Chapter 6
Vagus Nerve Stimulation

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6.1 Introduction

Vagus nerve stimulation (VNS) is a neuromodulatory treatment approach that has been used as an approved method for the treatment of epileptic seizures and depression since the mid-1990s, using implanted (invasive) VNS devices. Several studies in these patient groups also reported significant improvements in their migraines and cluster headaches [1–4]. Subsequently, several open-label and controlled studies have been conducted using a proprietary device that stimulates the vagus nerve non-invasively, via placement of the device on the neck, adjacent to the trachea. These studies seemed to support the original findings that VNS is an effective approach in the treatment of migraine [5–7] and cluster headache [8–10]. These data are further supported by preclinical studies demonstrating the efficacy of VNS in rodent models of primary headache [11–13]. Currently, via the proprietary gammaCore® device, non-invasive VNS (nVNS) is approved for the acute and preventive treatment of migraine, cluster headache, hemicrania continua and medication overuse headache, with a CE marking (Conformité Européene—European Conformity), within the European Economic Area (EEA) and EFTA (European Free Trade Association) member states, which includes all European Union member states, the United Kingdom, and also EFTA member states. It is also approved in Canada for acute and preventive treatment of migraine and cluster headache, and has FDA approval in the United States of America for acute treatment of episodic cluster headache and migraine. In this chapter, we will briefly review the anatomy and physiology of the vagus nerve, particularly in

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relation to headache, and review both clinical and preclinical data, which support the use of nVNS in primary headache and, potentially, facial pain treatment.

6.2 The Vagus Nerve

The vagus (*latin*, wandering) nerve is the tenth (X) cranial nerve and the major parasympathetic innervation of the autonomic nervous system. It is the longest of the cranial nerves, extending from the brainstem to the abdomen. It is primarily involved in many involuntary functions, including regulation of breathing, heart rate and digestion. It arises from the medulla and is composed of 80% afferent fibres, projecting to the brain, and 20% efferent fibres that project to the rest of the body. These nerve fibres originate from cell bodies in the superior (jugular) and the larger, inferior (nodose) vagal ganglion (Fig. 6.1a, b). These are made up of A-fibres, B-fibres and C-fibres, classified based on their conduction velocities, myelination and size [14]. A-fibres are large, myelinated, and carry afferent visceral information and motor output. B-fibres are smaller, also myelinated, and carry parasympathetic inputs. C-fibres are small, unmyelinated, and carry afferent visceral information [15].

Efferent fibres project to the larynx, lungs, heart, stomach, liver, pancreas and gut (Fig. 6.1b). These fibres are involved in the control of heart rate, respiration and digestion. The majority of afferent vagus nerve fibres, bringing information from the rest of the body, project bilaterally to the nucleus tractis solitarius (NTS) in the medulla. The remaining fibres project ipsilaterally to the spinal trigeminal nucleus (SpV), area postrema, the dorsal motor nucleus of the vagus (DMN) and nucleus ambiguus [16]. Visceral efferents participate in the preganglionic parasympathetic nervous system and arise from the DMN and nucleus ambiguous, innervating all thoracic and abdominal organs, and striate muscle. Fibres arising from DMN do not directly innervate peripheral organs, but on adjacent neurons in the parasympathetic ganglia close to these organs. Postganglionic parasympathetic neurons travel to cardiovascular, respiratory, and GI systems. Visceral afferent fibres from the thorax, heart and abdomen carry information whose cell bodies are located in the nodose ganglion and transmitted to the caudal NTS. Somatic afferents transmit sensory information from the lower part of the pharynx, larynx, trachea, bronchi, oesophagus, the ear and ear canal, and dura mater lining the posterior cranial fossa, via the jugular ganglion, terminating in the spinal trigeminal nucleus, where they project to somatosensory thalamic neurons. From the NTS, vagal afferents project to the locus coeruleus (LC), raphe nuclei, preganglionic parasympathetic neurons, the thalamus, the parabrachial nucleus, the periaqueductal grey (PAG), the amygdala and hippo-

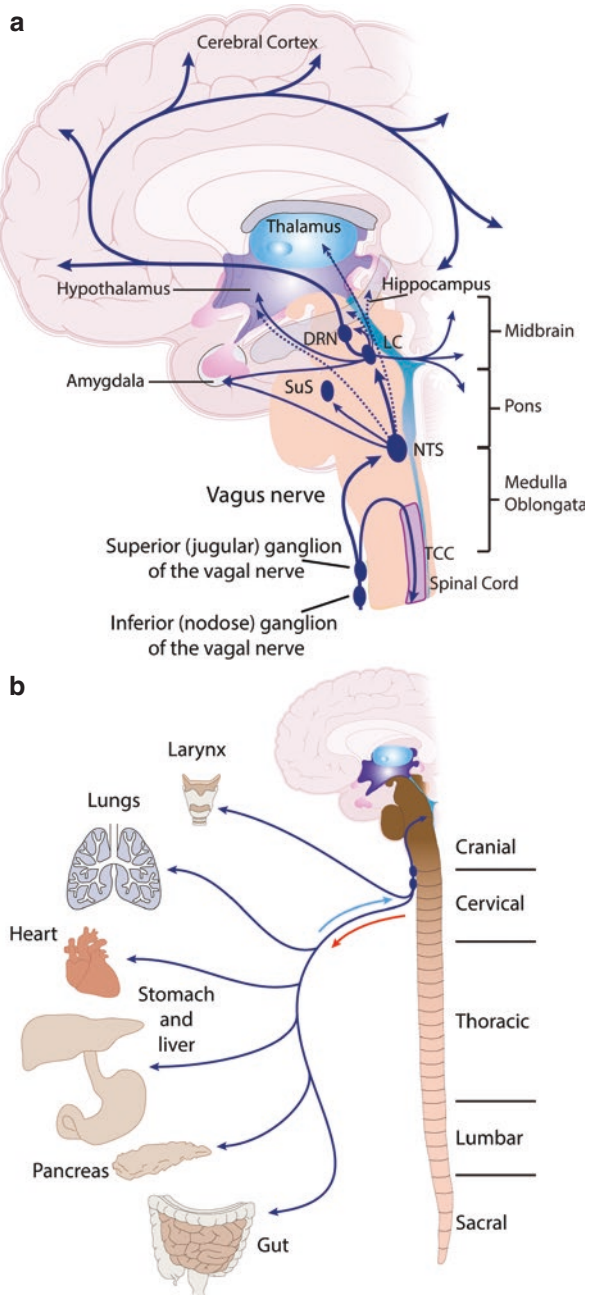

Fig. 6.1 Schematic representation of (**a**) afferent and (**b**) efferent projections of the vagus nerve. *DRN* dorsal raphe nucleus, *LC* locus coeruleus, *NTS* nucleus tractus solitaries, *SuS* superior salivatory nucleus (preganglionic parasympathetic neurons), *TCC* trigeminocervical complex (trigeminal nucleus caudalis and its cervical extension to C1 and C2)

campus, and the cerebral cortex, traversing many synapses in the process [15, 17, 18]. From the LC, there are direct projections to the cerebellum, raphe nuclei, hippocampus, amygdala and cortex (Fig. 6.1a). Through these projections, the NTS, via the vagus nerve, directly influences visceral sensory pathways, somatosensory, higher autonomic, extrapyramidal motor, and limbic systems. This series of vagal afferent connections, via the NTS and SpV, to brainstem and diencephalic nuclei, such as the LC, PAG, raphe nuclei, the cranial parasympathetic projection, hypothalamic, thalamic and cortical regions, implicate VNS in engaging headache pathophysiology [19–21], with therapeutic potential.

6.3 Clinical Studies: Clinical Trials

Since the original data from implanted VNS devices suggested that patients found relief from migraine and cluster headache [1–4], efforts have been made to determine the efficacy of VNS as a treatment for primary headaches, in a more controlled and user-friendly (less invasive) manner. The development of the proprietary gammaCore® device, which can be used to stimulate the vagus nerve non-invasively, has accelerated our understanding of this approach, and potentially the therapeutic mechanisms involved. The gammaCore® device uses stimulation of the vagus nerve through the skin via placement on the neck, adjacent to the windpipe. There is also an alternate device that stimulates the vagus nerve via the auricular branch of the vagus at the concha of the outer ear (NEMOS®), described as transcutaneous VNS (t-VNS®) [22–24]. This electrode device is essentially placed inside the ear, although currently it is not approved for use in headache, only in the treatment of epilepsy.

There is now growing clinical evidence that nVNS is highly effective in the treatment of migraine and cluster headache. Using the gammaCore® device acutely to treat migraine, in two open-label trials, response rates for pain-free at 2 h were 22% (27 patients with 80 attacks) for moderate to severe headache attacks [5] and 22.9% (48 patients with 131 attacks) for mild or moderate headache attacks [6]. This compares favourably with the standard of care (SoC), where in the triptan trials, there was 27–30% pain-free rate [25]. In a third study, acute and preventive treatment with nVNS was combined. For acute treatment, all patients self-reported some pain relief with nVNS, used in tandem with pre-existing acute treatments, with 9 of 20 patients achieving pain freedom at 2 h [7]. There is only one randomised controlled trial in the acute treatment of migraine to date, described as the PRESTO trial [26]. Here, nVNS used within 20 min of pain onset was significantly superior to sham for pain-free rates at 30 (12.7% vs. 4.2%; $p = 0.012$) and 60 (21.0% vs. 10.0%; $p = 0.067$) min, and based on a post hoc repeated measures analysis, also at 120 min (odds ratio: 2.3; 95% CI: 1.2, 4.4; $p = 0.012$). Secondary endpoints of mild or no pain at 120 min (40.8% vs. 27.6%; $p = 0.03$) were also significant. Further, in a randomised controlled trial for headache prevention in chronic migraine (The EVENT Study), data are inconsistent as to whether nVNS reduces number of headache days [27]. In the 2-month randomised phase, nVNS was not significant from

sham. However, in a subsequent 6-month open-label phase, patients did begin to experience a positive outcome. It is worth noting that the nVNS protocols were slightly different through these studies. Either two, 90-s doses with 15 min interval [5], or two, 2 min doses of nVNS with a 3 min interval [25], to the right cervical branch, independent of pain side, or two, 2 min doses, one stimulation on each side of the neck were employed [26]. Through all these studies, however, the VNS electrical parameters were the same (1 m pulse trains (5 pulses) of 5 KHz sine waves repeated at 25 Hz). There is also a single randomised study using the t-VMS® device with 40 patients [28]. Here, 1 Hz stimulation of the auricular vagal area caused a significant reduction in headache days compared to 25 Hz, with 29.4% of these patients reporting >50% reduction in headache days, compared to 13.3% in the 25 Hz group.

More extensive studies using nVNS, both open-label and controlled, have been conducted in cluster headache. In one open-label study, 47% of attacks were aborted within 11 ± 1 min, with approximately half of the patients reducing their use of other abortive treatments, such of oxygen and triptans [8]. In a randomised, double-blind, sham-controlled study (ACT1 Study) acute nVNS had a significantly higher response rate (proportion of patients to achieve pain intensity of 0–1 on a 5-point scale, with 4 very severe pain) compared to sham with episodic cluster headache, but there was no effect on responses in chronic cluster headache [10]. In a second (ACT2) study, nVNS was again superior to sham in treating episodic cluster headache, to pain-free within 15 min of initiation. In the chronic cluster group, nVNS was no different than sham [29]. Finally, in a randomised controlled study, VNS was used as an adjunct alongside SoC in chronic cluster headache. Abortive use of nVNS had no effect on attack duration or pain intensity; however, when used as a prophylactic, SoC plus nVNS caused a significantly greater reduction in the number of attacks. In each study, up to three doses of nVNS were used for abortive treatment. Combined, these data seem to suggest nVNS is effective as an abortive only in episodic cluster headache and when used prophylactically may also be effective in chronic cluster headache.

6.4 Clinical Studies: Evidence of Specific Vagus Nerve Stimulation

In the case of invasive VNS (iVNS), the electrode is in direct contact with the vagus nerve and usually requires minimal current to excite A- and B-fibres, to mediate the therapeutic mechanism of action [30]. However, nVNS requires the electrical current to pass through the skin and a sufficient electrical field needs to be generated to locate and stimulate the vagus nerve. Ordinarily the current necessary, using this mode of stimulation, to activate the vagus nerve would likely cause significant nociceptive pain, as well as tissue injury, to the extent that it is not a workable solution. However, recent advancements in nerve stimulation technology now allow non-invasive stimulation without causing these noxious effects. The gammaCore® device

produces an approximate sine wave stimulus, using alternating current. This allows passage of current 15 times greater than necessary for an implanted device, but with minimal nociceptive pain and only 'mild' skin sensation. Still, one of major concerns of this therapeutic methodology is whether it is actual stimulation of the vagus nerve that is mediating these effects. Several studies now confirm that the vagus nerve is selectively stimulated. Frangos and Komisaruk [31] used fMRI in healthy subjects to demonstrate that transcutaneous VNS in the 'vagus neck region' activates the NTS and several other brain regions that receive vagal inputs, including parabrachial and cortical regions. There is also deactivation of the trigeminal nucleus caudalis (TNC) region. A second study utilised vagus somatosensory-evoked potentials (vSEPs). These are short latency somatosensory nerve potentials attributed to activation of vagus nerve sensory afferents, which is produced by iVNS and recorded by placing electrodes over the scalp [32, 33]. Here, Nonis et al. [34] demonstrate that signature vSEPs are observed in over 80% of participants with cervical nVNS using the gammaCore® device and also using auricular stimulation. In both studies [31, 34] stimulation of the sternocleidomastoid muscles, situated in the posterolateral part of the neck, below the ear, was used as a control stimulus, and they were able to distinguish vagal afferents from muscular artefacts. Thus, the evidence suggests that transcutaneous stimulation of the cervical and auricular vagus nerve regions is selectively stimulating the vagus nerve and is the most likely mechanism in mediating the therapeutic benefits of this approach.

6.5 Preclinical Studies: Primary Headaches

The data from clinical studies for the use of nVNS in the treatment of migraine and other primary headache seem compelling. These data are further supported by preclinical studies. These studies offer the advantage of being able to more readily dissect the likely mechanism of action of VNS in headache treatment, and in some cases allows one to directly compare iVNS and nVNS methods. Unless otherwise stated these studies have used customised versions of the gammaCore® device, and its stimulus settings (single dose; 1 m pulse trains (5 pulses) of 5 KHz sine waves repeated at 25 Hz for 2 min) that is used clinically. In a rat model of chronic trigeminal allodynia that mimics intracranial 'migraine-like' mechanisms, where an inflammatory soup is repeatedly applied to the dura mater over many days, nVNS for 2 min decreased the resulting periorbital allodynia for up to 3.5 h [13]. In the same study, in the primed allodynic rats nitroglycerin (0.1 mg/kg, intraperitoneal), used as an experimental trigger of migraine in patients [35, 36], caused an increase in levels of glutamate in the TNC. This increase was both prevented and aborted by nVNS [13].

The direct effects of VNS have also been studied on the firing of central trigeminovascular neurons, using validated rat models of acute dural intracranial (migraine-like) [37] and trigeminal-autonomic (cluster headache-like) [38] head pain. Here, Akerman et al. [11] demonstrate that both ipsilateral and contralateral iVNS, to trigeminal recording side, inhibits spontaneous and noxious dural-evoked firing of

central trigeminovascular neurons. This effect is dose-dependent, with two doses of nVNS prolonging the inhibition of ongoing firing for up to at least 3 h, and dural-evoked responses for up to 2 h. Two doses of iVNS also suppressed responses of central trigeminovascular neurons to stimulation of preganglionic parasympathetic superior salivatory nucleus neurons, as a model of cluster headache, for up to 2.5 h [11]. Importantly, throughout there was no effect of iVNS on normal cutaneous facial responses, suggesting that VNS does not affect normal somatosensory nociceptive processing. These data provide the first opportunity to dissect the potential neurobiological mechanism of action of VNS in mediating a therapeutic benefit in primary headaches, including migraine and cluster headache. It seems clear now that this likely involves modulation of trigeminovascular nociceptive neurotransmission, of neurons that innervate the dural vasculature. As has been hypothesised from clinical studies, it is likely this is partly via the direct ipsilateral afferent projection to the TNC, mirroring the 'deactivation' observed in the fMRI study [31]. However, given the efficacy of VNS when applied to the contralateral side, in both clinical and preclinical studies, it also suggests VNS engages bilateral descending mechanisms involved in the control of trigeminovascular nociceptive transmission, via the major vagus-NTS afferent projection. Beyond the NTS we can only speculate on the descending mechanisms involved, but noradrenergic-LC and serotoninergic-raphe mechanisms could potentially provide descending modulation. Also, we know that neurons of the paraventricular hypothalamic nucleus directly project to TNC and superior salivatory nucleus, and GABAergic, serotoninergic and PACAPergic modulation here alters trigeminovascular nociceptive processing [39]. This descending mechanism is particularly relevant to cluster headache, which is thought to have a significant hypothalamic component to it.

6.6 Preclinical Studies: Migraine Aura/Cortical Spreading Depression

Cortical spreading depression (CSD) is a slowly propagating wave of neuronal and glial depolarisation that is believed to be the underlying mechanism of migraine aura [40]. In rats CSD has been shown to activate a dural inflammatory cascade, which can also mediate activation of the dural-trigeminovascular nociceptive pathway [41, 42]. Some believe this may be a mechanism through which migraine headache is triggered, although aura is only present in approximately 30% of migraine sufferers [43]. However, all migraine prophylactic drug classes have been demonstrated to prevent or abort CSD mechanisms [44, 45], suggesting that CSD is an important mechanism likely to be involved, in some way, in headache mechanisms related to migraine. While none of the clinical trials has specifically focussed on the ability of VNS to alleviate symptoms of migraine aura, there has been one preclinical study looking at the effects of VNS on CSD, as a surrogate for assessing migraine prophylactic efficacy [12]. A strong advantage of this study is the direct comparison of nVNS and iVNS, and the authors demonstrate that two doses of ipsilateral iVNS

and nVNS for 2 min each, are equally efficacious at suppressing CSD susceptibility. This was measured using threshold to produce CSD with electrical stimulation or CSD frequency with 1 M KCl. Similar to previous preclinical studies, the therapeutic effect persisted beyond 3 h. These data provide a further mechanism through which VNS may be efficacious in migraine treatment. VNS most likely influences cortical regions via the vagus afferent projection to the NTS and bilateral ascending projections thereafter (Fig. 6.1a).

6.7 Other Craniofacial-Related Pains

While VNS has only been used, and approved, for the treatment of primary headaches, several preclinical studies also suggest it could be a relevant avenue of therapy in pain affecting other craniofacial areas. Animal models of temporomandibular disorder (TMD)-like pain often inject inflammatory substances, such as complete Freund's adjuvant (CFA), into the masseteric musculature or temporomandibular joint (TMJ). This produces neuronal activation in the brainstem nuclei, including the spinal trigeminal nucleus and NTS, as well as nociceptive-specific craniofacial grooming behaviours [46, 47]. Unilateral vagotomy significantly reduces neuronal activation in the spinal trigeminal nucleus interpolaris/caudalis transition zone, as well as the NTS [47]. Likewise, TMJ inflammation with CFA reduced head withdrawal thresholds to mechanical and heat stimulation. However, in rats with vagus nerve transected, this effect was prolonged up to 14 days, compared to vagus-intact rats where recovery developed after 7 days [48]. Invasive VNS (0.2 ms, 0.2 mA pulses, at 10 Hz for 5–10 s) significantly reduced ongoing firing of paratrigeminal neurons in TMJ-inflamed rats and the response of nociceptive-specific neurons to mechanical and cold stimulation of the cutaneous facial region, compared to control rats [48]. These data suggest that somato-autonomic processing via the cervical vagus nerve is involved in modulating the consequences of orofacial deep tissue inflammation/injury. Therefore, manipulation of this afferent projection may be utilised for therapeutic purposes for inflammatory orofacial pain disorders.

Another approach looked at craniofacial nociceptive mechanisms mediated by formalin injection into the mystacial vibrissae (whisker pad) in conscious rats, characteristic of a TMD-like pain. Here, 5% formalin caused Fos-immunoreactivity in the TNC, as a marker of neuronal activation. It also caused nociceptive-specific behaviours: rubbing and/or scratching the injected area, measured in an early (0–6 min) and late (6–45 min) phase [49]. VNS was mediated by an implanted device (stimulation parameters: 2 mA, 20 Hz, 0.5 ms cycling with 20 s on/18 s off) and over 24 h. VNS significantly reduced nociceptive-specific behaviours in both early and late phases, but this was more pronounced in the early or acute phase. This suggests, in this model, VNS may have greater effects on peripheral nociception rather than centrally. In addition, VNS significantly reduced Fos counts in response to formalin in the TNC. A final observation linking the lower craniofacial region with the vagal nerve afferent input is that two case series reports suggest that tri-

geminal pain, described as trigeminal neuralgia-like with no dental or orofacial cause, may also be a side effect of VNS therapy [50, 51]. In both cases, VNS was via implanted devices and used to treat epilepsy. Also, the trigeminal pain appeared to be directly linked to VNS onset and also current dependent. Resolution of VNS-related orofacial pain was largely achieved by reducing the current. Taking all these data together, it suggests that the vagus nerve is involved in modulating craniofacial nociceptive mechanisms, and VNS may also be a relevant therapeutic approach in craniofacial pain disorders beyond primary headache, including TMD-related orofacial and cervical pains.

6.8 Conclusion

Non-invasive stimulation of the afferent projection of the cervical vagus nerve is efficacious in the treatment of various primary headache disorders, including migraine and cluster headache, particularly as an abortive therapy. This neuromodulatory treatment approach is now approved for use in the treatment of various primary headaches, across many countries, via the proprietary gammaCore® device. The reported clinical efficacy is supported by preclinical studies using rodent models of headache and orofacial-like pain. Together, the clinical and preclinical studies suggest that VNS may act via two mechanisms. First, via direct afferent projections to central trigeminal neurons, which relay all somatosensory information from the head and face, causing inhibition/deactivation of this activated neuronal structure. Second, it may act indirectly through many bilateral structures within the brainstem, hypothalamus, thalamus and cortex, via the cervical vagus afferent projection to the NTS and its subsequent projections to these nuclei. Perhaps what is still outstanding in our knowledge of VNS as a treatment is whether this modality will be efficacious as a preventive treatment, for highly episodic or chronic forms of these primary headaches. Finally, based on several preclinical studies, there is also a potential opportunity to pursue VNS as a treatment in various facial pain disorders, with the caveat of optimising our understanding of how VNS impacts lower craniofacial structures and, on the very rare occasions, actually be the cause of facial trigeminal-related pain.

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