Specific Vagal Nerve Stimulation Paradigms Differentially Engage the Neurons in the Medulla vs the Cortex: Treatment of Epilepsy

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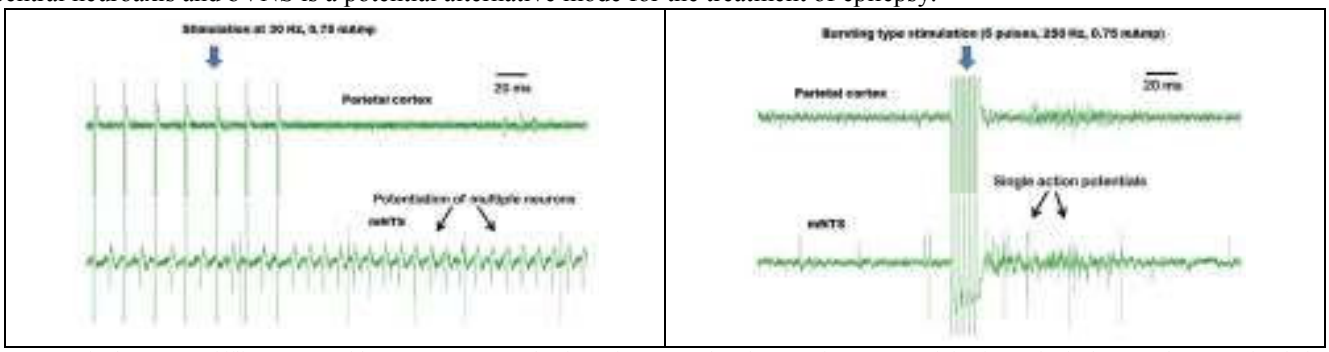
Background: Vagal nerve stimulation (VNS) in the treatment of epilepsy typically uses a pattern of charge-balanced current stimulation at frequencies of 20-30 Hz. Some patients do not respond to this regular pattern of VNS therapy (rVNS) or become unresponsive to it over time. Here, we compared these regular stimulus patterns (rVNS) to a novel bursting pattern (5 pulses generated at 250 Hz at every 0.5s, bVNS) in experimental animals while recording neurons in the medulla and cortex.
Methodology: To evaluate the differences between these stimulation paradigms, acute electrophysiological experiments were performed in rats under alpha-chloralose anesthesia. We assayed neuron activity in both the ipsilateral medial nucleus of the solitary tract – mNTS) (1;2) as well as a cortical region clinically targeted – the parietal cortex. Extracellular action potentials were recorded using high impedance electrodes simultaneously in each location. Principal component analysis techniques identified an average of 3 neurons per site per experiment (n=10 rats).
Results: Conventional rVNS (current intensities of 0.25-0.75 mA, pulse width of 500 μsec) at 30 Hz increased mNTS neuronal activity significantly during the stimulation phase. Specifically, activation of cervical vagus axons at 30 Hz evoked synchronous action potentials in mNTS at latencies averaging 16 ± 1 ms but following rVNS, action potentials persisted in amplitude beyond the stimulus period (Figure, left inset). This persistent discharge likely represents a developing neuronal synchronization beginning at low amplitude (c.f. a few neurons) and gradually increasing in amplitude (c.f. more neurons). This suggests recruitment of additional mNTS neurons that were inactive during baseline unstimulated conditions. In contrast, parietal cortex induced changes in activity was not detected in all animals.

Optimal bursting stimulation parameters (5 pulses, pulse width of 500 μsec at 250 Hz every 0.5 s) evoked single action potentials in the mNTS with every shock (0.25-0.75 mA) with latencies ranging from 8-50 ms. The latencies suggested activation of myelinated A,B-fibers and unmyelinated C-fibers, respectively. The bVNS shocks also activated short latency action potentials in the parietal cortex with latencies ranging from 20-50 ms (Figure, right inset). Spontaneous cortical activity decreased significantly during the non-stimulating phase of bVNS from 6.6±3.1 Hz to 1.6±0.3 Hz.
Conclusions: Conventional therapeutic patterns of vagal nerve stimulation at 30 Hz (rVNS) effectively synchronized and potentiated the amplitude of the neuronal activity in the mNTS without significant changes in cortical activity. The bursting pattern of VNS effectively facilitated the short latency neuronal responses in both the mNTS and the parietal cortex. Consequently, the cortical activity significantly decreased during the unstimulated periods. Since the parietal cortex receives direct projections from limbic structures, these data show that bVNS effectively recruited long lasting activation of the central neuroaxis and bVNS is a potential alternative mode for the treatment of epilepsy.



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