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Pain control by vagus nerve stimulation : from animal to man… and back

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Abstract

Vagus nerve stimulation (VNS), already used as a treatment for refractory epilepsy, has also been assessed for its analgesic effect. Numerous studies report that electrical stimulation of vagal afferents inhibits spinal nociceptive reflexes and transmission. However, results are partly contradictory, showing that the VNS effects depend on the stimulation parameters. Clinical data have been collected from VNS-implanted epileptic patients in whom pain thresolds were measured and the VNS effect on co-existing headaches was assessed. In addition, in 2 pilot studies of a few patients, VNS was used to treat resistant chronic headaches and migraines. Taken together these clinical studies tend to confirm the analgesic effect of VNS and to suggest its potential utility in chronic headache patients.

In order to better define the nature of neuronal and behavioural changes induced by VNS with devices used in humans and to determine the most adequate stimulation stimulation protocols, we have used a commercially available stimulator (NCP-Cyberonics®) for prolonged VNS in rats. Our results show a clear antinociceptive effect of VNS in models of acute or inflammatory pain with different stimulation protocols including the one used in epileptic patients. Using immunocytochemical methods, we find that activity changes in spinal trigeminal nucleus neurons could underlie at least part of the VNS-induced analgesia.

Key words : Vagus nerve stimulation ; pain ; analgesia ; migraine ; headache.

Studies on the role of vagal afferents in the modulation of nociception have been conducted in animals for more than 20 years. The effects of vagotomy with or without stimulation of the cut nerve were studied acutely on neuronal and behavioral responses to painful stimuli and the overall conclusion was that under certain conditions vagal afferent stimulation had an analgesic potential. The development of an implantable and portable vagus nerve stimulator (NCP-Cyberonics®), now in use for the treatment of refractory epilepsy in man, has opened new perspectives for the study of the analgesic properties of chronic vagus nerve stimulation (VNS) in animals and its potential clinical usefulness in chronic pain syndromes. We will summarize here some of the experimental data obtained in animals with acute stimulations of the cut vagal nerve, the pioneer algometric and clinical studies that have been performed with implantable VNS and results obtained in rats in our laboratory with the same VNS device.

Vagal afferent stimulation and nociception in animals

An anti-nociceptive action of VNS is reported in numerous behavioral studies which describe for instance inhibition of the nociceptive digastric reflex induced by intense tooth-pulp stimulation in cat (Maixner *et al.*, 1989, 1991 ; Bossut *et al.*, 1992) or latency increase of the tail-flick response to noxious radiant heat in rats (Randich and Aicher, 1988 ; Ren *et al.*, 1988, 1989 ; Aicher *et al.*, 1991 ; Thurston and Randich, 1991). However, pro-nociceptive effects have also been reported in the tail-flick test in rats (Ren et al, 1991a). These discrepancies can be explained by differences in stimulation parameters : low intensity stimulations of vagal afferents facilitate, while high intensity stimulations inhibit nociception (Randich and Gebhart, 1992 ; Ren *et al.*, 1993). According to Ren *et al.* (1993), the analgesic effect of VNS seems to depend on a critical stimulation intensity that activates C-fibers. More heterogenous results were found in electrophysiological studies investigating VNS modulation of the response of spinal neurons to noxious stimuli. Whereas neurons from lumbar and thoracic segments are in majority inhibited (Ammons *et al.*, 1983 ; Thies and Foreman, 1983 ; Hobbs *et al.*, 1989 ; Ren *et al.*, 1991b), more contrasted effects are observed on cervical and trigeminal levels with a predominant neuronal inhibition (Chandler *et al.*, 1991 ; Bossut and Maixner, 1996 ; Takeda *et al.*, 1998) or excitation (Fu *et al.*, 1992, Chandler *et al.*, 1996, 1998, 2002 ; Zhang *et al.*, 2003). Ren *et al.* have described a stimulus intensity-dependent effect on neuronal response as well at lumbar spinal cord

Table 1

Synopsis of clinical results obtained on pain after VNS

Studies	Subjects / experimental conditions	Results	Authors
Algometric studies	8 subjects epileptic patients, VNS	↓ heat pain thresholds	Ness *et al.*, 2000
	10 subjects epileptic patients, VNS	↑ mechanical pain threshold = heat pain thresholds	Kirchner *et al.*, 2000
	5 subjects epileptic patients, VNS	↓ thermal wind-up pain	Ness *et al.*, 2001
	30 healthy subjects gastric distention	↑ heat and laser induced pain thresholds = mechanical pain threshold and summation	Sedan *et al.*, 2005
Case reports	1 subject with chronic tention-type headaches epilepsy co-morbidity, VNS	↓ frequency of headaches	Kirchner *et al.*, 2000
	1 migraineur epilepsy co-morbidity, VNS	↓ frequency of migraine attacks	Sadler *et al.*, 2002
	4 migraineurs epilepsy co-morbidity, VNS	↓ frequency and intensity of headaches	Hord *et al.*, 2003
Pilot studies	7 subjects with chronic daily headaches, VNS	↓ frequency of headaches in 1/7 subjects ↑ quality of life in 4/7 subjects	Klapper *et al.*, 2003
	2 subjects with chronic cluster 3 subjects with chronic migraine 1 subject with basilar migraine VNS	↓ frequency of headaches in 4/6 subjects	Mauskop, 2005

level in the tail-flick test in rat (Ren *et al.* 1988, 1989). By contrast, this relationship between VNS intensity and facilitatory/ inhibitory effect was not found after tooth-pulp stimulations in trigeminal neurons of cats (Bossut and Maixner, 1996). With an other approach, Evans *et al.* (1994) have shown that VNS attenuated noxious heat-induced c-fos expression used as a marker for neuronal activity in rat lumbar spinal cord.

Vagotomy studies demonstrate that vagal afferent integrity is essential to the efficacy of different analgesic treatments like morphine (see Randich and Gebhart, 1992, for review). Furthermore, subdiaphragmatic vagotomy decreases the threshold for mechanically induced hind paw withdrawal in rats (Khasar *et al.*, 1998a ; Janig *et al.*, 2000), increases sensitivity to various noxious lesions (Miao *et al.*, 2001) and enhances hyperalgesia induced by the potent inflammatory mediator bradykinin (Miao *et al.*, 1994 ; Khasar *et al.*, 1998b). However, vagotomy also prevents the establishment of kainic acid-induced hyperalgesia in mice (Tien *et al.*, 2003) and reduces nociception in the formalin test in male rats (Khasar *et al.*, 2001). Several authors underline that the effects of vagotomy depend on gender and sex hormone status (Khasar *et al.*, 2001, 2003a, Bereiter *et al.*, 2002).

Vagus nerve stimulation and pain in humans

a) Algometric studies

More recently, cervical vagal nerve stimulators have been implanted in humans to treat refractory epilepsy and experimental pain studies have been conducted in implanted patients. Like the VNS effects in animals, these clinical data showed contradictory results for pain thresholds. In one study, VNS induced a significant decrease of thermal pain threshold with stimulation intensity of 33, 66 and 100% of that used to control seizures (compared to when generator is turn off) (Ness *et al.*, 2000) (Table 1). On the contrary, in another study, VNS produced an increase in mechanical pain threshold (tonic pressure and train of short impacts) but no change of heat pain thresholds, and this, independently of the ON-OFF cycles (Kirchner *et al.*, 2000). However, both teams seem to agree with the existence of VNS mediated central pain inhibitory mechanism affecting wind-up effect in response to repeated noxious stimuli, independently of the acute cycle of the stimulator (Ness *et al.*, 2001). Pain perception has also been assessed in healthy human volunteers after vagal afferent activation by a rapid filling of the stomach with water (Sedan *et al.*, 2005). Heat pain threshold and pain threshold to laser noxious stimulation were increased after such gastric distension while mechanical pain threshold and sensitivity to mecanical temporal summation were not significantly altered.

b) Headache case reports

Besides clinical research on acute pain, recent reports mention reduction in headache frequency and intensity after the initiation of VNS treatment in epileptic patients also suffering from headache or migraine. Kirchner *et al.* (2000) mention the

case of a patient with chronic tention-type headaches since more than 10 years. After receiving a vagal nerve stimulator for epilepsy, the patient had a 80% reduction in headache activity. Similar relief is reported in a migraineur, in whom the frequency of migraine attacks dropped from 2.7 to 0.2 per month after 2 months of VNS (Sadler *et al.*, 2002). Concomitant nausea, photophobia, sonophobia and vomiting are also decreased, while he had only a very modest improvement in seizure control. Hord *et al.* (2003) described 4 patients suffering from migraine without aura detected in an investigation about concomitant chronic pain in 27 persons who received VNS therapy for intractable epilepsy. Current pain measurements were compared to VNS pre-implantation by using Global Pain Relief Rating Scale. All patients with migraine reported reductions in headache frequency and intensity with VNS : 1 patient reported complete pain relief, 2 patients reported substantial pain relief and 1 patient reported slight pain relief.

c) Clinical pilot studies in headache

In addition to these case reports, 2 pilot studies have been conducted on non-epileptic patients in which a vagus nerve stimulator was implanted with the purpose to relieve headache. The 1st study showed a rather beneficial effect of VNS in 7 chronic daily headache patients (Klapper *et al.*, 2003, personal communication) unresponsive to at least 3 of the standard preventive drug treatments for migraine. After 6 months of VNS, 1 out of 7 patients experienced a greater than 50% relief in headache occurrence, duration and severity and 4 patients reported a 75% or greater improvement on the MIDAS scale which measures disability related to headache. A 2nd study of VNS was performed in 2 patients with disabling chronic cluster headache, 3 with chronic migraine and 1 with basilar migraine unresponsive to classical treatments (Mauskop, 2005). Excellent results were obtained in 2 subjects with chronic cluster headache and in 2 with chronic migraine who were able to return to work. There was no effect in the other 2 patients. One patient did not tolerate VNS because of disabling nausea. Both these open studies suggest therefore that VNS may be effective in chronic headaches, but a controlled trial has not been performed yet.

The neural mechanisms of VNS

The exact mechanisms by which VNS may reduce pain and headache remain to be determined. The central projections of the vagus nerve suggest that the upper cervical spinal cord could be involved (McNeill *et al.*, 1991 ; Hobbs *et al.*, 1992 ; Chandler *et al.*, 1996, 2000 ; Qin *et al.*, 2001). The observation that vagal stimulation inhibits spinal cord neurons in segments below C3 but excites C1-C3 neurons led to the hypothesis that propriospinal neurons from high cervical segments could be an important component of vagally mediated antinociception in distant spinal segments (Zhang *et al.*, 1996, 2003 ; Chandler *et al.*, 2002). Central terminals of primary vagal afferents are also largely found in the nucleus of the solitary tract (Beckstead and Norgren, 1979 ; Kalia and Sullivan, 1982 ; Berthoud and Neuhuber, 2000 ; Henry, 2002) which may be the initial relay for vagal afferent inhibition of pain (Beckstead *et al.*, 1980 ; Ren *et al.*, 1990a ; Randich and Gebhart, 1992). Experiments using local anesthesic blockade of nucleus tractus solitarius but also raphe magnus, locus ceruleus and periaqueductal gray suggests that these structures mediate part of the inhibitory effects of VNS (Randich and Aicher, 1988 ; Randich *et al.*, 1990 ; Ren *et al.*, 1990b ; Nishikawa *et al.*, 1999). Stimulation of vagal afferent fibers has been reported to affect the basal activity of raphe magnus neurons (Blair and Evans, 1991 a and b ; Thurson and Randich, 1992 ; Evans and Blair, 1993). Furthermore, positron emission tomography during VNS in epileptic patients showed changes in activity of structures belonging to the “pain network” such as thalamus and hypothalamus (Ring *et al.*, 2000 ; Van Laere *et al.*, 2000 ; Vonck *et al.*, 2000 ; Henry *et al.*, 2004).

Different neurotransmitter systems have been implicated in VNS-induced analgesia, in particular serotonin (Meller *et al.*, 1990 ; Evans et al, 1994 ; Tanimoto *et al.*, 2004), noradrenaline (Ren *et al.*, 1988) and opioïds (Randich and Maixner, 1984 ; Takeda *et al.*, 1998). GABA was found increased in the cerebrospinal fluid of epileptic patients treated with VNS (Ben-Menachem *et al.*, 1995). Vagal afferent impulses could also modulate pain perception via an indirect activation of the paraventricular nucleus, which in turn modifies adrenaline release from the adrenal medulla (Khasar *et al.*, 2003). Finally, VNS is able to increase plasma levels of ACTH and corticosterone (Hosoi *et al.*, 2000) which could mediate some of its antinociceptive and anti-inflammatory effects.

VNS (NCP-Cyberonics®) in animal pain models : personal contribution

Before specifically applying VNS in the treatment of refractory pain, its efficiency ought to be determined in animal experiments under conditions applicable in humans, i.e. use of the implantable devices employed in epilepsy, search of the most efficient and best tolerated stimulation protocol, identification of the pain types that respond to the treatment. Such studies in animal models are also suitable to better understand the underlying neuronal mechanisms involved.

We have therefore developed in our laboratory a model to study the effects of chronic left cervical VNS in rat using the commercially available device (NCP-Cyberonics®) and adapted electrodes (see description in Bohotin *et al.*, 2003a). The model allows to perform prolonged vagal nerve stimulations (up to several days) in the awake state which contrasts with the vagal afferent stimulations of previous animal experiments in which short-term preparations and electrodes tightly fixed around a desheathed or cut vagal nerve were used under light anesthesia. We have tested 2 types of experimental pain models : the hind paw hot water test (acute pain) and the orofacial formalin test (trigeminal inflammatory pain). The analgesic effect of two different stimulation protocols was examined, one with a stringent duty cycle (20s ON/ 18s OFF) and one with the duty cycle used in epilepsy (30s ON/ 5 min OFF). The more stringent duty cycle applied for 24 hours reduces significantly formalin-evoked nociceptive behaviour (Bohotin *et al.*, 2003a). Furthermore, VNS attenuates the increase of c-fos expression in trigeminal nucleus caudalis induced by the painful stimulation which suggests that activity changes in secondary trigeminal nociceptors may play a role in VNS analgesia. With the same protocol, we also observed that VNS increases heat pain tolerance in both hind paws as soon as 2 hours after turning on the stimulator (Bohotin *et al.*, 2003b). When the less stringent duty cycle used in epilepsy is applied, VNS first decreases heat tolerance after 2h, but then produces an antinociceptive effect starting 24 hours after stimulation onset (Bohotin *et al.*, 2003b). The neuronal activity and transmitter changes which are associated with the analgesic effect induced by VNS are currently under study. Taken together, our results demonstrate a clear antinociceptive effect with both VNS stimulation protocols including the one that should be best tolerable by patients.

Conclusions

To conclude, outcomes from investigations in animals and humans are promising, suggesting that VNS may be effective to alleviate pain and particularly useful in head and facial pain syndromes. However, VNS remains an invasive procedure which can only be considered in pain syndromes refractory to other available non-traumatic treatments. Before considering its clinical application in pain, further studies are thus clearly needed to better define its indications, limitations and mechanisms of action.

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