

Tonic GABA-A Inhibition

It is now well established that synaptic GABA-A receptors generate classical 'phasic' inhibitory postsynaptic currents (IPSCs), whilst extrasynaptic GABA-A receptors underlie a persistently active, or 'tonic', current that is elicited by ambient GABA (Fig. 1).

Tonic GABA-A current is restricted to specific neuron types. In cerebellar granule cells and dentate gyrus granule cells, the tonic GABA-A current is generated by

extrasynaptic receptors containing δ and $\alpha 6$ or $\alpha 4$ subunits, respectively, and in hippocampal pyramidal neurons and interneurons, by $\alpha 5$ and δ ; or $\alpha 2$ subunit containing receptors. Tonic inhibition has also been observed in cortical layer 2/3 and 5 pyramidal neurons, but only in the presence of the δ ; subunit selective GABA mimetic THIP. Tonic inhibition contributes to physiological functions, including information storage capacity, oscillations and learning, and the oestrus cycle. Pathophysiologically, tonic inhibition and the expression of extrasynaptic receptor subunits, are known to be altered in human temporal lobe epilepsy and in animal models of this disease.

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OUR RESEARCH

Our work has significantly contributed to an increased understanding of the role of the tonic GABA-A inhibition in epilepsy and sleep oscillations. In particular, our major findings in this field include:

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Ø Identification of the properties of the tonic GABA-A current in thalamocortical neurons of different thalamic nuclei (see publication 2, 3, 4 and 5, below)

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Ø Characterization of a tonic GABA-A current modulation of behaviourally relevant firing patterns and related sleep oscillations in thalamocortical neurons (Fig. 2)

(see publication 5, below)

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Ø Identification of an enhanced tonic GABA-A current in thalamocortical neurons as a necessary and sufficient condition for the expression of absence epilepsy (Fig. 3)

(see publication 1, below)

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We are now continuing to investigate the impact of the tonic GABA-A current in absence epilepsy and sleep, and conducting in vitro patch clamp recordings and in vivo experiments in order to i) investigate the modulation by monoamines and Ach of the tonic GABA-A current in thalamic neurons, and ii) the control of the tonic GABA-A current by GABA-B receptors in different brain regions, including thalamus, hippocampus and cerebellum.

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Details of our discoveries in this field can be found in the following publications and meeting presentations:

1. Cope, D.W., Fyson, S.J., Errington, A.C., Di Giovanni, G., Lörincz, M., Orbán, G., Gould, T.M., Carter, D.A. and Crunelli V. (2009). Enhanced tonic GABAergic inhibition in typical absence seizures. *Nature Medicine*, 15, 1392-1398.
2. Di Giovanni, G., Cope, D.W., Crunelli, V. (2008). Cholinergic and monoaminergic modulation of tonic GABA inhibition in the rat dorsal lateral geniculate nucleus. *Soc. Neurosci. Abstr.* 34, 531.2.
3. Fyson, S.J., Cope, D.W., Crunelli, V. (2008). Postsynaptic GABA-B receptors control 'tonic' GABA inhibition. *Soc. Neurosci. Abstr.* 34, 531.1.
4. Cope, D.W., Crunelli, V. (2007). Metabotropic glutamate receptor-mediated increase in vesicular GABA release enhances tonic GABA inhibition in thalamocortical neurons. *Soc. Neurosci. Abstr.* 33, 142.6.
5. Cope, D.W., Hughes, S.W and Crunelli V. (2005) GABA receptor-mediated tonic inhibition in thalamic neurons. *J. Neurosci.*, 25, 11553-11563.