of FS children.

Melatonin is an indoleamine secreted by the pineal gland. It can be used for the treatment of children with developmental disorders, such as ASD and attention deficit/hyperactivity disorder to improve their sleep disturbance (11, 12). Animal experiments and limited human data have confirmed the neuroprotective effect of melatonin on hypoxic-ischemic (HI) or developmental seizure-induced excitotoxic brain damage (13–15). Here, two studies have explored the molecular signaling mechanism of the neuroprotective effect of melatonin through the *in vitro* glutamate excitotoxic injury model and the *in vivo* cerebral palsy model. Wang et al. investigated the impact of melatonin on the parameters of glutamate cytotoxicity in mouse HT22 hippocampal neurons and tested the hypothesis that melatonin confers neuroprotective effects *via* mitochondrial oxidative stress/autophagy signaling. The findings indicate that melatonin exerts neuroprotective effects against glutamate-induced excitotoxicity by reducing mitophagy-related oxidative stress and maintaining mitochondrial function. Sun et al. used plppr5 knockout (plppr5-/-) mice and their wild-type littermates to establish a model of HI injury to further explore the effects of melatonin on brain injury and the role of plppr5 in this treatment in an HI model, which mainly focuses on cognition, exercise, learning and memory. They found that plppr5 knockout aggravated HI damage and partially weakened the neuroprotective effect of melatonin in some aspects (such as novel object recognition tests and partial nerve reflexes).

Interactions between the brain and distinct adipose depots have a key role in maintaining energy balance, thereby promoting brain development, among them, leptin play a key role (16). Recently, there has been renewed interest in the role of leptin in repairing developmental brain damage (17, 18). Here, a review article by Fujita and Yamashita summarize novel functions of leptin in animal models of neurodegenerative diseases. Specifically, they focus on the emerging evidence for the role of leptin in non-neuronal cells in the central nervous system, including astrocytes, microglia, and oligodendrocytes, which provides helpful information to establish therapeutic strategies to address the neurological diseases.

In addition, the study by Zhao et al. explored the significance of the α2 isoform of Na+/K+-ATPase in the regulation of the electrophysiological properties of skeletal muscle cells by β-Catenin. The review article by Wu et al. discussed the emerging roles of long non-coding RNAs in chronic neuropathic pain.

In conclusion, the present clinical and basic studies allow us a better understanding of the effects of endocrine modulators on pediatric neurological diseases. We hope that the information gathered from this Research Topic will help promote clinical translational medical research to better prevent and treat these injuries in the near future.

AUTHOR CONTRIBUTIONS

HN wrote the draft. GB, DU, and AC reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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