



# Mechanisms of Anticephalgic Action of the Vagus Nerve Electrostimulation: Experimental Study Results

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## Abstract

Cervical or auricular vagus nerve stimulation (VNS) is an effective and safe non-pharmacological treatment for epilepsy, depression, obesity, post-stroke motor impairments, and certain types of primary headaches (HA), including migraine. This review briefly summarizes data on various VNS device models, the pathophysiology of HA, and approved neuromodulatory therapies for headache management. Experimental findings have been analyzed regarding the role of sensory nuclei of the trigeminal and vagus nerves, as well as supraspinal structures of the central nervous system, particularly the dorsal raphe nucleus and locus coeruleus, in mediating the inhibitory effects of VNS on nociceptive transmission within the trigeminothalamic pathway, whose hyperactivity is a key mechanism in HA pathogenesis. The review details studies using rodent migraine models, which demonstrated VNS-mediated suppression of spinal trigeminal nucleus neuronal activity and cortical spreading depression, effects achieved through neurotransmitters such as serotonin, norepinephrine, and gamma-aminobutyric acid (GABA). The mechanisms of VNS therapeutic action in HA should remain a focus of experimental and clinical research, as current evidence in this field requires further updating and validation.

**Keywords:** *vagus nerve; electrostimulation; trigeminal nerve; headache; migraine; trigeminovascular system*

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# Механизмы антицефалгического действия электростимуляции блуждающего нерва: результаты экспериментальных исследований

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## Аннотация

Электрическая стимуляция шейного отдела или ушной ветви блуждающего нерва, она же вагусная нейростимуляция (ВНС) – эффективный и безопасный немедикаментозный метод лечения эпилепсии, депрессии, ожирения, постинсультных двигательных нарушений и некоторых форм первичных головных болей (ГБ), включая мигрень. В обзоре кратко представлены сведения о различных моделях вагусных стимуляторов, а также о патофизиологии ГБ и одобренных способах антицефалгической нейромодулирующей терапии. Проанализированы данные экспериментальных работ об участии сенсорных ядер тройничного и блуждающего нервов, а также ряда супраспинальных образований центральной нервной системы, в частности, дорсального ядра шва и голубого пятна, в обеспечении подавляющего влияния ВНС на ноцицептивную трансмиссию в тригемино-таламокортикальном пути, усиление которой является ключевым звеном патогенеза ГБ. Детально обсуждаются результаты исследований, выполненных на различных моделях мигрени с использованием лабораторных грызунов, где был показан супрессивный эффект ВНС на активность нейронов спинального тройничного ядра и распространяющуюся кортикальную депрессию, который реализуется при посредничестве различных нейромедиаторов, например, серотонина, норадреналина и гамма-аминомасляной кислоты. Представляется целесообразным, что механизмы терапевтического действия ВНС при ГБ должны оставаться предметом изучения в различных экспериментально-клинических проектах, поскольку накопленные к сегодняшнему дню сведения на эту тему нуждаются в дальнейшей актуализации.

**Ключевые слова:** блуждающий нерв; электростимуляция; тройничный нерв; головная боль; мигрень; тригемино-вазкулярная система

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## Introduction

Vagus nerve electrical stimulation (VNS) is a non-pharmacological treatment officially approved in several countries for epilepsy, depression, obesity, post-stroke motor impairments, and certain types of primary headaches (HA) [1, 2]. Additionally, the therapeutic potential of VNS is being explored for rheumatic diseases [3], traumatic brain injury [4], cardiovascular diseases [5], Parkinson's disease [6], Alzheimer disease [7], inflammatory conditions [8], gut dysbiosis [9], opioid use disorder [10], narcolepsy [11], disorders of consciousness [12], chronic pain of various origins [13, 14], and other pathological states [1, 15–17]. Results from numerous experimental and clinical studies suggest that

the broad applicability of VNS stems from its multifaceted effects, including immunomodulatory, anti-inflammatory, anticonvulsant, neuroprotective, and analgesic properties, as well as its ability to enhance neuroplasticity, modulate blood-brain barrier permeability, regulate neurotransmitter release, inhibit apoptosis and autophagy, improve metabolic profiles, and stimulate angiogenesis [2, 12, 15, 17, 18].

## Types and Modes of VNS

From a technical perspective, VNS can be invasive or non-invasive. The invasive method involves implanting a current generator under the skin and wire electrodes contacting the cervical portion of the left vagus nerve (e.g., SenTiva M1000

or Symmetry M8103 devices by LivaNova), requiring surgical intervention for both initial placement and subsequent battery replacement. This procedure carries inherent surgical risks and may cause side effects such as vocal cord paresis, bradycardia, asystole, paresthesia, pain, cough, dyspnea, pharyngitis, and infectious complications [19]. The indication for implanting these devices includes pharmacoresistant epilepsy and depression.

Non-invasive VNS utilizes portable devices for transcutaneous electrical stimulation of either the cervical or the auricular branches of the vagus nerve. For auricular VNS, devices like Vagustim (by the eponymous biomedical company) may be used, featuring bilateral electrodes wired to a generator unit, with a design enabling simultaneous stimulation of the tragus and concha. Notably, the manufacturer offers the Vagustim Animal Research Device (ARD) for experimental studies, which is a rodent-adapted system with ear-mounted electrodes. Multisana Ltd produces the ultra-compact AuriStim stimulator, where a miniature adhesive-backed generator with a power cell can be attached under the ear, with three thin short wires ending in contacts secured to the auricle with adhesive tape. tVNS Technologies GmbH manufactures the tVNS device for treating various conditions including migraine. The universal Soterix Medical taVNS systems device (Soterix Medical Inc.) features interchangeable wired electrodes for unilateral stimulation of both auricular and cervical vagus nerve branches. For transcutaneous cervical VNS, the gammaCore Sapphire device (electroCore, Inc.) is a market leader, holding U.S. FDA approval both for abortive and preventive migraine treatment, cluster headaches, hemicrania continua, and paroxysmal hemicrania, whose features are presented below.

### Classification and Pathophysiology of Headaches

The International Classification of Headache Disorders distinguishes between primary and secondary cephalalgias. Secondary headaches are symptoms of an underlying organic disease, while primary headaches include tension-type headache (TTH), migraine, a group of trigeminal autonomic cephalalgias (encompassing cluster headache, hemicrania continua, paroxysmal hemicrania, and SUNCT/SUNA syndromes – short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing or short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms), as well as other primary headache disorders. All of them are idiopathic disorders with no defined etiology and are diagnosed based on a typical clinical presentation after excluding other conditions that may cause similar symptoms [20].

A key pathophysiological mechanism of primary headaches involves trigeminal nerve activation, generating nociceptive signals through the trigemino-thalamo-cortical pathway. The trigeminal nerve forms a primary functional trigeminovascular (TVS) system with cranial vessels, whose dysfunction plays a significant role in primary cephalalgias, particularly migraine [21–24].

Pathological trigeminal activation can develop due to various causes, which predetermines some differences in the initial mechanisms underlying primary cephalalgias. For instance,

in TTH, prolonged tonic tension of the pericranial and cervicobrachial muscles, which initially arises as a protective-adaptive response to unresolved psychoemotional stress, may lead to vascular compression, spastic contraction of supplying arteries, ischemia of specific myofascial zones, and accumulation of underoxidized metabolic products and endogenous algogenic substances. These substances can activate and sensitize nociceptive endings of the trigeminal nerve. Combined with stress-induced central sensory processing alterations, this leads to the characteristic bilateral pressing pain of mild-to-moderate intensity [24–26].

A migraine attack occurs due to TVS activation, which arises spontaneously or under the influence of various exogenous and/or endogenous factors against a background of congenital or acquired deficiency of descending antinociceptive influences. This activation likely leads to the aseptic neurogenic inflammation in the meningeal vessels and perivascular tissues through antidromic release of vasoactive and algogenic substances (such as calcitonin gene-related peptide, pituitary adenylate cyclase-activating peptide, neurokinin A, nitric oxide, glutamate, and substance P) from peripheral terminals of trigeminal afferents. Under these conditions of meningovascular inflammation, orthodromic stimulation occurs in perivascular A $\delta$ - and C-fibers of the peripheral processes of trigeminal ganglion cells. These fibers transmit nociceptive information from cerebral and meningeal vessels to the trigeminal *nucleus caudalis* (TNC), where primary processing and subsequent relay to higher structures of the central nervous system take place. Axons of TNC neurons form ascending connections with various subcortical brain regions, including the ventral posteromedial nucleus of the thalamus, which serves as the final relay station for transmitting pain signals to somatosensory cortical areas. Neurovascular disturbances combined with enhanced nociceptive input lead to peripheral and central sensitization within the trigemino-thalamo-cortical pathway. This manifests clinically as characteristic pain syndrome, cutaneous allodynia, photo-/phono-/osmophobia, accompanying autonomic symptoms, and varying degrees of patient maladjustment [21, 22, 27–29].

In the pathogenesis of cluster headache, hypothalamic dysfunction and pronounced parasympathetic activation play a leading role. This determines the classic clinical presentation of this condition: a serial “cluster-like” pattern of excruciating pain following a specific circadian rhythm, accompanied by lacrimation, rhinorrhea, miosis, ptosis, and periorbital edema on the affected side. Increased parasympathetic tone leads to intracranial vasodilation, enhanced vascular permeability to plasma proteins, vascular wall edema, and consequent stimulation of perivascular trigeminal afferents. This irritation closes the trigeminal-facial reflex arc, creating a pathological cycle of progressive autonomic mediation amplification. Impaired hypothalamic control disinhibits trigeminovascular nociceptive signaling at the TNC level and likely underlies the strict periodicity of pain attacks [27, 30, 31].

Paroxysmal hemicrania and hemicrania continua are rare forms of trigeminal autonomic cephalalgias, collectively termed indomethacin-responsive headaches due to this drug's high therapeutic efficacy. While the pathogenesis of both

hemicranias remains unclear, similar to cluster headache, they involve enhanced trigeminal-facial parasympathetic reflex enhancement in TVS activation [23, 32, 33].

Despite variations in developmental mechanisms among primary headache forms, they share common pathogenetic features. These include persistent hyperexcitability of trigeminothalamic pathway neurons leading to peripheral/central sensitization, deficient modulatory control by endogenous antinociceptive system structures, and varying degrees of intracranial/extracranial vascular tone dysregulation [21, 24, 31].

### Neuromodulation for Headache Treatment

The management of primary headaches generally involves medications that can either stop or prevent pain attacks [21]. However, this strategy is not always effective, prompting the use of non-pharmacological therapies, primarily various methods of electrical neuromodulation [34, 35].

Technical devices approved by national regulators (primarily the FDA) for clinical use in cephalalgology as of spring 2025, which enable this type of intervention, include:

- A. Cefaly non-invasive neurostimulators (Cefaly Technology) and HeadTerm2 (WAT Medical Enterprise Ltd.), which are affixed to the forehead using adhesive electrodes to deliver electrical stimulation to the supraorbital and supratrochlear nerves. Approved for abortive and preventive migraine treatment.
- B. sTMS transcranial magnetic stimulator (eNeura Inc.), approved for acute and preventive migraine treatment. During the procedure, the patient presses the device against the occiput and activates the electromagnetic impulse via a button.
- C. Nerivio remote electrical neuromodulation device (Theranica Bio-Electronics Ltd.), affixed to the upper arm. The manufacturer claims that local stimulation of A-delta and C fibers activates the endogenous antinociceptive system to suppress headaches. Approved for acute and preventive migraine treatment.
- D. The Relivion device (Neuro Relief Ltd), a headband for simultaneous transcutaneous electrical stimulation of the supraorbital, supratrochlear, and occipital nerves. Approved for abortive migraine treatment.
- E. Transcutaneous cervical vagus nerve stimulators (gammaCore Sapphire) or auricular branch stimulators (tVNS), as previously discussed.

Results from numerous clinical trials demonstrate moderate efficacy and high safety of non-invasive VNS in migraine [13, 36] and trigeminal autonomic cephalgias [37, 38]. The mechanism of VNS anti-cephalgic action remains under investigation in animal studies.

### VNS Influence on Noniceptive Transmission in the Trigeminal Nerve System

The potential influence of VNS on trigeminothalamic nociceptive transmission is determined by the cross-anatomical relationships between brainstem sensory structures of the trigeminal and vagus nerves. In addition to

integration into the dorsal horn of the upper cervical spinal cord segments, forming the trigeminocervical complex (TCC), TNC establishes extensive bilateral connections with the nucleus of the solitary tract (NTS) – a structure shared by the facial (VII), glossopharyngeal (IX), and vagus (X) nerves [39–43]. There are both trigemino-solitary and solitary-trigeminal pathways, indicating bidirectional connectivity that forms a trigemino-solitary-trigeminal loop [40]. Furthermore, some sensory fibers of the trigeminal nerve terminate directly on NTS neurons, while TCC cells receive sensory inputs from vagal, facial, and glossopharyngeal nerve afferents [44–47]. Thus, TNC and NTS receive direct reciprocal afferent projections from the V, VII, IX, and X cranial nerves and maintain robust bidirectional internuclear connections. Functionally, these nuclei – together with the dorsal horn of the upper cervical spinal segments – constitute a unified neurosensory apparatus: the trigemino-cervico-solitary complex. This structure serves as a critical segmental relay station where somatovisceral afferent inputs from extracranial/intracranial structures, neck, and upper torso converge and interact, as evidenced by neurophysiological, neuroanatomical studies, and clinical observations [21, 48].

The first substantiated concept of the trigemino-cervico-solitary complex was introduced in the review by A.Yu. Sokolov et al. [48], followed by the term *trigemino-solitary complex* used in the work of O.A. Lyubashina et al. [49]. Subsequently, D.J.H.A. Henssen et al. proposed the concept of the trigemino-vagal complex with the caveat that its existence in humans remained unproven [43]. However, that same year, the same research team published a study using ultra-high-resolution magnetic resonance imaging and polarized light microscopy on postmortem isolated human brainstems, which revealed direct anatomical connections between the vagus nerve and the TNC, thereby confirming the existence of the trigemino-vagal complex in humans [50]. Later, the existence of a functionally unified trigemino-vagal system in humans was demonstrated in a randomized controlled trial involving healthy volunteers through a series of sensory tests [51].

Animal experiments have repeatedly demonstrated that VNS exerts bidirectional effects on the activity of central trigeminal neurons, though with a notable bias toward suppression. Specifically, invasive VNS in rats increased c-Fos expression in both the NTS and the caudal portion of the ipsilateral TNC, while suppressing formalin-induced c-Fos immunoreactivity in TNC neurons and nociceptive behavior in animals during both phases of the test [46]. Electrical stimulation of vagal afferents in rats significantly reduced responses to dental pulp stimulation in 86% and 82% of recorded TCC neurons, respectively. In contrast, 5.5% and 11% showed enhanced evoked activity, while 8.5% and 7% remained unresponsive to VNS [52, 53]. Regarding background activity, 4 of 13 neurons did not respond to VNS, 7 exhibited reduced spontaneous spike frequency, and 2 showed increased spike rates in response to VNS [52]. In the study by T. Tanimoto et al., VNS provoked increased background activity in 27% of cases, while the remaining 73% of cells were unresponsive [53].

In cats, VNS predominantly inhibited rather than enhanced or left unchanged the responses of TNC neurons to noxious thermal (21, 5, 6 out of 32 neurons, respectively) or electrical

facial skin stimulation (15, 4, and 5 cells with 24 neurons with A-delta inputs; 8, 0, 4 out of 12 neurons with C-fiber inputs) and dental pulp stimulation (7, 0, 1 out of 8 neurons), indicating a clear predominance of VNS-mediated antinociceptive effects [54]. Furthermore, VNS exerted primarily inhibitory effects on evoked responses of sensory nociceptive neurons in the trigeminal complex, regardless of their convergent input sources (skin/pulp), stimulus modality (electrical/thermal), nerve fiber type (A-delta/C), or supraspinal projection sites of the study cells (thalamus or other structures).

In a study conducted 28 years later, the authors compared the effects of non-invasive stimulation of the cervical and auricular branches of the vagus nerve using different frequency-to-intensity ratios (20–250 Hz and 0.5–1.0 mA) on the activity of NTS and TNC neurons in rats. Based on the enhancement/suppression or absence of changes in their spiking patterns, the multipolar action of VNS was established [55].

In experiments on cats, VNS predominantly inhibited spike responses of neurons in the ventral posteromedial thalamic nucleus receiving contralateral projections from TNC neurons to electrical stimulation of dental pulp (19 out of 25 neurons) and the trigeminothalamic tract (15 out of 25 neurons) [56].

The diametrically opposite effects of VNS on trigeminal neuronal excitability can theoretically be explained by the collision of two afferent streams at the level of the trigemino-cervico-solitary complex: trigeminal and vagal. Their interaction may be either synergistic (resulting in increased trigeminal neuronal activity) or antagonistic (with neural responses inhibited by competing vagal afferentation), where mechanistic understanding suggests equal probability for both scenarios. However, the aforementioned data indicate that VNS exerts predominantly inhibitory effects on trigeminothalamic nociceptive transmission. This effect appears to depend less on direct trigemino-solitary interactions at the segmental level and more on the involvement of brainstem structures of the endogenous antinociceptive system.

Indeed, neurons of the sensory nuclei of the trigemino-cervico-solitary complex widely project to the periaqueductal gray matter, rostral ventromedial medullary area, raphe nuclei, locus coeruleus (LC), parabrachial complex, and hypothalamus, which mediate descending modulatory influences on the trigeminothalamic pain pathway [21, 22, 27, 28, 41, 42, 44, 48, 57, 58]. VNS is known to enhance LC and, secondarily, dorsal raphe nucleus (DRN) activity via a bisynaptic (NTS → paragigantocellular nucleus → LC) glutamatergic pathway, leading to increased production of norepinephrine and serotonin, respectively [42, 58–60]. Through these mediators, VNS inhibits pain transmission in the TCC induced by extracranial receptive field stimulation. For instance, in the aforementioned study by T. Tanimoto et al., the suppressive effect of VNS on evoked activity of pulpal-sensitive TNC neurons was significantly reduced after intravenous administration of the  $\alpha$ -adrenergic blocker phenoxybenzamine and serotonin-3 antagonist ICS 205-930, leading the researchers to conclude that VNS stimulates descending serotonergic and noradrenergic projections [53]. Two years later, the same research team partially confirmed

their hypothesis under similar experimental conditions, demonstrating that the neuronal inhibitory effect of VNS was abolished by microiontophoresis of both ICS 205-930 and GABA-A antagonist bicuculline into the TNC, indicating the involvement of not only serotonin but also local inhibitory GABAergic networks in this process [61]. The suppressive effect of VNS on pulp-evoked TNC responses in rats was reduced after intravenous naloxone infusion, indicating the involvement of the opioidergic system in the neurochemical mechanisms of VNS-induced antinociception [52]. Blockade of the periaqueductal gray matter and/or dorsal raphe nucleus with a local anesthetic eliminated the inhibitory effect of VNS on pulpal-sensitive neuron responses in the ventral posteromedial thalamic nucleus to trigeminothalamic tract stimulation in cats, further confirming the activation of endogenous antinociceptive systems during VNS [56]. In rats, chronic VNS was associated with accumulation of c-Fos and  $\Delta$ FosB not only in the LC and DRN, but also in the parabrachial complex, hypothalamic paraventricular nucleus, and ventral bed nucleus of the stria terminalis [62]. Later, D.R. Hulseley et al. demonstrated in rat experiments that LC neuronal responses to VNS vary significantly across a wide range of stimulation parameters including current amplitude, pulse frequency, train duration, inter-train intervals, and pulse width [63].

## VNS Effects in Animal Headache Models

The findings of VNS-induced activation of the antinociceptive system structures and suppression of trigeminal pain traffic are often used to explain the anti-cephalgic effects of VNS. While this explanation is applicable, it is not entirely accurate, as the key player in the neurobiology of headaches (particularly migraine) is not the trigeminal nerve per se, but rather the TVS. The TVS includes neurons of the trigeminothalamic pathway that receive afferent input from meningeal structures and/or cranial blood vessels. Furthermore, it is widely accepted that the central components of the TVS – termed second- and third-order trigeminovascular neurons [21] – located in the TCC and the ventral posteromedial thalamic nucleus, respectively, should exhibit convergence. This implies that, in addition to the aforementioned inputs, they should ideally possess cutaneous receptive fields within the innervation area of the first branch of the trigeminal nerve. These considerations suggest that experimental studies investigating the mechanism of action of any anti-cephalgic intervention (whether pharmacological or non-pharmacological) in animal models must utilize specific headache models. A mandatory methodological requirement for such studies is the induction of TVS activation.

The results of the first study of this kind were published by O.A. Lyubashina et al. in 2012 [49]. The authors conducted a series of acute experiments using an electrophysiological model of trigemino-vascular nociception in rats, which involves extracellular microelectrode recording of spike activity in neurons of the trigeminothalamicocortical pathway; this method is unanimously recognized by experts as the most informative approach for studying migraine-related processes in animal experiments [64, 65]. It was shown that continuous electrical stimulation of the central segment of the vagus nerve predominantly (in 48% of cases) exerts an inhibitory

effect on the responses of convergent TNC neurons evoked by electrical stimulation of the dura mater. Simultaneously, the majority of studied cells exhibited VNS-induced reduction in background spike activity, which was more prolonged compared to the suppression of evoked responses. The observed effect depended on the mode, duration, and frequency of vagal stimulation: preconditioning VNS at 30 Hz for 200 ms was unequivocally less effective than continuous stimulation with the same current intensity but at 10 Hz. Considering that approximately one-third of recorded cells showed VNS-induced enhancement of spontaneous and evoked activity, while 22.5% of neurons did not respond to VNS, it can be concluded that its influence on pain transmission in the TVC may not only be inhibitory but also facilitatory or neutral, which generally aligns with the aforementioned experimental data [52, 53, 55] and clinical observations [19, 66, 67]. Nevertheless, the conducted experiments primarily demonstrated an antinociceptive effect of VNS in the headache model, mediated through suppression of second-order trigeminal sensory neuron activity [49].

The introduction of the gammaCore non-invasive cervical vagus nerve stimulator into clinical practice for headache disorders has maintained interest in studying the anticephalgic mechanisms of VNS. Since 2012, several studies considered relevant from this perspective have been published.

In awake rats sensitized over 3–4 weeks by periodic irrigation of the dura mater with prostaglandin E2 solution via a pre-implanted cannula, transcutaneous VNS reduced the severity of periorbital allodynia and decreased elevated extracellular glutamate levels in the caudal portion of the TNC following intraperitoneal nitroglycerin administration. The authors conclude that non-invasive vagus nerve stimulation decreases trigeminal nociceptive stimulation by suppressing the rise in glutamate after nitric oxide treatment [68].

During 2017–2020, the research team led by Dr. P.L. Durham published results from three studies conducted using a unified methodological template. In the first study, it was demonstrated that rats pre-sensitized by injection of complete Freund's adjuvant into the trapezius muscles 8 days prior to non-invasive VNS procedure, and subjected to olfactory provocation via forced inhalation of California bay laurel leaf extract vapors (containing umbellulone – a monoterpene ketone and TRPA1 channel activator that induces headaches in nearly 100% of cases) on the experimental day, showed normalized increased mechanical sensitivity in the supraorbital region when assessed with von Frey filaments. Additionally, VNS in these pre-sensitized animals reduced phosphorylated MAP kinase expression levels in trigeminal ganglion neurons and normalized glial fibrillary acidic protein content along with ionized calcium-binding adapter molecule (IBA1) levels – markers of astrocyte activation/microglial damage respectively – in TNC cells. The authors conclude that “VNS inhibits mechanical nociception and suppresses expression of proteins associated with peripheral and central sensitization of trigeminal neurons” [69].

In the second study, rats were also pre-sensitized via intramuscular injection of complete Freund's adjuvant and activated on the experimental day either by exposure to California

bay laurel leaf odor or through intraperitoneal administration of sodium nitroprusside. Non-invasive cervical vagus nerve stimulation demonstrated comparable efficacy to subcutaneously administered sumatriptan (a serotonin-1B/1D receptor agonist used for migraine attack relief) in normalizing mechanical sensitivity in the supraorbital region, which showed significant elevation following the aforementioned provocations. Intracisternal administration of the GABA-A antagonist bicuculline, the serotonin-7 blocker SB 269970, the 5-HT3 lytic agent ondansetron, or a combination of the latter two agents suppressed the allodynic effects of VNS, indicating the involvement of GABAergic and serotonergic mediation in its mechanism. The authors propose that the normalizing effect of VNS may occur, in part, through 5-HT3- and 5-HT7-mediated activation of GABAergic interneurons in the TNC, leading to subsequent GABA-A receptor-dependent inhibition of second-order trigeminal sensory neuron excitability. They emphasize that “in the episodic migraine model, VNS demonstrated efficacy comparable to sumatriptan through enhancement of central pain modulation mechanisms” [70].

In the third experimental series, complete Freund's adjuvant injections and California laurel vapor inhalations were combined with 24-hour sleep deprivation to induce what the authors described as a “sustained state of trigeminal nociceptive hypersensitivity”. This hypersensitivity was assessed using von Frey filaments to measure mechanical stimulation thresholds in the mandibular nerve innervation area, with head withdrawal responses interpreted as nociceptive reactions. Subsequently, rats received either transcutaneous VNS or subcutaneous morphine for 7 days. Both interventions demonstrated comparable efficacy in suppressing nociceptive responses, though hyperalgesic status recurred after treatment discontinuation. The authors' conclusion appears somewhat self-contradictory: initially stating that “these results demonstrate that nVNS and morphine can transiently inhibit trigeminal nociception to mechanical stimulation but are not able to reverse ongoing sensitization”, while later adding that “nVNS [...] may represent a safer, opioid-sparing therapeutic option for other chronic pain disorders involving sensitization of the trigeminal system” [71].

Another research team from 2016 to 2024 published the results of 4 studies investigating the influence of VNS on spreading cortical depression (SCD), traditionally considered as a neurophysiological correlate of migraine aura and recognized as one of the endogenous triggers for headache attacks [21].

The first study demonstrated that in rats, stimulation of the right cervical portion of the vagus nerve for 30 minutes more than doubled the threshold for electrical stimulation of the occipital cortex required to induce SCD, reduced the frequency of KCl-induced SCD by 40%, and decreased its spread rate by 15%. Non-invasive transcutaneous VNS was equally effective as invasive methods, and the side of vagus nerve stimulation did not affect the degree of SCD suppression in ipsi- and contralateral cerebral hemispheres [72].

In the second project, the authors first replicated their earlier findings and demonstrated that invasive stimulation of the intact vagus nerve in rats more than doubled the electri-

cal initiation threshold for CSD and reduced the frequency of KCl-induced CSD by 22%. Distal vagotomy did not affect these effects, while proximal vagotomy completely abolished them. Pharmacological NTS blockade with lidocaine or the AMPA/kainate glutamate receptor antagonist CNQX also prevented VNS-mediated suppression of CSD. Selective neurotoxins depleting neurotransmitter pools were used to investigate the roles of norepinephrine and serotonin in mediating the CSD-suppressing effects of VNS. To reduce noradrenergic neuronal activity in the LC, rats received intraperitoneal injections of DSP-4 toxin (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride) 15 days before experiments. This toxin accumulates in axon terminals and irreversibly inhibits norepinephrine transporters. To suppress serotonin transmission, rats received intraperitoneal injections of the tryptophan hydroxylase inhibitor PCPA (para-chlorophenylalanine) 3 days before testing. Individual administration of either toxin reduced the CSD-suppressing effect of VNS by over 50%, while combined administration completely abolished VNS effects on CSD. The authors conclude verbatim: "Our data indicate that CSD suppression by VNS is mediated by activation of the vagal visceral sensory afferents to NTS (A $\beta$  fibers), which in turn project to the LC and DRN providing NE and 5-HT innervation, respectively, throughout the brain. The data provide a mechanism of action of VNS in the prevention and treatment of migraine, especially with aura" [73].

The third study demonstrated that the degree of reduction in KCl-induced CSD frequency and the threshold for initiating electrically induced CSD in the pia mater are directly proportional to the intensity of non-invasive cervical VNS, classified as low (1 V), medium (11.4 V), and high (24.4 V) [74]. In an intensity-dependent manner, VNS suppressed the expression of cyclooxygenase-2, calcitonin gene-related peptide, and c-Fos proteins in cortical neurons, trigeminal ganglion, and the TVS, respectively, ipsilateral to the stimulation side. The authors state that they "provided insight on optimal VNS parameters to suppress CSD [...]. With the optimal VNS paradigm, our results suggest benefit on CSD-induced neuroinflammation and trigeminovascular activation in migraine treatment." [74].

The fourth study revealed that non-invasive electrical stimulation of the cervical *vagus nerve* suppresses KCl-induced CSD in rats by activating the "brain-derived neurotrophic factor  $\rightarrow$  tropomyosin receptor kinase B" signaling pathway in the NTS via NMDA- and/or AMPA-glutamate receptor mediation. According to the authors, this mechanism activates NTS projections to the DRN and LC, enhancing serotonergic and noradrenergic effects on the cortex, inhibiting CSD, suppressing cortical neuroinflammation, and reducing TVS activation [75].

Five years after the publication by Russian researchers of their work on studying the effects of VNS in an electrophysiological model of trigeminovascular nociception [49], similar results were reproduced by foreign scientists, which updated the previously presented information and confirmed the validity of the observations and conclusions. Colleagues

demonstrated that in rats, invasive VNS in different modes (ipsi- or contralateral, single [25 Hz stimulation for 2 minutes] or double [with a 3-minute interval between stimulation sessions]) suppressed background activity of durosensitive neurons in the TCC (maximum 60% reduction lasting up to 3 hours), as well as their A-delta and C-fiber responses to electrical stimulation of the dura mater (22% and 55% reduction respectively, lasting up to 2 hours). Additionally, VNS exerted similar effects on the excitability of TCC neurons responding to stimulation of the superior salivatory nucleus and did not affect skin sensitivity on the anterior facial surface. The authors assert that "these data provide a mechanistic rationale for the observed clinical benefits of nVNS in the abortive treatment of migraine and cluster headache, via the modulation of central trigeminovascular neurons" [76].

Four years later, researchers from the same scientific group demonstrated in rat experiments that the inhibitory effect of invasive VNS on the TCC neuronal responses evoked by electrical stimulation of the dura mater depends on the opioidergic system, as it was reversed by naloxone and the  $\delta$ -opioid receptor antagonist SDM25N. Notably, in a sample of 4 animals, VNS did not affect baseline neuronal activity, meaning the authors failed to replicate their own 2017 data despite using identical nerve stimulation parameters (25 Hz for 2 minutes) [77].

Since migraine is positioned as a neurovascular disorder, its animal modeling requires simulation of both neuronal and vascular components of pathogenesis, allowing evaluation of various interventions on the tone and/or permeability of intracranial arteries related to the TVS [64]. An example of such research is the work by the authors of this review, where using in vivo microscopy through a cranial window in rats, we studied the effect of invasive cervical vagus nerve stimulation on meningeal arteriole dilation induced by dural electrical stimulation, a validated marker of trigeminovascular activation in experimental cephalalgology [64]. In a series of controlled experiments involving 14 animals, VNS showed no significant effect on neurogenic dural vasodilation, indicating that the peripheral TVS component is not involved in mediating VNS anticephalgic action (data on file).

## Conclusion

Analysis of the results from the studies presented above allows us to conclude that the anticephalgic effect of VNS is achieved through at least two mechanisms: (1) suppression of TNC neuron activity and (2) inhibition of CSD, which are mediated by NTS through the involvement of subcortical structures of antinociceptive control, particularly the raphe nuclei and LC, with the participation of serotonin-, glutamate-, GABA-, opioid-, and noradrenergic ligand-receptor systems of the central nervous system. Further studies on specialized models of cephalgias are required to elucidate the role of other anatomical structures and biologically active substances in realizing the therapeutic potential of VNS for headache treatment.

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