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LETTERS TO THE EDITOR

Kleine-Levin syndrome, GABA, and glutamate

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In an interesting clinical case of Kleine-Levin syndrome (KLS)[1] intoxication by γ-hydroxybutyric acid acted as a trigger for the disease. γ-Hydroxybutyric acid is a metabolite of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. The relationship between GABA and glutamate (Glu), which promotes neuronal excitation, is already well known. Furthermore, Glu is a precursor of GABA, which, in turn, can be metabolized in Glu via the tricarboxylic acid cycle.

Clinical manifestations of KLS[2] could be classified as excitatory type (eg, insomnia, hyperphagia, anxiety, sexual disinhibition, compulsive behavior) and inhibitory type (eg, sleepiness, apathy, bradypsychia, anorexia, depression, dreamy state), both of which are able to coexist in the same patient and in the same episode. Because of this, we hypothesized that these symptoms could be related to an instability of the Glu–GABA system.

Supporting this, some triggers of KLS episodes (eg, alcohol, benzodiazepines, anesthetics, drugs) act directly on the GABA receptor; sleep deprivation may cause changes in the homeostasis of GABA and Glu receptors in excitatory cortical neurons[3]; microbial infections activate the GABAergic system through the GABA-A receptor, which promotes the "GABAergic defense" by the macrophages[4]; traumatic brain injuries can precipitate changes in the cortical circuits, which leads to an imbalance between excitation and inhibition via the Glu–GABA system.[5] Moreover, there was recently published a case of KLS with positive anti–N-methyl-D-aspartate-type Glu receptor antibodies.[6]

The sensitivity to these triggers could be related to central nervous system (CNS) development. In the early stages of the CNS, there is a unique excitatory pattern given by both GABA and Glu. As the CNS develops, GABAergic neurons mature, glutamatergic networks are configured, and the classic balance between both neurotransmitters is established in late adolescence. A disruption in this CNS development could explain why late adolescence is a critical period, coinciding with the onset of KLS episodes.

With regard to the treatment of KLS, there is class IV evidence of the benefit in using lithium for reducing the number of episodes in patients with frequent episodes.[2] In chronic treatment, lithium induces a downregulation of the NMDA receptor decreasing the glutamate, facilitates the presynaptic GABA release, and upregulates GABA-B receptors increasing the cerebrospinal fluid GABA.[2]

There is also class evidence of the role of intravenous steroids in reducing episode length during prolonged episodes. Intravenous methylprednisolone decreases the amplitude of the GABA-induced currents, whereas it increases the amplitude of the glutamate-induced currents.[7]

Finally, amantadine, an antiviral recommended at the beginning of symptoms to stop episodes,[3] is an antagonist of NMDA receptors.

Therefore, it seems reasonable to hypothesize that the imbalance between the neurotransmitters GABA and Glu plays an important role in the pathophysiology of KLS in a critical moment in the conformation of adult neural networks, creating temporary instability and a delay in final maturation of the CNS.

Treatment with GABAergics (amantadine, sodium oxybate) at the onset of excitatory symptoms; intravenous corticosteroids in long-term, predominantly during inhibitory-type episodes; and lithium for stabilization between attacks therefore seems the best therapeutic option.

CITATION

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REFERENCES

1. Vaillant G, Martin M, Groos E, Larabi I-A, Alvarez J-C, Arnulf I. A strange New Year's Eve: triggers in Kleine-Levin syndrome. *J Clin Sleep Med*. 2021;17(2):329–332.
2. Arnulf I. Kleine-Levin syndrome. *Sleep Med Clin*. 2015;10(2):151–161.
3. Del Cid-Pellitero E, Plavski A, Mainville L, Jones BE. Homeostatic changes in GABA and glutamate receptors on excitability cortical neurons during sleep deprivation and recovery. *Front Syst Neurosci*. 2017;11:17.
4. Kim JK, Kim YS, Lee H-M, et al. GABAergic signaling linked to autophagy enhances host protection against intracellular bacterial infections. *Nat Commun*. 2018;9(1):4184.
5. Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. *Curr Neurol Neurosci Rep*. 2015;15(5):27.
6. Tani M, Konishi Y, Nishida T, Takahashi Y, Kusaka T. A case of Kleine-Levin syndrome with positive anti-NMDA-type glutamate receptor antibodies. *Pediatr Int (Roma)*. 2020;62(3):409–410.

7. Foroutan A, Behbehan MM, Anderson DK. Effects of methylprednisolone on the GABA- and glutamate-induced currents: relevance to glucocorticoid-induced neurotoxicity and brain aging. *Steroids*. 1996;61(6):354–366.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.