# Vagus nerve stimulation [[mechanism of action]]

Vagus nerve stimulation (VNS) is approved as an adjunctive treatment for drug-resistant epilepsy. Although there is a substantial amount of literature aiming at unraveling the mechanisms of action of VNS in epilepsy, it is still unclear how the cascade of events triggered by VNS leads to its antiepileptic effect.

Objective: In this review, we integrated available peer-reviewed data on the effects of VNS in clinical and experimental research to identify those that are putatively responsible for its therapeutic effect. The topic of transcutaneous VNS will not be covered owing to the current lack of data supporting the differences and commonalities of its mechanisms of action in relation to invasive VNS.

Summary of the main findings: There is compelling evidence that the effect is obtained through the stimulation of large-diameter afferent myelinated fibers that project to the solitary tract nucleus, then to the parabrachial nucleus, which in turn alters the activity of the limbic system, thalamus, and cortex. VNS-induced catecholamine release from the locus coeruleus in the brainstem plays a pivotal role. Functional imaging studies tend to point toward a common vagal network that comes into play, made up of the amygdalo-hippocampal regions, left thalamus, and insular cortex.

Conclusions: Even though some crucial pieces are missing, neurochemical, molecular, cellular, and electrophysiological changes occur within the vagal afferent network at three main levels (the brainstem, the limbic system [amygdala and hippocampus], and the cortex). At this final level, VNS notably alters functional connectivity, which is known to be abnormally high within the epileptic zone and was shown to be significantly decreased by VNS in responders. The effect of crucial VNS parameters such as frequency or current amplitude on functional connectivity metrics is of utmost importance and requires further investigation [1)].

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Electrodes wrapped around the vagus nerve in the neck are connected to an implanted programmable generator to stimulate the nerve to reduce seizure frequency. As is also true with many AEDs, the mechanism of action is not well understood.

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It was found that intermittent Electrostimulation from the vagus nerve produces inhibition of neural processes, which can alter brain activity and terminate seizures. This paved way for the concept of vagal nerve stimulator (VNS).

Ogbonnaya and Kaliaperumal described the evolution of the VNS and its use in different fields of medicine. They also reviewed the literature focusing on the mechanism of action of VNS producing desired effects in different conditions. PUBMED and EMBASE search was performed for 'VNS' and its use in refractory seizure management, depression, obesity, memory, and neurogenesis. VNS has been in vogue over for the past three decades and has proven to reduce the intensity and frequency of seizure by 50% in the management of refractory seizures. Apart from this, VNS has been shown to promote neurogenesis in the dentate gyrus of rat hippocampus after 48 hours of stimulation of the vagus nerve. Improvement has also been observed in non-psychotic major depression from a randomized trial conducted 7 years ago. The same concept has been utilized to alter behavior and

cognition in rodents, and good improvement has been observed.

Studies have proven that VNS is effective in obesity management in patients with depression. Several hypotheses have been postulated for the mechanism of action of VNS contributing to its success. VNS has gained significant popularity with promising results in epilepsy surgery and treatment-resistant depression. The spectrum of its use has also extended to other fields of medicine including obesity, memory, and neurogenesis, and there is still a viable scope for its utility in the future [2].

1)

Carron R, Roncon P, Lagarde S, Dibué M, Zanello M, Bartolomei F. Latest Views on the Mechanisms of Action of Surgically Implanted Cervical Vagal Nerve Stimulation in Epilepsy. Neuromodulation. 2022 Sep 1:S1094-7159(22)01222-3. doi: 10.1016/j.neurom.2022.08.447. Epub ahead of print. PMID: 36064522.

2)

Ogbonnaya S, Kaliaperumal C. Vagal nerve stimulator: Evolving trends. J Nat Sci Biol Med. 2013 Jan;4(1):8-13. doi: 10.4103/0976-9668.107254. PubMed PMID: 23633829; PubMed Central PMCID: PMC3633308.