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Attention Deficit Hyperactivity Disorder

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Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, which is estimated that approximately 5% of children are afflicted [1]. ADHD subjects experience difficulty especially in adapting school life, which results in emerging worldwide problems. The symptoms of ADHD consist of attention deficit, hyperactivity and impulsivity. In general, it is suggested that hyperactivity and impulsivity wane as afflicted subjects grow into adulthood, whereas attention deficit persists into even adulthood [2].

The pathogenesis of ADHD is thought to involve all of genetic, environmental and psychosocial factors. In genetic aspects of ADHD, the genetic polymorphisms of dopamine D1 [3], D4 [4, 5], and D5 [4] receptor and dopamine transporter [6] are suggested. Environmental factors, such as antenatal maternal alcohol consumption [7], smoking [8], and exposure to toxicants including polychlorinated biphenyls [9], during pregnancy are suggested to increase the risks of ADHD in offspring. Moreover, associations of increased prevalence of ADHD with low family income [10, 11] and insufficient nurture during early development [11, 12] are often reported.

A current therapeutic strategy of ADHD primarily depends on pharmacological treatments. The widely prescribed therapeutic agents are psychostimulants, such as methylphenidate, pemoline and dextroamphetamine [13]. However, these therapeutic agents have substantial side effects including insomnia or irritability [13], and thereby better pharmacotherapeutic drugs that can alternate to the currently prescribed ones is essential. Accordingly, my research has been focusing on development of a new pharmacotherapeutic strategy using natural products for treatments of ADHD symptoms. In this research, I have been employing *in vivo* animal model and *in vitro* cellular system approaches.

One of the animal models for ADHD, which is thought to be the best model, is spontaneous hypertension rats (SHR) [14, 15]. Nevertheless, SHR still have many problems that fail to represent all aspects of ADHD. For instance, SHR exhibits long-term memory deficits [16], although ADHD children usually do not show impairments in learning and memory. In addition, although ADHD symptoms dynamically change across development, such as waning of hyperactivity and impulsivity into adulthood, such developmental dynamics are not observed in SHR. Indeed, ADHD subjects are also not always associated with hypertension. A lack of a better animal model of ADHD, especially the one that mimics developmental aspects of ADHD, have made difficult to understand the biological mechanisms that cause ADHD. I have recently developed a new rodent model of ADHD that has overcome this issue [17]. The habenula is the epithalamic brain area relaying inputs from the limbic system and basal ganglia and sending outputs to the midbrain nuclei where dopamine and serotonin neurons are located [18]. Because of its network connections linking the limbic system and basal ganglia to dopamine and serotonin neurons, the habenula plays important roles in motivation, reward, and cognitive function [18]. Whether and how habenula abnormalities impacted on neurodevelopment and consequent brain function had remained unknown. I addressed this question by conducting excitotoxic lesion of the habenula during a neonatal period in rats. This manipulation caused an assortment of behavioral alterations, hyper locomotion, augmented impulsivity, and impairments in sustained attention, which are similar to the symptoms of ADHD, in juvenile rats with neonatal habenula lesion compared to normal age-matched rats. Importantly, hyper locomotion and augmented impulsivity disappeared when neoantal habenula lesioned rats were tested in adulthood, whereas attention deficits remained even when these rats reached adulthood. Such developmental patterns of behavioral manifestations therefore resemble the dynamic changes of ADHD symptom over development. In addition, I also found that these neonatal habenula lesion-induced behavioral changes were normalized by amphetamine treatments with dose-dependent manner [17]. Further histological and biochemical analyses of brain tissues from neonatal habenula lesion rats unveiled that prefrontal cortical volume of neonatal habenula

lesion animals was smaller than that of control animals, and this alteration was observed regardless of the ages of animals (observed both in both juvenile and adult periods). This finding is consistent with the studies showing volumetric reduction of the prefrontal cortex area in ADHD subjects [19, 20]. Moreover, decreased expressions of both dopamine receptor D3 in the prefrontal cortex and dopamine transporter in the nucleus accumbens were observed in rats with neonatal habenula lesion, but these alterations were present in juvenile, but not adult animals. Collectively, it appears that dopamine receptor and transporter alterations in the cortico-striatal pathways may be associated with hyper locomotion and augmented impulsivity, whereas decreased volume of the prefrontal cortex may cause attention deficits with neonatal habenula lesion. Based on these observations, I have proposed that habenula abnormalities occurring during early brain development may be involved in the pathogenesis of ADHD.

In conclusion, using this novel animal model could be a useful tool for further investigation about development of novel therapeutic treatments with natural products for ADHD. We have been currently investigating a couple of natural products and their extracted substances that have been shown to affect the dopamine pathways, using both *in vitro* culture system to identify the molecular and cellular mechanisms of their actions and *in vivo* animal model to examine their effects on brain function.

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