MOLECULAR AND NEUROPHYSIOLOGIC EFFECTS OF VAGAL NERVE STIMULATION (VNS) IN EXPERIMENTAL ANIMALS AND HUMANS

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Vagal nerve stimulation (VNS) has been used all over the countries in more than 50.000.000 patients affected by medically refractory epilepsy. Although, VNS represents the only non pharmacological, non surgical option for epilepsy treatment and its use has been prescribed in depressive syndromes, the precise mechanism by which the device exerts its action remains still elusive. Recent studies on chronic VNS with long-term EEG monitoring in humans have revealed a progressive reduction in the frequency and duration of sharp waves as well as a substantial decrease in interictal spiking.These studies suggest that VNS modifies interictal activity, although it has remained unclear whether modification of the EEG pattern by long-term VNS plays a role in the observed therapeutic action. We have shown that VNS increases the power spectrum as well as the intra- and interhemispheric synchronization of EEG frequencies between 20 and 50 Hz (gamma band), whereas it reduces the synchronization of frequencies under 20 Hz (delta, theta, alpha, and beta bands) without substantially affecting their power spectra. Moreover, among the most important factors that can contribute to the effects of VNS a special place should be deserved to the possible effects on GABA-ergic neurotransmission. Although previous studies focused on the modifications of GABA contents in cerebro-spinal fluid revealed inconclusive, we mapped GABA receptors with the inverse agonist Iomazenil using a single photon tomography (SPECT) before VNS device implant followed by a control 13 months after. Our results show that only the subjects responding to VNS with a clinical significant improvement exhibits a dramatic increase in GABA receptor density in cortical areas where SPECT has proved a severe reduction before the implant. Given that neurotrophic factors and monoamines could play a crucial role in the pathophysiology of depression we tested whether VNS could increase the expression of brain-derived neurotrophic factor, fibroblast growth factor, and nerve growth factor as well as the concentration of norepinephrine in the rat brain. The effects of VNS were evaluated on the growth factors in RNA levels and NE concentrations by ribonuclease protection essay and microdialysis respectively. We found that acute VNS increased the expression of brain-derived neurotrophyc factor and fibroblast growth factor in the hippocampus and cerebral cortex, decreased the abundance of NGF mRNA in the hippocampus and increased NE concentration in the prefrontal cortex. This study demonstrates that acute VNS triggers neurochemical and molecular events in the rat brain that might facilitate neuronal trophism.