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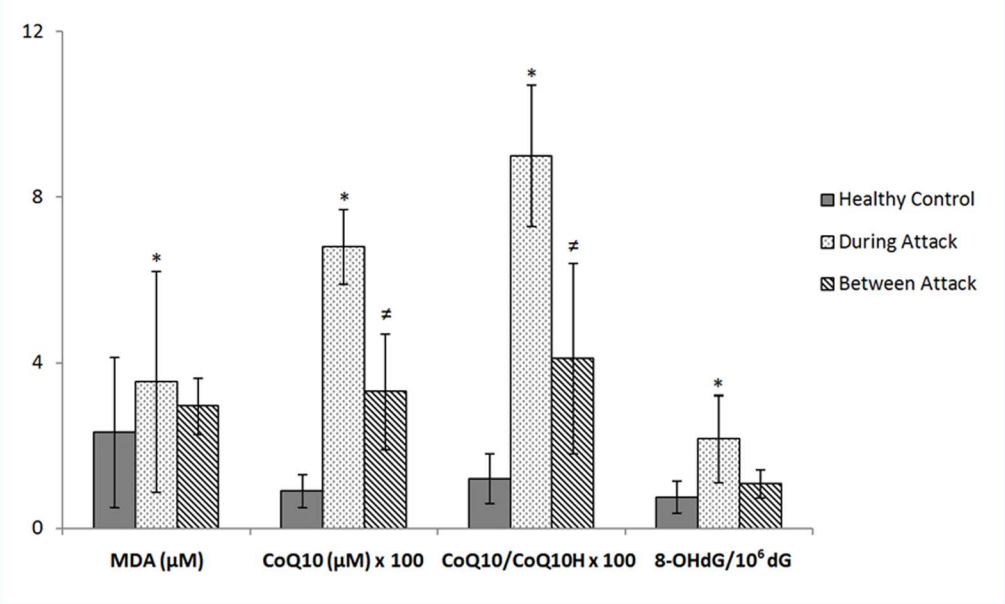

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Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

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B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

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RESEARCH ARTICLE

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Tryptophan-enriched antioxidant cereals improve sleep in children with autistic spectrum and attention deficit hyperactivity disorders

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Abstract

The intake of foods rich in tryptophan produces beneficial effects on sleep. The majority of children with neurological disorders like autistic spectrum disorder (ASD), cerebral palsy or attention deficit hyperactivity disorder (ADHD) have sleep problems. To evaluate the effect of tryptophan-enriched cereal intake on sleep of children with neurological disorders. Involving 7 children with ASD, 9 children with cerebral palsy and 6 children with ADHD. They carried a wrist actimeter to record activity. The second and fourth week children ingested control cereals at breakfast and dinner. The first, third and fifth week test cereals were administered at breakfast and dinner double-blinded, i.e., participants didn't know if they ingested tryptophan-enriched cereals or control cereals. Sleep efficiency improved in children with ASD after tryptophan-enriched cereals consumption at dinner. Sleep efficiency and wake bouts improved in children with cerebral palsy after consumption of tryptophan-enriched cereals at dinner. Assumed sleep improved in volunteers with ADHD after consumption of tryptophan-enriched cereals at dinner. Actual sleep time, sleep efficiency and immobile time improved in these children with ADHD after consumption of tryptophan-enriched cereals at dinner and when they ingested tryptophan-enriched cereals at breakfast and dinner too. In conclusion, intake of tryptophan-enriched cereals improves sleep of children with ASD and ADHD.

Keywords: Actigraphy**;** Child; Chronobiology disorders; Neurological disorders; Sleep; Tryptophan

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List of Abbreviations;

ADHD, attention deficit hyperactivity disorder; **AFTEA,** Association of Families of People with Autistic Spectrum Disorder from Cáceres; **APNABA**, Association of Parents of Children with Autism from Badajoz; **ASD**, autistic spectrum disorder; **ASPACEBA**, Association of Cerebral Palsy from Badajoz; **DSM-5,** diagnosis and statistical manual of mental disorders; **EEG,** electroencephalographic; **OSAS,** obstructive sleep apnea syndrome

Introduction

Sleep problems are usual on children with neurological disorders. 40% of children that have sleep problems are children that have neurological disorders (Muratorio et al., 1984). Fifty one percent of them have big problems to get sleep overnight as a consequence of their high activity at night. This fact causes sleep peaks and low activity during the day, thereby these patients show sleep-wake reversal pattern (Zucconi and Bruni, 2001). Children with neurological disorders like autistic spectrum disorder (ASD), cerebral palsy or attention deficit hyperactivity disorder (ADHD) are three groups with high risk of having sleep problems.

ASD is associated with aggressive behaviour, developmental delay and a high level of anxiety (Polimeni et al., 2005). Furthermore, it shows irregularities on sleep-wake rhythms, no fixed time for the sleep beginning and several naps spread along the day and the night (Miano et al., 2007). ASD patients have emotional disorders which cause them problems to sleep all night long (Malow and McGrew, 2008). They also spend too much time to fall asleep and they wake up many times during the night (Kotagal and Broomall, 2012). These children show low levels of melatonin (Johnson et al., 2009), which could be the explanation for sleep problems in ASD patients.

Children with cerebral palsy have a lot of chances to have sleep problems. An article published by Newman et al. (2006) showed that 23% of children with that disorder had sleep problems. In a paper published by Hemmingsson et al. (2009), sleep disorders were examined in children with physical disability (cerebral palsy, spina bifida and another disorders). That trial showed that 48% of these children had sleep problems. Cerebral palsy patients were the ones that suffered more sleep problems among all the patients that were studied (Wiggs and Stores, 1996). Having problems to sleep at night means problems during the day related to behaviour and school performance. These results are found in children with cerebral palsy and children with no disorders at all (Quine, 1991; Didden et al., 2002). Furthermore, these children have a high risk of having breathing problems like obstructive sleep apnea syndrome (OSAS) (Kotagal et al., 1994; Goodlin-Jones et al., 2008). Some scientific studies have shown low levels of melatonin in children with cerebral problems related to cerebral palsy (Pillar et al., 1998; Zucconi and Bruni, 2001). This could be associated with sleep problems that are usual in this kind of patients.

In case of children with ADHD some sleep disturbances have been described. Cortese et al. (2009) carried out a meta-analysis and they examined 16 sleep studies about children and teenagers with ADHD and they observed a higher bedtime resistance, more sleep onset difficulties, night awakenings, difficulties with morning awakenings, breathing disorders during sleep and daytime sleepiness compared with the controls. Sleep assessment using objective measures showed that children with ADHD had an increase in sleep latency and a low sleep efficiency. Besides, these children had less actual sleep time determined by actigraphy and an excessive somnolence in comparison with children without ADHD. By polysomnography, it has been observed an increase in sleep latency, a lot of wake bouts and daytime sleepiness in children with ADHD in comparison with healthy children (Choi et al., 2010).

Tryptophan is an essential amino acid and it is a precursor for serotonin. In darkness, tryptophan is a precursor for melatonin through the activation of N-acetyltransferase. The intake of tryptophan supplements decreases sleep latency because of an increase in serotonin. Melatonin synthesis improves sleep maintenance and sleep quality overnight (Bravo et al., 2013). When children with DSA took melatonin, sleep latency and actual sleep time improved. These results were confirmed by actimetry (Wasdell et al., 2008; Malow et al., 2012). Besides, tryptophan administration to ADHD children improves their behaviour (Nemzer et al., 1986) and melatonin administration increases sleep quality (Van Den Heuvel et al., 1997). Finally, scientific studies carried out in children with cerebral palsy have shown an improvement in sleep quality with melatonin administration (Braam et al., 2008; Wasdell et al., 2008).

This trial has been carried out based on the previous results obtained by our research group using tryptophan concentrations similar to those of breast milk (Cubero et al., 2005), therefore those concentrations aren't toxic. On the other hand, when elderly humans ingested tryptophan-enriched cereals at dinner, their sleep improved (Bravo et al., 2013). When newborns drank milk enriched with tryptophan, adenosine, uridine and medium chain triglycerides at night, an improvement in their sleeping patterns was observed.

This scientific study was made in harmony with the light/dark changing environment (Cubero et al., 2006). Considering sleep problems that children with neurological disorders have, the objective of our trial is to assess if the intake of tryptophan-enriched cereals can help to solve sleep problems of these children. This scientific study has the novelty of trying to improve sleep with a new functional food and not with another drug. These children already receive a lot of medication.

Materials and Methods

Sample

Most patients come from Association of Families of People with Autistic Spectrum Disorder from Cáceres (AFTEA, in Spanish), Association of Parents of Children with Autism from Badajoz (APNABA, in Spanish), Association of Cerebral Palsy from Badajoz (ASPACEBA, in Spanish) and Centre of Special Education Ntra. Sra. De la Luz from Badajoz too. The rest of patients come from medical consultation of specialists of this kind of disorders. The sample was composed of 7 children with autistic spectrum disorder (ASD) (10.43 ± 3.78 years; 3 boys and 4 girls), 9 children with cerebral palsy (10.22 ± 4.94 years; 5 boys and 4 girls) and 6 children with attention deficit hyperactivity disorder (ADHD) (8.67 ± 2.73 years; 3 boys and 3 girls), with a diagnostic based on Diagnosis and Statistical Manual of Mental Disorders, DSM-5 (2013). Children involved in the scientific study took more than 30 minutes to fall asleep and they had more than 3 wake bouts during the night. To carry out this trial their parents received some recommendations. For example, children had to stay in total darkness and without noise during the night. Besides, they had to have a regular schedule to go to bed and to get out of bed. It is recommended room temperature above 17-20 ºC and a relative humidity above 50-70% during the night. Children with DSA took their regular medicines during the scientific study: Risperidone, Aripiprazole and Paliperidone. Volunteers with cerebral palsy took low doses of Benzodiazepine, Tryhexyphenidyl, Polyethylene or Antihistamines. Patients with ADHD took Methylphenidate, long-acting Methylphenidate or Fluoxetine. It depends on state of mind. We didn't change their regular medicines during the study. We supplemented their diet with tryptophan-enriched cereals. Each patient was his or her own control in the trial.

Diets

It was administered 30 g of control cereals, which contained 22.5 mg of tryptophan, and it was administered 30 g of tryptophan-enriched cereals, which contained 60 mg of tryptophan. The scientific study took 5 weeks. The second and fourth week, children ingested control cereals at breakfast and dinner. The first, third and fifth week, cereals test were administered at breakfast and dinner double-blinded, i.e., participants and researches didn't know if they ingested tryptophan-enriched cereals or control cereals. These cereals were labelled with different colours by ORDESA Laboratories S.L. (red week, green week and blue week). During the previous week children ingested their usual diet and we studied their sleep parameters too. Control cereals were Blevit plus 8 Cereales©. These cereals were already on the market and they had 75 mg of tryptophan per 100 g of product. The tryptophan-enriched cereals were Blevit plus 8 Cereales© modified with a content of 200 mg of tryptophan per 100 g of product. All these products were produced and manufactured by ORDESA Laboratories S.L. (Barcelona, Spain). Once researches gave statistic results to ORDESA Laboratories, the laboratories revealed what kind of cereals, control or enriched, were administered each week (Table 1).

Measurement of sleep

Activity data were collected by a wrist actimeter (Actiwatch©, Cambridge Neurotechnology Ltd, UK), which participants wore in their non-dominant hand during the weeks of the trial. The actimetry data were analysed with the Sleep Analysis 5© v.5.48 (Cambridge Neurotechnology Ltd, UK) Software to obtain the following parameters: time in bed, assumed sleep (difference between sleep onset and the final awakening), actual sleep time (assumed sleep minus awake time), sleep latency (time period measured from going to bed until the onset of sleep), sleep efficiency (sleep percentage while the volunteer is in bed), wake bouts (number of high activity episodes during sleep), immobile time (minutes when mobility is zero) and total activity (total activity pulses during sleep).

Table 1. Information about kinds of cereals (control or tryptophan-enriched). This information was revealed by ORDESA Laboratories S.L. once researchers gave them statistic results.

Weeks	Red (D-week)	Green (B-week)	Blue (B&D-week)
Breakfast	Control cereals	Tryptophan-enriched cereals	Tryptophan-enriched cereals
Dinner	Tryptophan-enriched cereals	Control cereals	Tryptophan-enriched cereals

Ethical issues

This study was approved by the Ethical Committee of the University of Extremadura (Badajoz, Spain) in accordance with the Declaration of Helsinki, the Council of Europe, and the Universal Declaration of UNESCO.

Statistical analysis

Statistical analysis was made with GraphPad Prism© V 5.02 using Kolmogorov-Smirnov test, ANOVA test and Kruskal-Wallis test; post-tests were performed with Dunn's multiple comparison test. The data are indicated as means ± standard deviation (SD).

Results

Figure 1 shows the results of the quantification of activity/inactivity as an assessment of sleep-wake cycle in children with autistic spectrum disorder. When children ingested tryptophan-enriched cereals at dinner, sleep latency levels were significantly ($p < 0.05$) lower than control levels. Besides, sleep efficiency levels were significantly ($p < 0.05$) higher when children ingested tryptophan-enriched cereals at dinner than when they ingested them at breakfast. Finally, total activity levels were significantly ($p < 0.05$) lower in D-week than in control week.

The results of sleep-wake cycle in cerebral palsy children are shown in Figure 2. On the one hand, sleep efficiency levels were significantly ($p < 0.05$) higher when children ingested tryptophan-enriched cereals at dinner than in basal, control and B-week. On the other hand, when children ingested tryptophan-enriched cereals at dinner, the number of wake bouts was significantly ($p < 0.05$) lower than in basal, control and B-week.

In Figure 3, the results of the quantification of activity/inactivity as an assessment of sleep-wake cycle in children with attention deficit hyperactivity disorder are shown. Firstly, assumed sleep levels were significantly ($p < 0.05$) higher in D-week than in basal, control and B-week. Moreover, actual sleep time levels were significantly ($p < 0.05$) higher when these children ingested tryptophan-enriched cereals at dinner or breakfast and dinner than in control and B-week. Furthermore, when children ingested tryptophan-enriched cereals at dinner, sleep latency levels were significantly ($p < 0.05$) lower than control levels. Sleep efficiency levels were significantly ($p < 0.05$) higher in D-week than in basal, control and B-week. Besides, sleep efficiency levels were significantly ($p < 0.05$) higher in B&D-week than in control and B-week. Immobile time levels were significantly ($p < 0.05$) higher in D-week than in basal, control and B-week. In addition, immobile time levels were significantly ($p < 0.05$) higher in B&D-week than in basal and control week. Lastly, total activity levels were significantly ($p < 0.05$) lower when children ingested tryptophan-enriched cereals at dinner than in control week.

Figure 1. Effect of tryptophan-enriched cereals intake in children with Autistic Spectrum Disorder (ASD) on sleep parameters: time in bed (A), assumed sleep (B), actual sleep time (C), sleep latency (D), sleep efficiency (E), wake bouts (F), immobile time (G) and total activity (H). (Mean ± SD and n=7). Basal: habitual diet; control: second and fourth week (22.5 mg of tryptophan was consumed in breakfast and dinner; treatment: **D-week** (22.5 mg of tryptophan was consumed at breakfast and 60 mg of tryptophan was consumed at dinner), **B-week** (60 mg of tryptophan was consumed at breakfast and 22.5 mg of tryptophan was consumed at dinner) and **B&D-week** (60 mg of tryptophan was consumed at breakfast and dinner). *p < 0.05 D-week vs. control week (Sleep latency); *p < 0.05 D-week vs. B-week (Sleep efficiency); *p < 0.05 D-week vs. control week (Total activity).

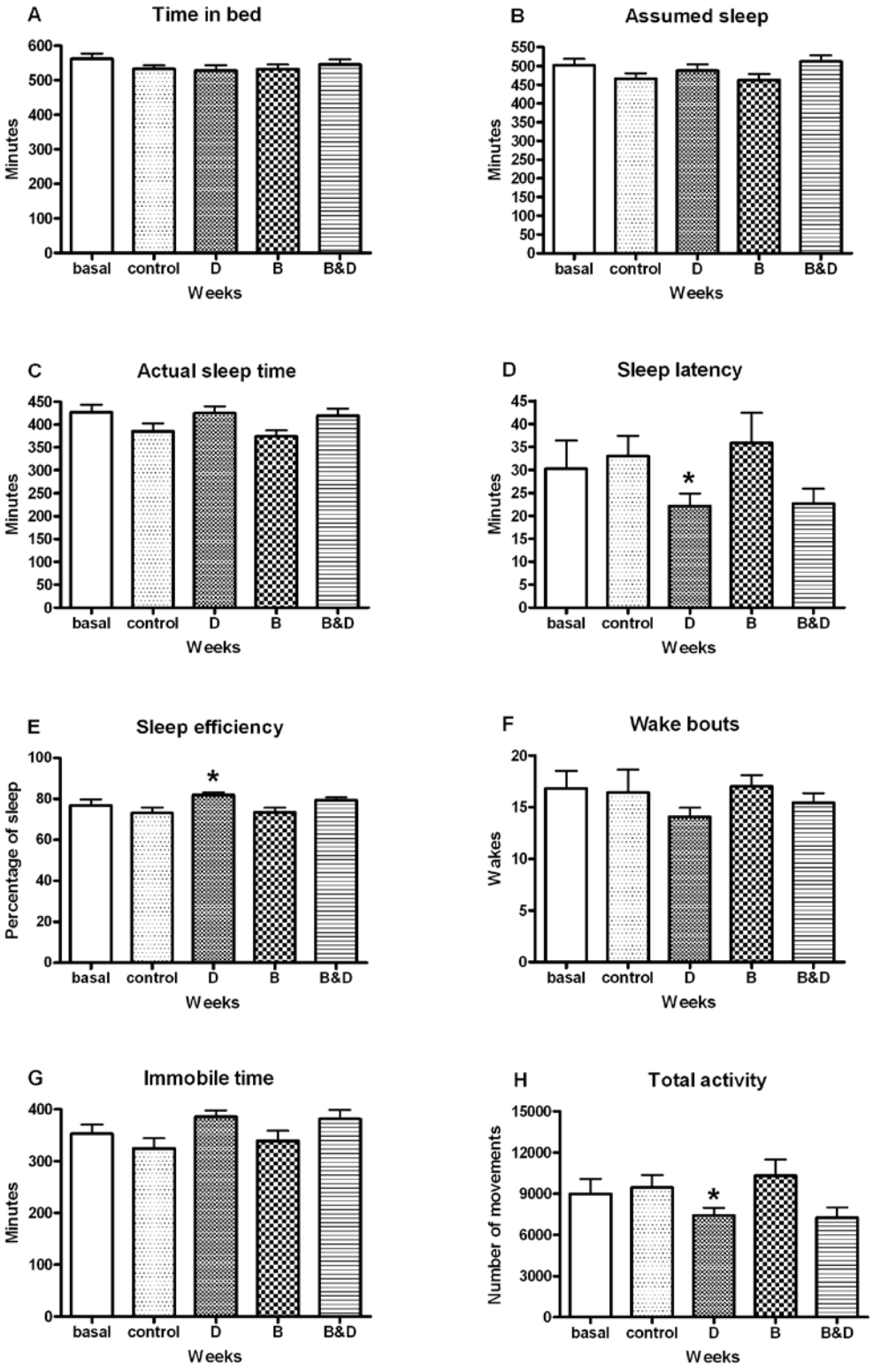


Figure 2. Effect of tryptophan-enriched cereals intake in children with Cerebral Palsy on sleep parameters: time in bed (A), assumed sleep (B), actual sleep time (C), sleep latency (D), sleep efficiency (E), wake bouts (F), immobile time (G) and total activity (H). (Mean ± SD and n=9). Basal: habitual diet; control: second and fourth week (22.5 mg of tryptophan was consumed in breakfast and dinner; treatment: **D-week** (22.5 mg of tryptophan was consumed at breakfast and 60 mg of tryptophan was consumed at dinner), **B-week** (60 mg of tryptophan was consumed at breakfast and 22.5 mg of tryptophan was consumed at dinner) and **B&D-week** (60 mg of tryptophan was consumed at breakfast and dinner). *p < 0.05 D-week vs. Basal, Control, B-week (Sleep efficiency and Wake bouts).

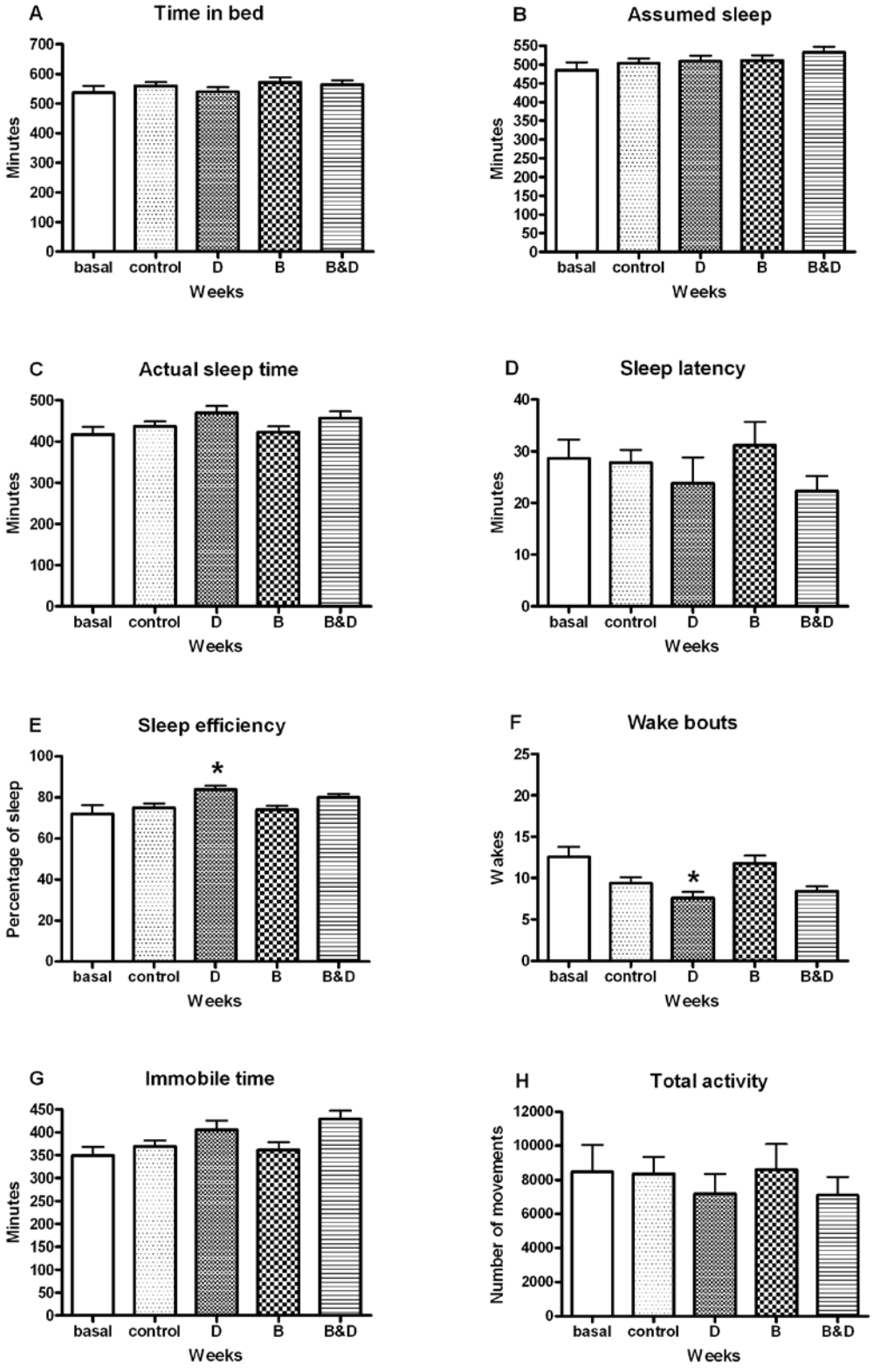
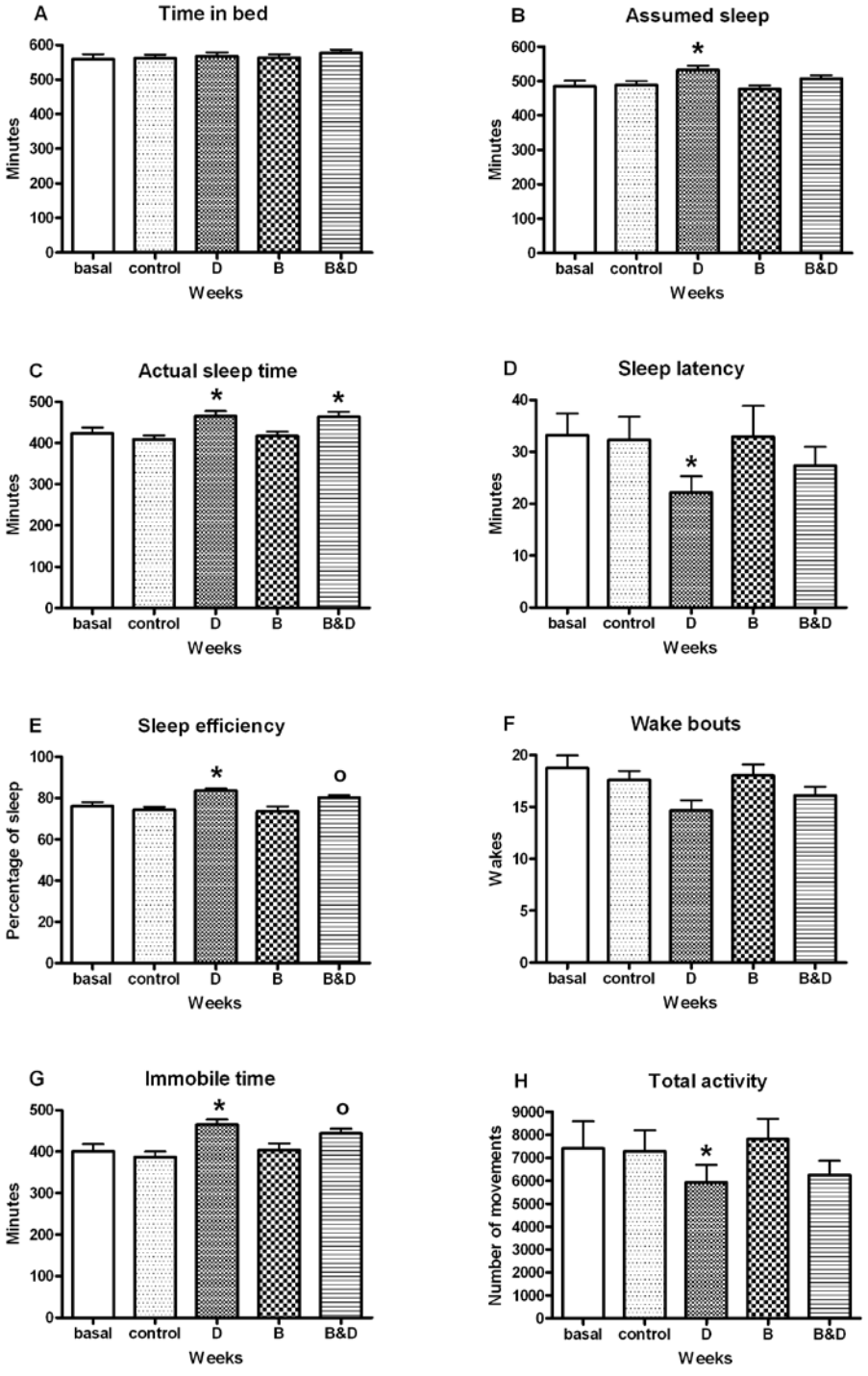


Figure 3. Effect of tryptophan-enriched cereals intake in children with Attention Deficit Hyperactivity Disorder (ADHD) on sleep parameters: time in bed (A), assumed sleep (B), actual sleep time (C), sleep latency (D), sleep efficiency (E), wake bouts (F), immobile time (G) and total activity (H). (Mean ± SD and n=6). Basal: habitual diet; control: second and fourth week (22.5 mg of tryptophan was consumed in breakfast and dinner; treatment: **D-week** (22.5 mg of tryptophan was consumed at breakfast and 60 mg of tryptophan was consumed at dinner), **B-week** (60 mg of tryptophan was consumed at breakfast and 22.5 mg of tryptophan was consumed at dinner) and **B&D-week** (60 mg of tryptophan was consumed at breakfast and dinner). **p* < 0.05 D-week *vs.* Basal, Control, B-week (Assumed sleep); **p* < 0.05 D-week, B&D-week *vs.* Control, B-week (Actual sleep time); **p* < 0.05 D-week vs. control week (Sleep latency); **p* < 0.05 D-week *vs.* Basal, Control, B-week (Sleep efficiency); ^{o}p < 0.05 B&D-week *vs.* Control, B-week (Sleep efficiency); **p* < 0.05 D-week *vs.* Basal, Control, B-week (Immobile time); ^{o}p < 0.05 B&D-week *vs.* Basal, Control (Immobile time); **p* < 0.05 D-week vs. control week (Total activity).



Discussion

Our results related to DSA children are similar to the results obtained in other studies where DSA children ingested hormone melatonin. The tryptophan is a precursor for this hormone. In a double-blinded trial, controlled-release melatonin was administered to 16 DSA children (age range 2-18 years). These children had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance (Wasdell et al., 2008). The melatonin was administered 20-30 min before the child's most desirable bedtime and it improved sleep. Total nighttime sleep and sleep latency showed significant improvement of approximately 30 min. In another trial, 24 DSA children ingested 1-3 mg of melatonin and it was observed an improvement in sleep latency, determined by actigraphy (Malow et al., 2012).

Sleep problems cause severe disruptions in the lives of cerebral palsy children (Richdale et al., 2000). Due to this problem, they need a solution to improve their sleep. If sleep improved, their behaviour and school performance would be better. This improvement would create a good family atmosphere. Some studies with cerebral palsy children were carried out in 2008. In these trials, they administered melatonin instead of tryptophan to cerebral palsy children. For example, Braam et al. (2008) observed an improvement in sleep latency after melatonin ingestion. This is similar to our results. Wasdell et al. (2008) carried out another trial with cerebral palsy children who ingested melatonin before bedtime. It was observed a decrease in sleep latency and an increase in the length and the quality of sleep during all the night. Regarding these trials and our results, both tryptophan and melatonin administration improve sleep of cerebral palsy children.

Concerning ADHD children, our results show the intake of tryptophan-enriched cereals has beneficial effects to sleep. Nemzer et al. (1986) administered tryptophan at night to 14 ADHD children. They found significant differences between placebo and tryptophan in the character of the children according to parental ratings. Parents observed improvements in children behaviour, like in our trial when we administered tryptophan-enriched cereals at dinner. Van der Heijden et al. (2007) didn't get this improvement administering melatonin. They administered 3-6 mg of melatonin to ADHD children before going to bed. They observed a decrease in sleep latency and an increase on total sleep time. But, ADHD symptoms, cognitive performance and quality of life didn't improve with melatonin.

To sum up, results obtained in our trial show that the intake of tryptophan-enriched cereals improves both sleep parameters associated with neurotransmitter serotonin (sleep latency) and sleep parameters related to melatonin (parameters associated with sleep quality) in children with neurological disorders who have participated. The best results about sleep in the three groups of children were obtained when tryptophan-enriched cereals were administered at dinner. These children with neurological disorders usually take a lot of medicines. The benefit of tryptophan enriched cereals is that it is a functional food that improves sleep and it isn't a drug. It would be interesting to carry out another trials using EEG recording to obtain more data to help these children.

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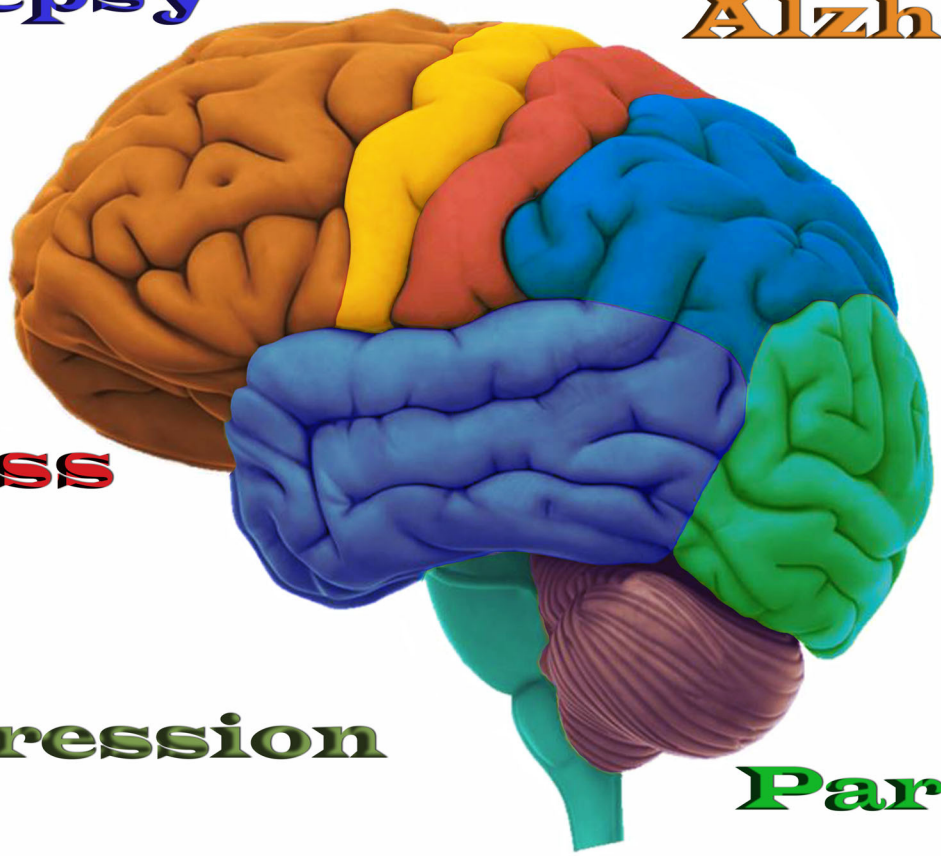

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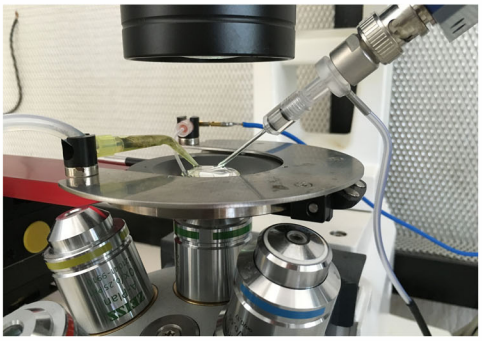

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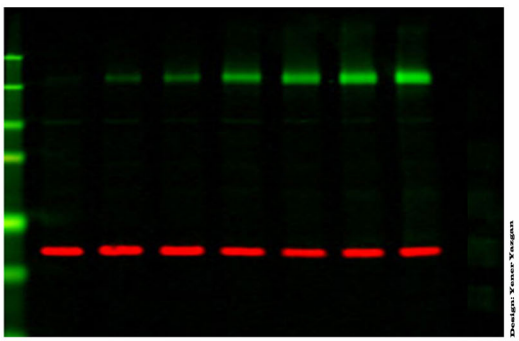

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