Age-dependent, lasting effects of methylphenidate on the GABAergic system of ADHD patients

Michelle M. Solleveld, Anouk Schrantee, Nicolaas A.J. Puts, Liesbeth Reneman, Paul J. Lucassen

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Abstract

Stimulants are the main pharmacological treatment for patients with attention-deficit/hyperactivity disorder (ADHD). Their current prescription rates are rising, both in children, adolescents and adults. Related to the impulse control phenotype, both preclinical and clinical studies have demonstrated lower γ-aminobutyric acid (GABA) levels in prefrontal brain regions in ADHD. Whereas stimulant treatment increases GABA levels, preclinical studies have suggested that stimulant treatment effects may be age-dependent.

As the long-term consequences of stimulant use in ADHD children and adolescents have so far been poorly studied, we used magnetic resonance spectroscopy to assess GABA + and glutamate + glutamine (Glx) levels in the medial prefrontal cortex (mPFC) of adult ADHD patients, both before and after an oral methylphenidate (MPH) challenge. Three groups were studied: 1) ADHD patients who were first treated with stimulants before 16 years of age, i.e. during periods of ongoing brain development (early-stimulant-treated, EST); 2) patients first treated with stimulants in adulthood (i.e. > 23 years) (late-stimulant-treated, LST), and 3) stimulant-treatment-naive (STN) ADHD patients.

Reduced basal GABA + levels were found in EST compared to LST patients (p = 0.04), while after an MPH challenge, only the EST patients showed significant increases in GABA + (p = 0.01). For Glx, no differences were found at baseline, nor after an MPH challenge.

First stimulant exposure at a young age is thus associated with lower baseline levels of GABA + and increased responsivity in adulthood. This effect could not be found in patients that started treatment at an adult age. Hence, while adult stimulant treatment seems to exert no major effects on GABA + levels in the mPFC, MPH may induce long-lasting alterations in the adult mPFC GABAergic system when treatment was started at a young age.