Generation of EEG Oscillations in Isolated Neocortical Brain Slices

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Introduction: Different frequencies of oscillatory neuronal activity can be produced in rodent neocortical slices by pharmacologically mimicking cholinergic inputs to the cortex during attention and increased glutamatergic excitation during active behaviors. The present study looked at neocortical oscillations produced by application of combined neurotransmitters in rat brain slices.

Methods: 400 µm-thick brain slices were prepared from 24-28 days old Sprague-Dawley rats, and they were incubated for two hours at 32°C with oxygenated Artificial Cerebrospinal Fluid (ACSF). Extracellular neuronal population activity (micro-EEG) was recorded with glass microelectrodes from layer 2/3 of neocortex (Oc2MM in the Retrosplenial cortex). We stimulated cortical neurons in two ways: electrically by driving and thalamic and cortical inputs or chemically by adding combinations of drugs that activate glutamatergic, histamine or cholinergic pathways. Data were collected, analyzed and stored using Igor Pro software (Wavemetrics, OR).

Results: We found that *in vivo*-like EEG oscillations are produced in slices with application of drugs influencing glutamatergic and cholinergic or histaminergic receptors. Most past work has shown that the production of oscillations is dependent on two factors: excitation of neuronal populations and a level of disinhibition. In this study, we show that application of carbachol (cholinergic agonist) and bicuculline (competitive antagonist of $GABA_AR$) effectively produced EEG oscillations. We also show that theta oscillations can be produced without disinhibition, using carbachol and by activating glutamatergic inputs through the addition of kainate. We show that muscarinic and not nicotinic receptors are more important in the production of these oscillations. Lowering the magnesium concentration from control conditions (2 mM) to 0.5 mM allowed NMDA gated glutamate receptors to also come into play and this produced even more robust oscillations. Moreover, the importance of glutamatergic stimulation was observed with the reversible block of oscillations by 2-amino-5-phosphonovaleric acid (APV, 100 μM), an NMDA receptor antagonist.

Conclusions: We report for the first time that theta oscillations can occur without disturbing GABA-mediated inhibition by co-activating kainate receptors. Our ultimate goal is to mimic *in vivo* EEG oscillatory behavior in brain slices. This would facilitate the mechanistic studies of normal cognitive signal processing circuitry and also how anesthetics alter this circuitry.