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Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD

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ABSTRACT

The neuroendocrine mediators that may contribute to ADHD (Attention deficit and hyperactivity disorder), serotonin and melatonin, are both thought to regulate circadian rhythms, neurological function and stress response. The objective of this study was to determine the effect of the chronic administration of prolonged release methylphenidate (PRMPH) on daily variations in blood serotonin and melatonin and on the excretion of 6-sulphatoxy-melatonin. A total of 179 children (136 males, 42 females) between the ages of 5 and 14 (9.70 ± 2.55) years were enrolled in a controlled quasi-experimental open clinical study. Of the sample, there were 136 Children with ADHD (based on DSM-IV-TR criteria), who were further grouped into subtypes, and the 42 siblings of the participants who did not ADHD patients. Blood samples were taken at 20:00 and 09:00; urine was collected between 21:00 and 09:00. In the ADHD group, the study protocol was repeated after 4.61 ± 2.3 months of treatment. Measurements included melatonin and serotonin by RIA and urine 6-S-aMT by ELISA. Factorial analyses were conducted by STATA 12.0.

Results: ADHD patients showed reduced morning serotonin with a daily profile that was different than the control group due to the predominance of nocturnal concentrations. PRMPH did not result in any significant changes. Melatonin and its daily profile did not differ between controls and the ADHD group with a diurnal rhythm showing higher morning levels that disappear after PRMPH administration. Melatonin was higher in children with predominantly hyperactive–impulsive/conduct disorder subtype. PRMPH resulted in a decrease in 6-S-aMT excretion for both ADHD subtypes.

Conclusion: Chronic treatment with prolonged release methylphenidate induces subtle changes in the daily fluctuations and concentrations of both serotonin and melatonin. Improvement in Children's Depression Inventory (CDI) scores was not related to a morning increase in serotonin.

Attention deficit/hyperactivity disorder (ADHD) is a neuro-developmental disorder (Nigg and Casey, 2005) that involves an apparent delay in the development of impulse control. The core symptoms of ADHD include inattention, hyperactivity and impulsivity that are long-lasting and atypical in comparison with people at a similar developmental level. The rate of comorbid disorders in this population is quite high, and children with ADHD subtypes have been found to have more severe depressive symptoms than in community control groups (Connor and Ford, 2012). Therefore, ADHD must be viewed in the context of what is developmentally appropriate. That is, clinicians must account for age-related changes in the neurobiology of children with ADHD, while also bearing in mind that genetically mediated neurological deficits can lead to secondary functional or psychological impairment that may not necessarily stem directly from the primary neural insult. Frontal and striatal abnormalities have been associated with ADHD. The underlying pathophysiology of ADHD may involve dysregulation of the noradrenergic frontocortical inhibition of dopaminergic striatal structures (Kelly et al., 2007; Wiltschko et al., 2010).

5-HT and melatonin perform a broad range of physiological functions. Serotonin participates in the regulation of emotional and behavioural control processes (Cools et al., 2008). Melatonin is

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a critical circadian synchroniser with a pleiotropic biologic signal that exerts multiple effects (Hardeland et al., 2012), including increasing tyrosine hydroxylase activity and activating dopamine receptors (Alexiuk and Vriend, 2007). The circadian rhythm of pineal melatonin secretion, which is controlled by the suprachiasmatic nucleus (SCN) (Stehle et al., 2011), is reflective of the mechanisms that are involved in the control of the sleep/wake cycle. It has been reported that approximately 25% of children with ADHD have some type of sleep disorder, such as delayed sleep phase syndrome (DSPS) (Walters et al., 2008). Melatonin is considered an effective therapy for DSPS (Bendz and Scates, 2010), as it can significantly advance the phase of the sleep/wake rhythm (Cardinali et al., 2012). Discontinuation of melatonin treatment usually leads to a relapse in sleep-onset insomnia; thus, clinicians may recommend continuing melatonin treatment even several years after symptom resolution (Hoebert et al., 2009).

Our hypotheses were that both serotonin and melatonin participate in neuroendocrine mechanisms that may underlie the clinical improvement observed during treatment with prolonged release methylphenidate (PRMPH). Consequently, the aim of this paper is to examine, for the first time, the diurnal fluctuations in blood levels of 5-HT and melatonin in ADHD patients before and after PRMPH.

Table 1
Somatometrics, vital signs, and haematological, biochemical and sleep data of the study groups at inclusion in the protocol.

	Control ($n = 42$)	ADHD ($n = 136$)	Statistics	
			t	p
Age (y)	10.35 ± 2.55	9.45 ± 2.52	2.111	0.036
Sex (M/F)	30/12	106/30	$chi^2 = 2.371$	0.124
Height (m)	1.47 ± 0.17	1.37 ± 0.17	3.441	0.001
Weight (kg)	44.179 ± 15.14	36.50 ± 15.35	2.793	0.007
BMI (kg/m^2)	19.81 ± 4.01	18.76 ± 4.17	1.384	0.169
HR (bpm)	80.39 ± 12.45	78.84 ± 10.62	0.707	0.481
SBP (mmHg)	105.95 ± 13.85	101.70 ± 14.05	1.621	0.107
DBP (mmHg)	65.17 ± 9.01	64.17 ± 13.05	0.444	0.658
Hb (g/L)	13.80 ± 1.02	13.87 ± 0.80	0.499	0.619
MCV (fl)	78.71 ± 8.62	79.08 ± 8.63	0.228	0.820
Iron (mg%)	83.68 ± 29.39	86.00 ± 30.97	0.399	0.691
Ferritin (ng/L)	37.40 ± 13.53	41.50 ± 19.79	1.172	0.243
TSH (UUI/L)	2.49 ± 1.30	2.89 ± 1.34	1.571	0.119
SOD	None	30 (23.07%)	–	–
Enuresis	None	16 (12.30%)	–	–
KBIT score	107.88 ± 12.29	103.99 ± 11.23	0.777	0.210

Data are expressed as mean ± SD. M: male; F: female. BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure. *t*: *t*-test for unrelated samples. SOD: sleep onset delay (<60' in all subjects). MCV: mean corpuscular volume; TSH: thyroid stimulating hormone; KBIT: combined punctuation of the Kauffman abbreviated intelligence test.

1. Materials and methods

1.1. Sample

Of the 226 children we evaluated in our Neuropediatrics, Neuropsychology and Early Intervention Service between September 2007 and May 2010, 178 children (136 males, 42 females) between the ages of 5 and 14 years (mean: 9.70 ± 2.55 y) were included in a prospective, controlled, quasi-experimental (lack of random assignment) open clinical study.

The sample consisted of two groups. A total of 136 children who met the DSM-IV-TR/ICD-9 criteria for ADHD and whose symptoms could not be better explained by another mental health disorder (American Psychiatric Association, 2002) were included in the ADHD group after completing the clinical protocol. The DSM-IV-TR and ICD-9 require the presence of at least 6 out of 9 behavioural features for at least 6 months. These features must be present in all settings, have their onset prior to the age of 7 and cause significant distress or impairment. Upon the inclusion of an ADHD patient in the study, we included a control subject. We requested that the parents of patients involved in the study allow us to evaluate one of the subjects' siblings, if the child had any, for the study protocol. Siblings or unrelated subjects had to meet the following requirements to be eligible for inclusion: 1) similar age (within 1 year); 2) absence of acute or chronic disease; and 3) adequate educational performance. A total of 42 children were included in this group. The somatometric characteristics, vital signs, haematological and biochemical data of the study groups are given in Table 1.

In the ADHD group, 77% of children lived with both parents, 16% had divorced parents, and 8% of children were adopted. A total of 15 subjects were excluded because of previous or current treatment for epilepsy (8% of the sample; Supplementary Fig. S1), and 15% had a history of significant perinatal pathology without cerebral palsy but showed normal cognitive ability (KBIT test). Overall, 21% of the ADHD group had been treated with different formulations of methylphenidate for several months to years prior to being included in the clinical protocol.

1.2. Clinical method

For the purposes of the study protocol, each child with ADHD was assessed at least twice. The initial assessment was independent of subsequent inclusion in the study. We obtained a personal medical history and physical examination and distributed the following documents: a) DSM-IV-TR criteria assessment, to be completed by the child's teacher; b) EDAH scale (Spanish acronym of scale for Evaluation of Deficit of Attention and Hyperactivity), in duplicate, one for the teacher and the other for the child's parents; c) CDI (Children's Depression Inventory), to be completed by patients aged ≥8 years; and d) a sleep diary to be completed for 1 week. The EDAH contains some of the main American Psychiatric Association (APA) criteria recommended in the DSM-IV-TR to aid in identifying children with ADHD and conduct disorder (CD). It was translated into the Spanish language and administered in an easy-application format for examiners and responders. The test does not require complicated commands. The EDAH test also includes a questionnaire for teachers. The EDAH questionnaire is a 20-item scale for teachers (Farré-Riba and Narbona, 1997) that provides a structured observation by teachers that is divided into two 10-item subscales for ADHD and conduct disorder, respectively. The cut-off point (95th percentile) for fulfilling the criteria for ADHD hyperactivity–impulsivity subtype or ADHD attention deficit subtype is ≥10, while the cut-off for fulfilling CD criteria is ≥11. In cases presenting with both conditions (ADHD combined type), the cut-off point is ≥18, and for "global" disorder the cut-off is ≥30. According to EDAH punctuations, the ADHD group was sub-classified into two clinical subgroups as follows: children with predominantly attention deficit (PAD; if AD > 9; HI < 10; and total punctuation <30) and children with predominantly hyperactive–impulsive/conduct disorder (PHI/CD; if AD < 10; H > 9; and/or total punctuation >29).

The CDI (Kovacs, 1992) is a self-report of depression for children whose two subscales (Negative Mood and Negative Self-Esteem) consist of the items that are most unique to depression and least related to anxiety. For analytical purposes, we considered the sum of both subscales, with a cut-off of >17 points being considered pathological.

All children completed the Spanish version of the Sleep Diary of the National Sleep Foundation for one week, and the ADHD group completed the diary once again after treatment.

After completing the protocol and establishing a clinical diagnosis for each patient, we approached parents about their child's participation in the study. We also requested that parents allow us