

## **ATTENTION DEFICIT AND BEHAVIORAL DISORDERS**

### **ALTERED ANANDAMIDE DEGRADATION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER**

Anandamide (AEA) metabolism was investigated in 15 drug-free boys with ADHD (aged 6.5-13 years) and 15 age- and gender-matched healthy controls, in a study at Università Tor Vergata, Rome, Italy. AEA, an endocannabinoid, reduces the activity of the dopamine transporter. The activity of fatty acid amide hydrolyse (FAAH), which is responsible for AEA degradation, was significantly decreased in lymphocytes from peripheral blood of subjects with ADHD. This finding suggests that AEA catabolism is dysregulated in ADHD, whereas the synthesis of AEA was unaltered. Stimulation of dopamine (DA) D2 class receptors inhibits FAAH activity and increases the level of AEA in the brain. A complex interaction between DA and the AEA endocannabinoid system (ECS) is found experimentally, and ECS is implicated in other DA-related disorders such as Parkinsonism. Dysfunction of the dopamine system is proposed to explain the clinical manifestations of ADHD. (Centonze D, Bari M, Di Michele B, et al. Altered anandamide degradation in attention-deficit/hyperactivity disorder. **Neurology** April 28, 2009;72:1526-1527).(Respond and reprints: Dr Diego Centonze, Clinica Neurologica, Università Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. E-mail: [centonze@uniroma2.it](mailto:centonze@uniroma2.it)).

COMMENT. The endocannabinoid system plays an important role in brain development (Fride E. **J Neuroendocrinol** 2008;20(suppl 1:75-81), and anandamide (arachidonylethanolamide [AEA]) impairs memory and attention by reducing the activity of the dopamine transporter system. An anandamide transporter inhibitor, 4-OH phenyl-arachidonamide (AM404), is found to reduce the hyperactive behavior elicited by a dopamine D2 receptor agonist in rat brain (Beltramo M et al. **Jrnl Neuroscience** 2000;20:3401-3407). Molecular genetic studies support the involvement of the dopamine receptor and dopamine transporter genes in the etiology of ADHD. Environmental factors such as prenatal exposure to nicotine, premature birth, head injury, and viral infections also play a role. (Millichap JG. **Pediatrics** 2008;121:e358-e365). Relation of dopamine deficits to fetal and perinatal stresses may explain the mechanism of environmental etiologies. (Swanson JM et al. **Neuropsychol Rev** 2007;17:39-59). Preterm birth and cerebral ischemia may contribute to deficient dopaminergic neurotransmission and symptoms of ADHD. Evidence of environmental mediators in ADHD are demonstrated in twin studies, affected twins having greater exposure to risk factors compared with unaffected co-twins. (Lehn H et al. **J Am Acad Child Adolesc Psychiatry** 2007;46:83-91). Gene-environment interaction is an important mechanism in the etiology of ADHD, some genes (DAT1) affecting the individual sensitivity to environmental factors. (Thapar A et al. **Brit J Psychiatry** 2007;190:1-3).

### **SLEEP DURATION AND BEHAVIORAL SYMPTOMS OF ADHD**

To evaluate the association of short sleep duration with behavioral symptoms of ADHD, a cross-sectional study of children born in 1998 in Helsinki, Finland, was conducted

by researchers at the Universities of Helsinki and Oulu, Finland. Sleep quality was measured using actigraphs, and the Sleep Disturbance Scale for Children and the ADHD Rating Scale IV were administered to parents. Of 280 children (134 boys, 146 girls) with a mean age of 8.1 years (range 7.4-8.8), those with a short average sleep duration (<7.7 hours) had higher hyperactivity/impulsivity and ADHD total scores, but similar inattention scores compared with children sleeping 7.7 to 9.4 hours or >9.4 hours. Short sleep duration remained significantly associated with hyperactivity/impulsivity when controlling for basic confounding variables and also for sleeping difficulties and somatic illnesses, but it was not related to inattention or the ADHD total score. Short sleep duration was not correlated with sleeping difficulties, but sleep-breathing disorder was significantly associated with hyperactivity/impulsivity, inattention, and ADHD total score. Parent-reported short sleep duration was not related to hyperactivity/impulsivity, inattention, and the ADHD total score. (Paavonen EJ, Raikkonen K, Lahti J, et al. Short sleep duration and behavioral symptoms of attention-deficit/hyperactivity disorder in healthy 7- to 8-year-old children. **Pediatrics** May 2009;123:e857-e864). (Respond: Dr Paavonen. E-mail: [juulia.paavonen@helsinki.fi](mailto:juulia.paavonen@helsinki.fi)).

COMMENT. Short sleep duration measured objectively with the actigraph and parent-reported sleeping difficulties are independently associated with increased risk of behavioral symptoms of ADHD. One third of children in the US are estimated to have inadequate sleep (Smaldone A et al. **Pediatrics** 2007;119(suppl 1):S29-S37). Questions regarding sleeping habits are important in the evaluation of children with ADHD, especially in relation to the symptoms hyperactivity/impulsivity and their association with short sleep duration or sleeping difficulties, such as sleep-breathing disorder and snoring. Short sleep duration is not correlated with the symptoms of inattention. A causal relation between sleep duration and behavioral symptoms is not established, but maintaining regular sleeping schedules may help to ameliorate the hyperactivity and impulsivity of ADHD. Sleep duration and sleeping difficulty studies are often inaccurate, relying heavily on parental reports, which are susceptible to bias. In a child with hyperactive behavior, excessive snoring should prompt referral to ENT, and sleeping difficulties may indicate the need for a polysomnograph. However, polysomnographic sleep scores are not related to academic functioning, IQ and neuropsychological test cores are powerful predictors of achievement. (Mayes SD et al. 2008). Inattentive symptoms are sometimes related to daytime sleepiness. (Willoughby MT et al. 2008).

Girls with ADHD generally have a greater frequency of the inattentive subtype than boys, but overall, boys outnumber girls with a 4:1 ratio for the ADHD-HI and 2:1 for ADHD-AD. (Wolraich ML et al. 1996). The preponderance of girls in the above study is unusual, but apparently, gender was not a modifying factor.

## **STRUCTURAL CEREBRAL CHANGES AND CONDUCT DISORDER**

Voxel-based morphometry was used to analyze structural MRI scans from 23 boys with callous-unemotional conduct problems (mean age 11 yrs 8 months) and 25 healthy controls, in a study at the Institute of Psychiatry, King's College, London, UK, and other centers in London and Germany. Both grey matter volume and concentration were examined, controlling for cognitive ability and ADHD. Boys with unemotional conduct problems showed increased grey matter concentration in the medial orbito-frontal and anterior