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Review

Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects

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Abstract

Vagal nerve stimulation (VNS) is an approved treatment for epilepsy and is currently under investigation as a therapy for other disorders, including depression, anxiety and Alzheimer's disease. This review examines the pre-clinical and clinical literature relating to VNS. A brief historical perspective is given, followed by consideration of the efficacy of the various clinical applications of VNS. Finally, what is known about the mechanism by which VNS exerts clinical benefit is considered. It is concluded that although the precise mechanism of action of VNS is still unknown, the search for the mechanism has the potential to lend new insight into the neuropathology of depression. It is important that prior assumptions about the influence of VNS on particular aspects of brain function do not constrain the investigations.

Keywords: Vagus nerve; Seizures; Electroconvulsive therapy; Antidepressant; Brain stimulation

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1. Introduction

By June 2004, more than 29,000 patients, in 24 different countries, had been implanted with a vagus nerve stimulator device from Cyberonics, Inc.; who estimate that this amounts to more than 50,000 patient years of experience

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with VNS (source: http://www.cyberonics.com/pdf_files/Press_Info/CYBX_Milestones.pdf; date of download 05/01/05). However, research into the physiological and functional effects of VNS is a relatively recent development—

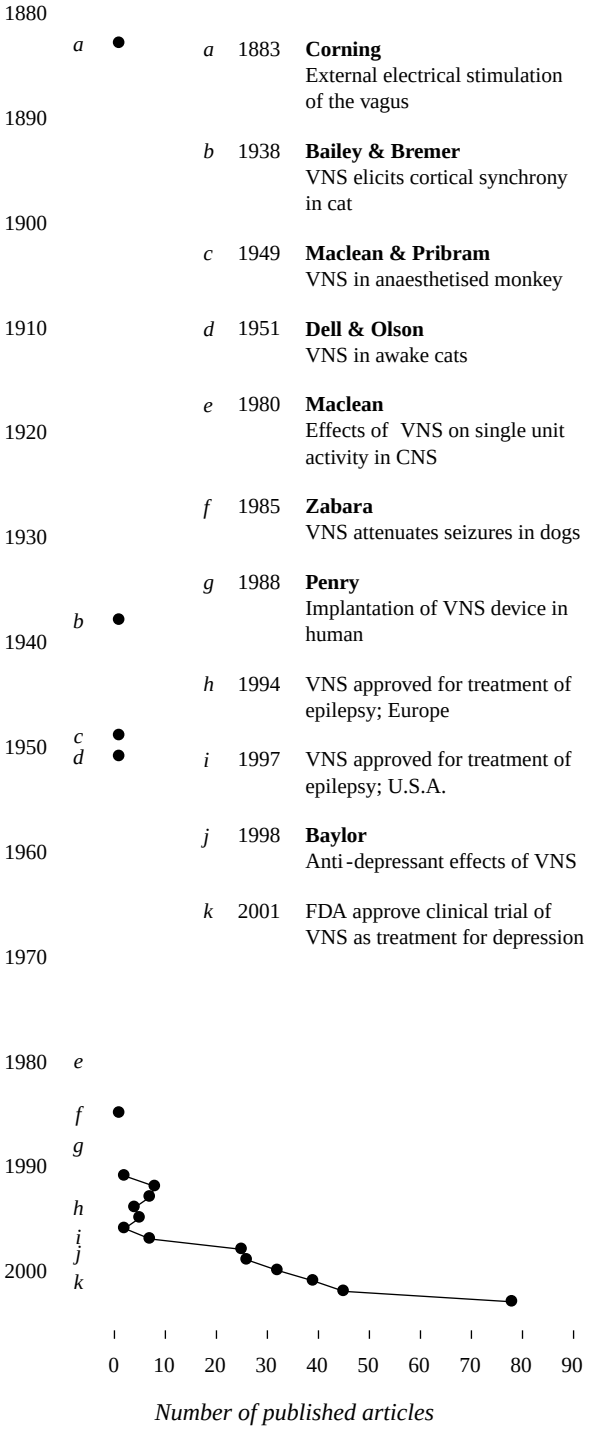

Fig. 1. Time-line illustrating the major events in the history of stimulation of vagus nerve as a treatment for seizures and depression over the past 125 years, with a graph showing the recent surge (to 2003) in the number of published articles. (Source of information: Thompson ISI Web of Science[SM] database, search on search term: [Vag* nerve stim* AND (epil* OR depress*)]. Limits of search set to English language/Articles.

which is surprising considering the number of patients with the device and the fact that the first reported use of VNS was in 1883—and the effects of VNS on central nervous system physiology remain a subject of speculation. There is some evidence to indicate that VNS may exert its anticonvulsant effects via the locus coeruleus (Krahl et al., 1998) but whether the locus coeruleus is a critical structure for all the effects of VNS, is unknown. The surge of original articles in the scientific literature investigating the functional and physiological effects of VNS started around 1991 (see Fig. 1). This article reviews this literature and considers what is known about the mechanisms mediating the clinical effects of VNS.

2. The vagus nerve

The vagus nerve is the longest of the cranial nerves, innervating organs of the neck, thorax and abdomen and reaching to the colon. The origin of the vagus nerve in the CNS is the medulla. The nucleus ambiguous contributes fibres to the vagus nerve, as well as to two other cranial nerves: the glossopharangeal (cranial IX) and the accessory nerve (cranial XI). The dorsal motor nucleus of the vagus gives rise to the visceromotor efferent component of the vagus (Gray, 1918).

Traditionally, the vagus nerve was considered a parasympathetic efferent nerve, controlling and regulating autonomic functions, such as heart rate and gastric tone. This view of the vagus nerve changed in 1938, with the observation that VNS resulted in changes in the EEG (Bailey and Bremer, 1938), and it is now accepted that it is a mixed nerve, with 80% of the fibres carrying afferent (sensory) information and 20% carrying efferent (motor) information (Foley and DuBois, 1937; cited by George et al., 2000). Cardiovascular efferents of the vagus regulate heart rate and blood pressure, however, in this respect, the right and left vagus nerves differ. The right vagus innervates the sinoatrial node (involved in the pace-maker function of the heart), whereas the left vagus innervates the atrioventricular node (regulating the force of contraction of the heart muscle as a function of the volume of blood returned to the heart, with less influence over heart rate). Randall and Ardell (1985) showed in the dog that stimulation of the right vagus, compared to the left, caused a greater reduction in heart rate and Woodbury and Woodbury (1990) reported that high-level stimulation of the left vagus had no effect on heart-rate, but there was a cessation of respiration of approximately 1-s before returning to baseline within a few seconds.

The sensory afferent cell bodies, residing in the nodose and the jugular ganglia, project to the nucleus of the solitary tract (NTS), terminating in a topographical manner, so resulting in functional subdivisions of the NTS (Maier et al.,

Table 1
Table 1 A summary of the characteristics of the fibre components of the vagus nerve (compiled from data in Bailey and Bremer (1938), Chase et al. (1966) and Woodbury and Woodbury 1990, (1991))

	FIBRE		
	A	B	C
Fibre diameter (mm)	5–20	<3	0.4–2
Gross anatomical	Large	Small	Small
Main Function	Fast pain, temperature, touch, Muscle tone	Vasomotor, visceromotor	Vasomotor, visceromotor, slow pain, temperature, touch
Myelinated	✓	✓	✓
Threshold (mA)	0.02–0.2	0.04–0.6	2.0+
Conductance velocity (ms)	30–90	10–20	0.3–6
Information conveyed	Mechano sensitive cardio-pulmonary	Mechano sensitive cardio-pulmonary	Cardio-pulmonary chemoreflexes
Recruitment order	1st	2nd	3rd
Effect of VNS on EEG	Synchronisation	Synchronisation	Desynchronisation

1998). Direct and indirect projections from the NTS—hence, the brain areas over which the vagus nerve has influence—are widespread. Recently, data from functional imaging (see Barnes et al., 2003) has supplemented traditional anatomical studies to provide a comprehensive map of central nervous system areas of influence of the vagus.

In 1930, Erlanger and Gasser (1930) described the physical and electrical conductance properties of the A, B and C fibres in cranial nerves (summarized in Table 1). The majority of the fibres in the vagus nerve are C-fibres: Woodbury and Woodbury (1990) quote an estimate of 65–80% in the cat.

3. The history of VNS

The American neurologist, James L. Corning (1855–1923), has been described by Lanska (2002) as '*an enigmatic and controversial figure*' (Lanska, 2002, p. 452). The controversy surrounds allegations of plagiarism against him, and yet Lanska (2002) observed that several significant scientific contributions by Corning have gone unrecognised, among these being his development of a primitive device for stimulation of the vagus for the suppression of seizures. Corning believed that seizures were caused by 'venous hyperaemia' and that manual compression of the carotid artery would correct this, thus suppressing the seizures, by decreasing heart rate and thereby lowering cardiac output (Corning, 1883). Although Corning reported that this form of VNS was dramatically effective for seizure-suppression, it was not widely accepted by his contemporaries and was largely forgotten about for a century (Lanska, 2002).

By 1938, Bailey and Bremer had recognized the potential for using VNS for its direct influence on central nervous system function, rather than for its indirect physiological effects, which had been the assumption of Corning's approach. They reported that, in the cat, VNS elicited synchronised activity in the orbital cortex. Maclean and Pribram (cited in MacLean, 1990), in 1949, applied VNS to anaesthetised primates and reported that VNS-evoked slow waves were generated from the lateral frontal cortex. In 1951, Dell and Olson (cited by George et al., 2000) reported that electrical stimulation of the cut vagus nerve evoked responses in the ventroposterior complex and intralaminar regions of the thalamus in the awake cat. In 1985, Zabara (1985a; 1985b) reasoned, from what was known about the anatomy and from these earlier reports, that VNS had clinical potential for the control of epilepsy. He went on to demonstrate that VNS not only attenuated motor seizures induced by strychnine and tremors induced by pentylenetetrazol in dogs, but that the beneficial effects of VNS in seizure suppression outlasted acute stimulation (Zabara, 1992). The first reported implant of a VNS device into a human for chronic VNS for the treatment of drug-resistant epilepsy was in 1988 (reported by Penry and Dean, 1990) and this was soon followed by more human implants (Rutecki, 1990; Penry and Dean, 1990).

4. Stimulation parameters

There are a number of variables that can be adjusted in the clinic to tailor the stimulation delivered to the patient: current intensity; pulse width; frequency; duration of the '*on*' and '*off*' period can all be easily varied and adjusted externally. When the stimulating device is first activated in a patient, typically only low stimulation parameters are tolerated (0.25–0.75 mA) (DeGiorgio et al., 2000). The stimulation parameters are increased gradually; indication that the maximum tolerable level has been exceeded is immediately obvious, as the patient will report pain or may suffer bouts of coughing. The stimulating device is then reset to the highest 'comfortable' setting.

In the experimental literature a wide range of stimulation parameters are reported: from 0.2 mA (sufficient to maximally recruit A-fibres) to 3.0 mA (supra-maximal for the recruitment of A-, B- and C- fibres—see Table 1). Effective stimulation parameters that are used in the clinic originate from the experimental investigations. Agnew and McCreey (1990) investigated the effects of a range of differing stimulation frequencies and showed that stimulation frequencies of 50 Hz and above caused major irreversible damage to the vagus. Following this observation, which was confirmed by others (Woodbury and Woodbury, 1990, 1991; Zabara, 1992), the FDA approved

stimulation frequencies between 20 and 30 Hz for clinical use.

Stimulation of the different fibres of the vagus individually and together (achieved by varying the stimulation parameters and taking advantage of different stimulation thresholds of the different fibres—see Table 1), can evoke dramatically different responses in electroencephalogram (EEG) recordings—weak stimulation of the vagus recruits the A and B fibres and causes a synchronisation of the EEG, whereas higher stimulation, which also recruits C-fibres, causes a EEG desynchronisation (Chase et al., 1966). Woodbury and Woodbury (1990) reported that high-level stimulation of the vagus (maximally recruiting C-fibres), prevented chemically or electrically-induced seizures and reduced the length of seizures in progress. They concluded: '*antiepileptic potency is directly related to the fraction of the vagal C fibres stimulated*' (p. S17). However, this conclusion requires reconsideration, as seizure suppression is seen in rats even following selective, capsaicin-induced, destruction of C-fibres (Krahl et al., 2001). Furthermore, stimulation parameters which are clinically effective for seizure suppression are below those that would recruit C-fibres (Koo et al., 2001). Finally, Chase et al. (1966) noted an immediate (within 1 or 2 s) onset of hippocampal theta rhythm at a level of stimulation which does not recruit C-fibres but which does induce cortical synchrony. Taken together, these studies suggest that C-fibre activation is not required for inducing hippocampal theta rhythm or for seizure suppression. Furthermore, they indicate that low and high level stimulation of the vagus can have different central effects.

5. Clinical applications

Cyberonics, Inc., have proposed that VNS has the potential for treatment of a large number of clinical conditions, including partial complex epilepsy, generalized epilepsy, involuntary movement disorders, depression, migraine and neuropsychiatric disorders.

5.1. Epilepsy

Zabara (1992) speculated that whilst the acute effect of VNS is to terminate a seizure, there is also a chronic effect, such that sustained VNS treatment results in increased inhibition of seizure activity and thus decreased likelihood of seizure onset. Morris and Mueller (1999) reported data to support the prediction arising from this, namely that there would be increasing efficacy of VNS over time. They analysed the long-term effects of VNS in the patients who participated in three studies of epilepsy (coded EO3, EO4 and EO5) sponsored by Cyberonics, Inc. EO3 was a double-blind active control assessment of VNS in patients ($n=135$) reported by Ben-Menachem et al. (1994); EO4 was the Cyberonics, Inc., open compassionate study ($n=124$) (Labar et al., 1999) and EO5 was a one-year double-blind trial assessment ($n=195$) reported by DeGiorgio et al. (2000). The total group size was therefore 454 patients. 'VNS responders' were defined as patients who reported 50% or greater reduction in seizure frequency. The results indicated that over a 3-year period, the number of responders steadily increased. Notwithstanding this effect, Cyberonics, Inc., recommend that if a reduction of 50% in seizure frequency is not observed after 18 months, the device is deactivated and removed (the leads are left in place, to avoid the possibility of nerve damage with removal).

5.2. Depression

A significant improvement in mood, independent of seizure activity, in patients with epilepsy receiving VNS was noted by Elger et al. (2000), who suggested that further research should investigate the use of VNS as a therapy for depression. The first study of the effects of VNS in patients with depression was published by Rush et al. (2000). The 30 patients did not have a history of epilepsy and they all had a DSM-IV diagnosis of major depressive disorder. They all had suffered four or more major depressive episodes in their lifetime and had a current depressive episode that was unresponsive to treatment. Twelve patients (40%) had an improvement in mood after just ten weeks of VNS. These data prompted the US FDA to approve the one-year clinical trial—led by Dr L. Marangell—to follow the same 30 patients over an additional 9 months. The response rate of 40%, originally reported by Rush et al. (2000), was maintained over the extended period (Marangell et al., 2002). Marangell et al. (2002) concluded that VNS offered a sustained symptomatic benefit after one year and that additional, longitudinal, clinical studies, with larger patient cohorts, were required. A Web of Science search (Thompson ISI Web of Science^{SM} database, http://wok.mimas.ac.uk/about/) on the keywords [vag* nerve stimulation AND depression] restricted to English language articles only, identified 63 articles. Fifteen of these were original articles looking at the anti-depressant properties of VNS in human patients (although it should be noted that five of the fifteen were reporting the longitudinal effects of VNS in the same patient cohort). With one exception (Chavel et al., 2003), all concluded that VNS improved mood. Interestingly, Chavel et al. (2003) were investigating the anti-depressant effects of VNS in a cohort of epileptic patients, whereas in the other studies, the patients were clinically depressed but without a history of epilepsy. Although reporting no effect on mood, Chavel et al. (2003) did report a reduction in anxiety in the epilepsy patients treated with VNS. This reduction was correlated with the reduction in seizure frequency and therefore it might possibly be a secondary, psychological, benefit of treatment.

Nevertheless, it is consistent with previous reports of a therapeutic benefit of VNS for anxiety.

5.3. Anxiety

It has long been known that the vagus nerve is involved in modulating, in part, anxiety. The James-Lange theory of emotion states that the experience of emotion depends upon the perception of autonomic signals for particular emotions. The modern view, largely based on the work of Schacter and Singer in the 1960s (for example, Schacter and Singer, 1962), stresses the importance of the cognitive interpretation, based on the context, but does not dismiss the importance of perception of autonomic arousal. Thus, signals of autonomic arousal are transmitted via the vagus to the brain, where the arousal is interpreted to lend emotional valance.

As noted above, Chavel et al. (2003) reported that patients responding to VNS for epilepsy (defined as experiencing $\geq$50% reduction in seizure frequency) were also significantly less anxious. Rush et al. (2000) had also noted that there may be an effect of VNS on anxiety, having assessed several 'quality of life' measures (including anxiety) in patients being treated with VNS. Of the 30 depressed patients assessed by Rush et al. (2000), nine also suffered from agitation, 10 reported psychic anxiety and 11 reported somatic anxiety. All of these patients reported some improvement: the mean improvement in agitation was 73%; the mean improvement in psychic anxiety was 50%; the mean improvement in somatic anxiety was 36%. These suggestive results led to the approval of a multi-centred open trial for VNS as a treatment for anxiety, which began in 2001. The trial involved 10 patients (mean age 38 years) suffering from obsessive-compulsive disorder ($n=7$), post-traumatic stress disorder ($n=2$) and panic disorder ($n=1$). At 10-weeks, all patients reported some improvement, with the mean reduction in Hamilton Anxiety Scale (HAM-A) scores being 23% (George et al., 2003).

5.4. Cognitive enhancement and Alzheimer's disease

The idea that VNS might be an effective treatment for Alzheimer's disease comes from suggestions that VNS has cognitive enhancing effects. Clark et al. (1999) reported enhanced verbal recognition memory in patients with epilepsy receiving VNS. Furthermore, this improvement was related to stimulus intensity, with the optimal stimulation being 0.5 mA, which is at the low end of the range of clinically effective doses for attenuation of seizures. There was no effect, or even slight impairment, when stimulation was at higher intensities (0.75–5 mA), which are more typical of the intensities effective for the treatment of epilepsy. Sackeim et al. (2001a; 2001b) tested 27 of the 30 patients from the cohort of depressed patients reported by Rush et al. (2000). They reported improvements in motor speed, psychomotor function, executive function and language, but no effect on specific tests of attention and memory. The authors admit that they were unable, from these data, to conclude that VNS was enhancing cognitive function, as they found the improvements were in some cases correlated with the degree of improvement in depressive symptoms and in other cases it was not possible to rule out practice effects. For this reason, the data regarding cognitive enhancement from patients with epilepsy and depression are difficult to interpret—particularly with regard to extrapolating them to make predications about efficacy in treatment of Alzheimer's disease.

Sjogren et al. (2002) reported the effect of VNS in 10 patients with Alzheimer's disease (mean age 67 years), in an open-label study. At 3 months, seven out of 10 patients showed improved scores on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and nine on out of 10 had improved scores on the Mini-Mental State Examination (MMSE). At 6 months, the scores of seven out of 10 patients were still improved relative to their baseline test scores on the ADAS-cog and seven patients were still improved on the MSME. Nevertheless, as Alzheimer's disease is a degenerative disorder, it is problematic to conclude from these low numbers and short time scale that VNS is having cognitive enhancing or disease modifying effects.

Studies in animals could potentially provide interesting additional information that may allow identification of other clinical conditions in which there is significant cognitive impairment, which may be amenable to treatment with VNS. Contrary to the largely inconclusive results in the clinical literature, Clark et al. (1995, 1998) reported that VNS had memory-enhancing effects in rats in an inhibitory-avoidance task. Rats received a single exposure to foot-shock in the dark end of runway followed immediately by VNS (or sham stimulation) in the home cage. Twenty-four hours later, rats were returned to the runway and the step-through latency was found to be significantly longer for the stimulated rats compared to the controls (over 10 min versus under 1 min). This effect was dependent upon the intensity of the stimulus, with 0.4 mA being an effective level of stimulation and 0.2 mA and 0.8 mA having no significant effect. Clark et al. (1998) replicated the effect reported by Clark et al. (1995) and further showed that lidocaine infused below the point of stimulation did not block the effects of VNS, indicating that it was vagal afferents, and not efferents, that were mediating the memory modulating effects.

5.5. Migraines

Hord et al. (2003) hypothesised that VNS may be beneficial in the treatment of migraines, based largely on the observation that VNS increases thermal pain thresholds in animals (Bohotin et al., 2003). In a post-hoc interview study, sponsored by Cyberonics, Inc., Hord et al. (2003) contacted 62 patients that had been implanted with a VNS device between 1993 and 1999 at Southern Illinois

University. Of these, seven patients reported having a history of migraine headache. These patients were asked to score the pain and frequency of the migraines, for before and after implantation of the stimulating device. When so prompted, all four patients reported a decrease in the number of migraines and the severity of the headaches since the VNS device had been implanted. Hord et al. (2003) concluded that the VNS device could be sold as a treatment for migraines. Nevertheless, one must regard this conclusion as tentative given the retrospective nature of the data collection and the (very) small sample.

6. Possible mechanisms

There is considerable evidence indicating that VNS changes brain function by direct afferent action, rather than indirectly via the effects of the efferent projections. The pathways by which VNS exerts its various effects is, nevertheless, poorly understood, however, there is a growing body of evidence to implicate noradrenaline. VNS has been shown to result in a long-lasting (greater than 80-min) increase in release of noradrenaline in the basolateral amygdala, the origin of which could be the locus coeruleus, the largest population of noradrenergic neurons in the brain and in receipt of projections from the nucleus of the solitary tract (Van Bockstaele et al., 1999), thus could be modulated by the vagus. Alternatively, it is also possible that noradrenaline in the amygdala is increased by the direct projections of the noradrenergic neurons of the nucleus of the solitary tract (the A2 noradrenergic cell group), which project to the amygdala (Herbert and Saper, 1992) as well as the locus coeruleus.

Krahl et al. (1998) demonstrated that the locus coeruleus has a key role in modulating the seizure-attenuating effects of VNS, by showing in rats that lesions prevented the ability of VNS to suppress seizures induced by corneal shock. Furthermore, direct electrical stimulation of the locus coeruleus inhibited the development of kindling produced by electrical stimulation of the amygdala (Jimenez-Rivera et al., 1987). Taken together, this evidence is consistent with the suggestion that the locus coeruleus mediates, at least some, of the effects of VNS in attenuating seizures.

Nevertheless, much of the evidence linking noradrenaline to VNS is circumstantial. Undoubtedly, the diverse functions in which noradrenaline is thought to be involved overlap the functions in which VNS is thought to be involved (most notably, including both epilepsy and depression; for review see Jobe et al., 1999), however, this could be because the search for applications of VNS has focussed on the functions of noradrenaline. An alternative approach is to consider what is known about the mechanisms of action of other treatments for depression such as electroconvulsive therapy (ECT) and other pharmacological treatments. In our own laboratory, we have found effects of acute VNS on the firing rate of rat hippocampal neurons (D.A. Groves, E.M. Bowman and V.J. Brown, unpl. obs.). Changes in hippocampal volume have been observed in patients with depression (see Sheline, 2002), as well as changes in other aspects of hippocampal function. For example, both chronic treatment with antidepressant medication and ECT cause an increase in BDNF in the hippocampus (Nibuya et al., 1995). From this observation, (Duman et al., 1997) proposed a neurotrophic model to explain the clinical efficacy of ECT and antidepressant medication, which suggests that hippocampal BDNF promotes the survival and growth of neurones in patients that are at risk of depression (Duman et al., 1997). To our knowledge, the effect of VNS on hippocampal BDNF has not been examined.

In addition to the effects of ECT on BDNF, ECT also induces mossy fibre sprouting in the hippocampus of the rat, unlike either chronic fluoxetine or desipramine treatment (Lamont et al., 2001). It is unknown whether VNS induces mossy fibre sprouting in the hippocampus: on the one hand, VNS does not induce seizures, whereas ECT does. Sub-convulsive ECT and pharmacological treatments of depression do not induce mossy fibre sprouting suggesting that the sprouting could be due to the seizure, in which case VNS would not be expected to induce it. On the other hand, sub-convulsive ECT is clinically ineffective for depression; if mossy-fibre sprouting is related to the clinical efficacy of electrical stimulation, one would expect that VNS would induce it.

The anti-epileptic effects of VNS were initially attributed to the increase in extracellular noradrenaline (in keeping with the noradrenergic hypothesis of epilepsy), however, this may not be the case. VNS has been shown to increase the levels of free GABA in the cerebrospinal fluid (Ben-Menachem et al., 1995); but see also (Carpenter et al., 2004)). In epileptic patients receiving VNS for a year, $GABA_A$ receptor density in the hippocampus was significantly increased in the responsive patients compared to controls and non-responders (Marrosu et al., 2003) from which the authors conclude that $GABA_A$ receptor density may contribute to the seizure attenuating effects of VNS.

The history of biological psychiatry and neurology clearly indicates that therapeutic benefits of many neurological interventions are discovered serendipitously and exploited as treatments without full (or, sometimes, without any) understanding of the mechanism of action. Nevertheless, clues may be obtained and new insights reached when research is aimed at this understanding. The rapid expansion of research into the effects of VNS could provide an important impetus in the search for explanations of the pathogenesis of depression and other disorders for which the therapeutic potential of VNS is being explored. It is important that this search is not constrained by prior assumptions about the influence of VNS on particular aspects of brain function.

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