Metabolic dysregulation of the neuromodulator adenosine as a possible cause of Idiopathic Hypersomnia. A case study with promising results about the treatment with 1,3-dimethylxanthine.

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June 2023

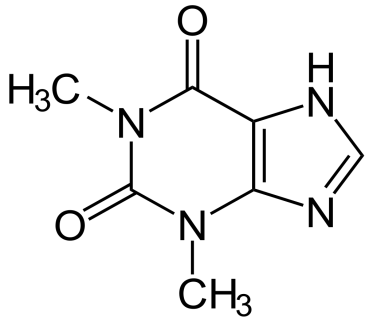

Figure 1: Structure of 1,3-dimethylxanthine

Abstract
The neuro-regulator adenosine plays an important role in controlling sleep-wake cycles. Studies have shown that during sleep deprivation, adenosine concentration increases in the basal forebrain [1][2]. There are currently no studies investigating the role of adenosine in somnological disorders such as idiopathic hypersomnia.

Idiopathic Hypersomnia (IH) is a rare neurological disorder characterized by excessive daytime sleepiness (EDS) despite a sufficient amount of sleep, with sleep inertia (impaired cognitive and sensory- motor performance), long and unrefreshing naps and a prolonged night-time sleep [3].
Within the EMEA region there are currently no approved medications for IH, sodium oxybate is the only approved medication in the USA. The current gold standard for the treatment of EDS is modafinil, with second string options such as methylphenidate, dexamphetamine, pitolisant, and solriamfetol [4].

Hypothesis
We suspect that the main symptoms of idiopathic hypersomnia, including the long sleep period, severe sleep inertia and lack of daytime awareness, may be due to metabolic dysregulation of adenosine in the basal forebrain (BF). To investigate this hypothesis, a self-experiment with an adenosine A_1 and A_{2A} receptor antagonist was performed. Other novel adenosine antagonists exist but these were unavailable to us [5].

Presentation
Our subject is 27-year-old German female patient with a clinical diagnosis of IH. She exhibits the classic symptoms of the disorder including long night time sleep, severe sleep inertia, excessive daytime sleepiness manifesting as a loss of alertness, and brain fog along with vivid nightmares and daily headaches. Her disease onset was in 2016 with diagnosis in 2020; since then, her symptoms have worsened.
Her current medications include Methylphenidate 20mg IR/ER or Modafinil 200 mg (during drug holiday), Pitolisant 18 mg, Naltrexone 4.5 mg, Clonidine 37.5 µg and Pantoprazole 40mg. The medications are only moderately effective at addressing the EDS and the nightmares.
The patient has been diagnosed with orthostatic hypotension and Hashimoto's thyroiditis. No medications are currently being taken for either condition.

Due to several side effects and a lack of effectiveness with current treatment options available the subject was urged to find an effective way to self-manage her disorder.

Since the subject responded so well to this treatment, we are looking to extend our studies and investigations on the use of adenosine antagonists and the role of adenosine in patients suffering from idiopathic hypersomnolence.
Based on the hypothesis, we believe that the symptoms of idiopathic hypersomnia are caused by an increased level of adenosine in the BF, she tried to treat the dysregulation with the adenosine A_1 and A_{2A} receptor antagonist 1,3-dimethylxanthine known as theophylline, a second line bronchodilator used in the treatment of asthma and COPD [6].

The subject performed this treatment experiment on herself, starting with 250mg of extended-release theophylline before going to sleep, three days later an additional 125mg dose in the morning.

Results

By day three of the treatment the subject's sleep inertia completely disappeared. On day seven she also did not experience EDS; therefore, the use of stimulants was no longer necessary and she ceased taking methylphenidate or modafinil. She continued to take the pitolisant as it is more difficult to withdraw this medication. Further studies need to be undertaken without pitolisant still being taken.

In addition, the subject no longer suffers from hallucinations, headaches, brain fog or any difficulties to focus, and is alert during the day. All of her hypersomnolence related symptoms completely disappeared. Overall, she responded markedly to the treatment without any noticeable side effects.

Discussion

Adenosine Antagonists are known for their CNS-stimulating effects [7]. In our case the stimulation action is not the desired effect unlike with previous experiments with theophylline on non hypersomniacs [8]. Our aim was to address the adenosine dysregulation. Unlike other medications currently in use for IH, our approach potentially treats the cause and not just the symptoms of hypersomnia. In addition, we hope that this initial case study will spur the sleep medicine community to undertake original research and to formally study the role of adenosine antagonists in the treatment of this disorder.

Our hypothesis could also have a possible link to the current main focus on the research of IH, the GABAergic system as it is believed that methylxanthines also modulate the GABA-A receptors.

Finally, if proven correct, this may allow idiopathic hypersomnia to move beyond the name coined by Bedrich Roth and to be known as Roth’s disorder.

About the Authors

Lisa Hoffmann is a student of medical informatics at Hochschule Kaiserslautern, Germany. Matthew Baker currently works for the NHS in the UK in an information technology role and has a degree in Chemistry.

Both suffer from IH and are members of the Living with IH EMEA support group. They are not affiliated with any drug manufacturer.

The authors started research on the role of adenosine in idiopathic hypersomnia due to the current lack of original research in the disorder. The motivation was to investigate whether other most cost-effective medications could be repurposed to treat the ignored symptoms of the disorder which, for many, are more detrimental that the EDS.

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