

Absence Epilepsy

Epilepsy is one of the most serious and widespread neurological diseases, that affects about 1% of the population with significant morbidity and mortality. It is still often associated with social segregation and its presence from a young age to senility represents a substantial economical burden to

society. Notwithstanding these health and financial implications, and because of the unwelcome lack of interest by the media, publicly-funded financial support for research into epilepsy as well as interest by the next generation of neuroscientists into this multi-faceted disorder has drastically decreased in the last 10 years. Moreover, all the large pharmaceutical companies have withdrawn from active research into epilepsy treatment, because of the perceived smaller market compared to neurodegenerative disorders. Clinical and basic research into the mechanism(s) of this debilitating disease, therefore, has now shrunk to its lowest, leading to a highly uncertain future, particularly for patient cohorts suffering from those forms of epilepsy with a complex genotype.

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Absence Epilepsy

A typical absence episode is a non-convulsive epileptic seizure that is characterized by a sudden and relatively brief impairment of consciousness, occurring concomitantly with a generalized and bilaterally synchronous (poly)spike and wave discharge (SWD) paroxysm at 2.5-4 Hz in the EEG (Fig. 1). Typical absence seizures are part of the complex clinical and EEG presentation of a number of idiopathic generalized epilepsies (IGEs), though in childhood absence epilepsy these seizures very often represent the only neurological symptom and are not accompanied by metabolic, neuropathological or other neurological deficits. Typical absence seizures are genetically determined, and there is strong consensus in describing this type of epilepsy as a familial disease with a complex genotype. Indeed, increasing evidence suggests that absence seizures may represent a complex channelopathy of multifactorial genetic background.

This view is supported by many association studies and by the presence of genetic abnormalities and/or mutations in various neurotransmitter- and voltage-gated channels in different IGE cohorts. Among these, GABA-A receptors and low-voltage activated T-type Ca²⁺ channels are undoubtedly those for which the most solid evidence is available, though due to the diverse and complex clinical and EEG presentation of the majority of the investigated cohorts, it is still difficult to unequivocally link these genetic abnormalities with a well-defined epileptic phenotype except in the case of a few rare families. Data from some old invasive studies and recent PET, fMRI and high density EEG investigations have also brought about a general consensus on the key involvement of reciprocally connected thalamic and cortical territories, i.e. what are generally referred to as thalamo-cortico-thalamic networks (Fig. 2), to the expression of human absence seizures. However, the notion that typical absence seizures are truly 'generalized' from the very start of the EEG manifestation of a seizure has been recently challenged by the observation that seizure onset is associated with paroxysmal activation of discrete, often unilateral, frontal cortical regions before spreading to the entire cortical mantle. This scenario is also evident in experimental models of absence epilepsy, though in this case the electrographic component of the seizure appears first over the somatosensory cortex. Indeed, the anti-absence drug Ethosuximide has a much stronger effect when administered in this cortical site than in the thalamus (Fig. 3).

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OUR RESEARCH

Our work has significantly contributed to an increased understanding of the pathophysiological mechanisms of absence epilepsy. In particular, our major findings in this field include:

- Ø identification of an altered GAT-1 activity leading to an enhanced tonic GABA-A current of thalamocortical neurons as a requisite for the expression of typical absence seizures, and of the its (Figs. 4 & 5)
(see publications 1 and 5, below)

- Ø elucidation of the mechanism and site of action of ethosuximide, one of the most widely used drugs for treatment of absence epilepsy (Fig. 3)
(see publications 8, 9, 12, 13 and 15, below)

- Ø characterization of the paroxysmal activity expressed by the main neuronal cell types in thalamus and cortex during spike and wave discharges of typical absence seizures (Fig. 6)

(see publications 4, 10, 11, 12, 14 and 16, below)

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We are continuing to investigate the cellular and network basis that underlie the generation of absence seizures, with the aim of improving our knowledge and provide novel avenues of therapeutic interventions. We are thus conducting in vitro and in vivo experiments in different models of this neurological disease, and in particular, we are i) studying the firing dynamics of large cortical and thalamic neuronal ensembles during absence seizures in vivo, ii) testing novel selective antagonists of different neuronal membrane channels involved in absence epilepsy, and iii) investigating the role of thalamic and cortical astrocytes in this type of epilepsy.

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

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10. Gervasi, N., Monnier, Z., Vincent, P., Paupardin-Tritsch, D., Hughes, S.W., Crunelli, V. and Leresche, N. (2003) Pathway specific action of GHB in sensory thalamus and its relevance to absence seizures. *J. Neurosci.*, 23, 11469-11478.
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