Why is methylphenidate effective in ADHD?

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Abstract

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurobehavioral disorders. Methylphenidate (MPH) is a psychostimulant widely used for the treatment of ADHD. MPH is an inhibitor of dopamine transporter (DAT), and increases dopamine (DA) levels by inhibiting dopamine uptakes in patient brains. On the other hand, the involvement of NMDA type glutamate receptors (NMDARs) in the pathogenesis of ADHD has been also postulated. Magnetic resonance spectroscopy (MRS) study showed a decrease of combined glutamate/glutamine to creatinine ratio in the right anterior cingulated cortex in ADHD adults. In addition, a NMDA subunit gene polymorphism (GRIN2B rs2284411) has been reported to be an important predictor of MPH response in ADHD. Taken together, NMDAR functions are somehow disturbed in ADHD. However, the relationship between the increment of dopamine levels and the improvement of NMDAR functions is largely unknown. Recently, Shibasaki et al. have reported that DA
causes a functional reversal of glycine transporter 1 (GlyT1), causing astrocytes to release glycine. Glycine is a very important co-agonist for NMDARs and plays a role in treating ADHD by modulating the glutamatergic neurotransmission system through activating NMDARs. Thus, I postulate the following hypothesis. MPH blocks DAT and increases dopamine levels. The increment of dopamine levels activates astrocyte to release glycine. The increment of glycine levels improves NMDAR functions, resulting in improvement of ADHD.

**Key wards:** ADHD, dopamine, glycine, glycine transporter 1

**Introduction**

Methylphenidate (MPH) is a psychostimulant widely used for the treatment of attention-deficit/hyperactivity disorder (ADHD) [1]. ADHD is one of the most prevalent neurobehavioral disorders, affecting ~12-15% of children worldwide and persisting into adulthood in ~4-5% of individuals [2,3]. The symptoms of this disease include hyperactivity, impulsivity in motor, emotional and social response, a general lack of inhibition and pervasive inattention (DSM-V) [4]. Therapeutic dose of MPH effectively improves cognitive function and reduces hyperactivity [5]. MPH is an inhibitor of dopamine transporter (DAT), with Ki value for inhibition of dopamine (DA) uptake of 160 nM [6], indicating that MPH increases DA levels by inhibiting DA uptakes in patient brains. However, there remains unknown how the increased dopamine levels result in the improvement.

On the other hand, the involvement of NMDA type glutamate receptors (NMDARs) in the pathogenesis of ADHD has been also postulated [7,8]. Magnetic resonance spectorpy (MRS) study showed a decrease of combined glutamate/glutamine to creatinine ratio in the right anterior cingulated cortex in ADHD adults when compared with normal adult ADHD pathogenesis. In
addition, a NMDA subunit gene polymorphism (GRIN2B rs2284411) has been reported to be an important predictor of MPH response in ADHD [9].

Taken together, NMDAR functions are somehow disturbed in ADHD. However, the relationship between the increment of DA levels by MPH and the improvement of NMDAR functions is largely unknown. Thus, in this manuscript, I try to find the missing link between them.

**Hypothesis**

Recently, Shibasaki et al. have reported that DA induces glycine release from astrocytes, where DA causes a functional reversal of glycine transporter 1 (GlyT1), causing astrocytes to release glycine [10]. As glycine is a very important coagonist for NMDARs [11], the increment of glycine levels might improve NMDARs functions. Taken together, I speculate the following hypothesis.

Here, the hypothesis is as follows (Fig. 1):

1. MPH blocks DAT and increases DA levels.
2. The increment of DA levels activates astrocyte to release glycine via GlyT1.
3. The increment of glycine levels improves NMDAR functions, resulting in improvement of ADHD.

**Evaluation of the hypothesis**

**NMDARs and ADHD**

NMDARs are ionotrophic glutamate receptors that play fundamental roles in neurocognition and synaptic plasticity [13]. Animal studies suggest that the hypofunction of NMDARs may be an etiology of ADHD [14]. Impaired function of NMDARs in the prefrontal cortex and hippocampus has been also found in the rat model of ADHD [15,16]. Interestingly, spontaneous hypertensive rats (SHR) are a very good genetic model for ADHD [17]. Takita et al. have reported that NMDA-stimulated calcium uptake in prefrontal cortex tissues of SHR rats is lower than that of
controls [18]. In addition, Jensen et al. found that SHR rats expressed dysfunctional NMDAR subunit NR2B and had reduced synaptic transmission [19], suggesting that functional impairments in NMDARs may be involved in the underlying mechanisms leading to the abnormal behavior in SHR. Taken together, NMDAR functions are somehow disturbed in ADHD.

**DA enhances glycine release from astrocytes**

Astrocytes are known to express GlyT1 [20]. Although GlyT1 normally takes up glycine from the extracellular space, under a reversal mode, GlyT1 can release glycine from intercellular space to extracellular space [21]. In addition, an in vitro microdialysis-based capillary electrophoresis study in astrocyte cell line also showed glycine release from the astrocytes [22]. Interestingly, previous reports have demonstrated a functional expression of dopamine receptors D1, D3, D4 and D5 in astrocytes [23]. In addition, recently, Shibasaki et al. have reported that DA induces glycine release from astrocytes, where DA causes a functional reversal of GlyT1 via D5, causing astrocytes to release glycine [10]. These results indicate the possibility that increased extracellular DA levels by MPH stimulate D5, and D5 activation enhances reversal glycine release via GlyT1 from astrocytes, resulting in the increment of extracellular glycine levels.

**Glycine and NMDARs**

Glycine is a very important co-agonist for NMDARs and extracellular glycine levels are tightly controlled by GlyT1 expressed in astrocytes [11]. Thus, using GlyT1 inhibitors, such as sarcosine (also named N-methylglycine), extracellular glycine levels can be up-regulated. In fact, sarcosine is reported to enhance reversal release of glycine [21]. In addition, clinical studies indicate that sarcosine improves psychotic, depressive, and cognitive symptoms of schizophrenia [24,25]. In addition, many
lines of evidence have shown that sarcosine also improves memory and other cognitive domains [26-28]. Interestingly, also for ADHD, sarcosine improves symptoms of ADHD by blocking GlyT1 to enhance glutamatergic neurotransmission [29]. Therefore, controlling extracellular glycine levels might be very important for improving ADHD.

**Consequences of the hypothesis and discussion**

ADHD is one of the most prevalent neurobehavioral disorders. MPH is a psychostimulant widely used for the treatment of this disease. Here, I build the following hypothesis. MPH blocks DAT and increases dopamine levels. The increment of dopamine levels activates D5 in astrocyte, resulting in the enhanced glycine release. The increment of extracellular glycine levels improves NMDAR functions, resulting in improvement of ADHD. For clinical relevance, the adequate combinations of MPH treatment and GlyT1 inhibitors' treatment might be effective.

**Conflict of interest statement**

None declared

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Methylphenidate blocks dopamine transporters and increases dopamine levels

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The increment of dopamine levels activates astrocyte to release glycine

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The increase of glycine levels improves NMDAR functions, resulting in improvement of ADHD

Fig. 1 Basic concept