Letter: Anterior Nucleus of the Thalamus Deep Brain Stimulation With Concomitant Vagus Nerve Stimulation for Drug-Resistant Epilepsy

To the Editor:

The physiopathological mechanism associated with the well-known efficacy of vagal nerve stimulation (VNS) in the treatment of epilepsy remains to be fully elucidated in the literature. The current evidence for this is primarily based on clinical observations. The article titled "Anterior Nucleus of the Thalamus Deep Brain Stimulation with Concomitant Vagus Nerve Stimulation for Drug-Resistant Epilepsy," which was recently published by Parisi et al,[1] is extremely noteworthy because, despite being a clinical study, it also provides clues about the functional anatomic basis of the mechanism of action of VNS in the treatment of epilepsy. In this article, the authors clinically observed that the anterior nucleus of the thalamus deep brain stimulation (ANT-DBS) and VNS can have a certain synergistic effect in reducing epileptic seizures when used together. However, the authors' deduction that these effects were independent of each other needs to be further commented.

Reviewing past anatomic studies, especially those related to the functional anatomy of white matter, may help better understand the basics of clinical observations.[2-4] Previous anatomic reports suggested that the mechanism of action of the ANT-DBS and VNS may follow the same anatomic paths.[2,5-7] One of the most compelling indications of this is the close anatomic relationship that exists between the vagal nuclei and the Gudden nucleus of the mammillotegmental tract in the brainstem and, consequently, the connections of the anterior thalamic nucleus through the mammillothalamic tract.[2,8-10] The mammillary body is linked to the tegmental pontine and reticulotegmental nuclei through the mammillotegmental tract.[11] Furthermore, the mammillotegmental tract is believed to play a role in visceral functions by affecting the autonomic nuclei through the fasciculus retroflexus and dorsal longitudinal fasciculus in the brainstem.[2] There are also afferents, which are essentially GABAergic, that ascend from the paramedian midbrain zone to the mammillary body through a bundle known as the mammillary peduncle.[2,12] Thus, the mammillary body and the hippocampus may be influenced by activity in the upper brain stem through the mammillotegmental tract and the mammillary peduncle. The antiepileptic action of VNS is mainly based on the molecular mechanisms of the synaptic transmission in the central nervous system.[5] VNS can modulate the activity in the vagal nuclei, such as in the dorsal motor nucleus of the vagus nerve, nucleus ambiguus, and the solitary nucleus in the brainstem. Through their associated nuclei, the afferent fibers of the vagus nerve, which receives peripheral information through VNS, can send projections to various parts of the brain and can alter functional connectivity and the synaptic activities in the hypothalamus and the anterior thalamic nucleus through the mammillotegmental tract, mammillary peduncle, and mammillothalamic tract.[2-8] Given the functional anatomic network in the central nervous system and considering that the anticonvulsant activity of VNS may occur because of decreased hippocampal activity and changes in the thalamic synaptic activities (possibly through increased GABAergic signaling), it could be possible that the antiepileptic effects of VNS and ANT-DBS are not independent of each other but, rather, are complementary.

In conclusion, although Parisi et al[1] did not engage in basic science discussions regarding functional anatomy and physiology in their clinical article, they have presented their clinical observations related to the functional neurosurgical treatment of epilepsy in great detail. This will undoubtedly guide future basic science studies aimed at understanding the mechanism of action of VNS. Therefore, the authors should be commended for their contribution.

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Naci Balak, MD

Department of Neurosurgery, Istanbul Medeniyet University, Göztepe Hospital, Istanbul, Turkey

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