Effects of vagal nerve stimulation in the rat orofacial formalin model of pain

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In refractory epilepsy patients treated by vagal nerve stimulation (VNS) contradictory effects have been found on pain thresholds. In small groups of such patients and in 2 pilot studies, VNS was nonetheless found to have a beneficial effect on chronic daily headache and migraine. In order to optimize VNS protocols in future clinical protocols of pain therapy, it seems necessary to define in animals its analgesic effect, its mechanisms of action and the most efficient stimulation parameters.
We have studied the effect of prolonged left cervical VNS on orofacial, formalin-induced, inflammatory pain in rats. We have used the implantable commercially available device (NCP-Cyberonics°) and applied a stimulation protocol tolerable by patients, i.e. the one used in epilepsy therapy (duty cycle of 30 s ON/ 5 min OFF) for several days. We observed that the time spent rubbing the painful formalin-injected area was significantly shorter in rats that received VNS for 3 days.
Morphological studies showed that 4h post-formalin c-Fos Ir neurons were more numerous in the Kölliker-Fuse nucleus in VNS-treated animals. Moreover, in the latter enkephalin and GABA immunoreactivities were increased at the level of the trigeminal nucleus caudalis (TCN) during the tonic phase of formalin-evoked pain (24 min post-injection), while NOS expression was decreased.
Our behavioural results show a clear antinociceptive effect of VNS with an “epilepsy-like” protocol, suggesting that VNS may be an effective treatment option in refractory headaches. As possible neurobiologic substrates for this effect, we identified activation of Kölliker-Fuse neurons possibly projecting to TCN and increased expression of anti-nociceptive versus pronociceptive transmitters in the superficial TNC laminae.