

## **A novel Kv3 positive modulator augments gamma frequency oscillations in the mammalian neocortex *in vitro*.**

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Neocortical neuronal networks produce synchronized gamma frequency oscillations (30-80 Hz) that are critical for processing and integrating cognitive modalities. Experimental studies have demonstrated that, in the presence of an appropriate pharmacological drive, such neuronal network activity is orchestrated by inhibitory mechanisms, notably GABA<sub>A</sub> receptor mediated events. Within this context, perisomatic targeting fast-spiking parvalbumin-containing (PV<sup>+</sup>) interneurons are capable of sustaining action potential output in the gamma frequency range. PV<sup>+</sup> interneurons entrain the population of neocortical pyramidal neurons via gamma frequency GABA<sub>A</sub>-mediated IPSPs. This synchronised synaptic activity manifests at a population level as a coherent gamma frequency oscillation recorded as a local field potential (LFP).

Kv3-family potassium channels such as Kv3.1 are selectively expressed in PV<sup>+</sup> interneurons in the neocortex. Kv3 channels allow fast-spiking PV<sup>+</sup> interneurons to fire accurately at high frequencies to orchestrate the activity of neocortical networks. Such high rates of firing, with high temporal accuracy, are required for the generation of neocortical gamma rhythms. Previous studies in patients suffering from schizophrenia<sup>1</sup> and putative animals models<sup>2</sup> of the condition demonstrate an inability of neocortical networks to generate coherent gamma frequency oscillations. In addition, post-mortem studies using cortical tissue obtained from patients with schizophrenia report reductions in PV and in the expression of Kv3.1 channels in the remaining PV<sup>+</sup> interneurons.

Given that pharmacological manipulation of PV<sup>+</sup> interneurons is a tangible therapeutic target for schizophrenia, we have examined the effect of a novel class of agents that positively modulate Kv3 channels. Rodent brain slices containing primary auditory neocortex were prepared as previously detailed<sup>3</sup>. Using kainate (400 nM), persistent gamma frequency oscillations were recorded as LFPs using extracellular microelectrodes. Application of AUT1 and AUT6 significantly increased the peak power and area power of persistent gamma activity in the auditory cortex. The peak frequency of gamma frequency oscillations was not altered. Using slices of human inferior temporal neocortex obtained from elective neurosurgery, persistent gamma frequency oscillation elicited by kainate, were also augmented with the addition of AUT1.

Our results suggest that modulation of Kv3 channels by these novel compounds may have the potential to correct disruptions in neuronal synchronization in schizophrenic patients by augmenting gamma frequency oscillations.

1. Uhlhaas PJ et al., J Neurosci. 2006 26(31): 8168-75

2. Cunningham MO et al., J Neurosci. 2006 26(10): 2767-76

3. Cunningham MO et al., Proc Natl Acad Sci U S A. 2004 101(18): 7152-7.