Investigation of neural desynchronization as a mechanism of seizure suppression by nonperiodic electrical stimulation

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Introduction: In the animal model of seizures induced by pentylenetetrazole (PTZ), electrical stimulation (ES) applied with a random interpulse interval (nonperiodic stimulation - NPS) to the amygdala has anticonvulsant properties [1-3]. According to the notion that seizures are episodes of neural hypersynchronism [4,5], our hypothesis is that NPS may wield its effect by desynchronizing neural networks involved in the ictogenic process. One way to measure neural synchronism would be through the interaction of neural oscillations in different frequency bands. There has been particular interest in the modulation of the amplitude of high frequency oscillations by the phase of low-frequency oscillations (phase-amplitude coupling - PAC), which can be measured by the modulation index (MI) [6]. In this sense, the aim of this study is to investigate - by means of behavioral and electrophysiological assessments - the hypothesis that NPS suppresses seizures by desynchronizing neural oscillators responsible for ictogenesis.
Materials and Methods: Electrophysiological recordings from cortex (CX), hippocampus (HP), and thalamus (TH) were performed and NPS was applied to the bilateral amygdala (AMY) in animals subjected to the PTZ continuous infusion model (10 mg/ml/min). Seven groups were evaluated according to the thresholds (t) of convulsant insult and the use or not of NPS until the onset of forelimb clonus (FC) or generalized tonic-clonic seizures (GTCS): CTRL-GTCS (n=15), CTRL-FC (n=14), NPS-GTCS (n=16), NPS-FC (n=12), NPS-FCt (n=7), NPS-GTCSt (n=13), NPScont-GTCSt (n=14). Threshold of PTZ required to trigger FC and GTCS behaviors were calculated. The MI technique used to evaluate PAC between different frequency bands (phase frequencies: 0-2 Hz, 2-6 Hz, and amplitude frequencies: 8-14, 14-30, 30-60, 60-100, 100-200, 200-300 Hz) in electrographic recordings is described elsewhere [6] (ethical protocol 31/2014).
Results: The PTZ threshold to FC and GTCS were significantly increased in NPS-FC and NPS-GTCS when compared to control groups. Survival time of all NPS groups was statistically greater than that of control groups. NPS-GTCSt and NPScont-GTCSt groups had a lower number of convulsive behavior occurrence and deaths. For the analysis of the coupling between frequencies, the CTRL-GTCS and NPS-GTCS groups were compared. Analyses are related to the following five electrographic periods: 30 seconds (s) of PTZ infusion onset, 30 s preceding the FC, during FC, tonic phase, and clonic phase. For 0-2 Hz phase frequency, MI was significantly higher for CTRL-GTCS in the last 30 s preceding the FC in the amplitude frequencies of 8-14 Hz (in HP), 14-30 Hz (in HP and TH), and 30-60 Hz (in CX, HP and TH). It was also significantly higher in the tonic phase in the range of 30-60 Hz (in HP and TH), and in the clonic phase in the range 30-60 Hz (in TH). For the phase frequency of 2-6 Hz, MI was significantly higher for the CTRL-GTCS in the last 30 s preceding FC in the 8-14 Hz amplitude frequency range (in CX and HP), and in the tonic phase in the amplitude frequencies bands 8-14 Hz (in HP) and 14-30 Hz (in HP and TH).
Discussion and Conclusion: Our results corroborate previous studies relating epilepsy to hypersynchronism and the notion that NPS suppresses seizures by desynchronization of epileptogenic networks. Furthermore, additional behavioral findings of groups with different thresholds of convulsant insult suggest that NPS interferes with the levels of excitability / neural synchronism, generating variations in the behavioral responses, and survival time and rate. Finally, new findings from electrographic studies contributed to characterize a new form of desynchronization, considering that the use of NPS was able to promote substantial decrease of the PAC between specific pairs of frequencies in particular periods during seizure evolution.
References: [1]doi:10.1016/j.yebeh.2008.09.006; [2]doi:10.1016/j.yebeh.2014.05.005; [3] doi:10.1016/j.yebeh.2012.01.004; [4]doi:10.1016/j.neuron.2006.09.020; [5] doi:10.1016/j.yebeh.2013.12.034; [6] doi:10.1152/jn.00106.2010