

COMMENTARY

Astrocytes and absence epilepsy

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This commentary discusses the importance of a new study entitled 'ONO-2506 inhibits spike-wave discharges in a genetic animal model without affecting traditional convulsive tests via gliotransmission regulation' by Yamamura *et al.* (2013) from Dr Okada's laboratory. The results from this study suggest that specific astrocyte modulating approaches should be developed for managing non-convulsive forms of epilepsy. In addition, the authors have advanced our understanding of astrocytic signalling and glial transmission. Their findings point to kynurenic acid as one of the key transmitters in the bi-directional communication between astrocytes and neurons.

LINKED ARTICLE

This article is a commentary on the research paper by Yamamura *et al.*, pp. 1088–1100 of this issue. To view this paper visit <http://dx.doi.org/10.1111/j.1476-5381.2012.02132.x>

Abbreviations

GAERS, genetic absence epilepsy rats from Strasbourg; WAG/Rij, Wistar albino Glaxo rats from Rijswijk

Yamamura and colleagues demonstrated that the molecule, ONO-2506 (arundic acid), an astrocyte-modulating agent, is active against spike-and-wave discharges of absence epilepsy in a *Cacna1a* gene knock-down mouse model. They also reported the glial release of kynurenic acid, which extends previous observations from other laboratories showing that various transmitters, such as L-glutamate, D-serine, GABA and kynurenic acid, are released from astrocytes (Hamilton and Attwell, 2010). In addition, they demonstrated that systemic administration of ONO-2506 increases the basal release of GABA and kynurenic acid in a dose-dependent manner without affecting the level of L-glutamate or D-serine in the prefrontal cortex.

The Commission on Classification and Terminology of the International League Against Epilepsy defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and states that these transient recurrent signs or symptoms are due to abnormally excessive or synchronous neuronal activity in the brain (Fisher *et al.*, 2005). Epilepsies and/or epileptic syndromes can be grouped into two major classes, generalized or localization-related (focal), on the basis of their clinical and electroencephalographic features including the topical (or spatial) distribution of ictal discharges and the seizure type (Berg *et al.*, 2010). The heterogeneity of epilepsies and epileptic seizures arises from both the numerous underlying cellular

and molecular mechanisms of the neural processes. Neural dysfunctions as well as physiological neural processes and mechanisms are tightly modulated and controlled by a variety of neuronal and non-neuronal cells, in particular by glial cells. In addition to the well-known roles of glial cells in normal physiological processes, astrocytes and microglia play prominent roles in epileptic events in the brain. Several lines of evidence have demonstrated that astroglial excitability and glial transmission are critical players in epileptogenesis and seizure generation. Evidence that astrocytes can amplify, maintain and expand neurogenic seizure activity raises a major question: do astrocytes, directly or indirectly through their actions on neurons, have a detrimental or beneficial effect on epileptogenesis?

Numerous studies have shown that glial cells are involved in the pathophysiology of convulsive events (de Lanerolle *et al.*, 2010). Activated astrocytes and microglia are major sources of inflammatory molecules in the brain during epileptic activity induced in experimental animal models of human limbic seizures and temporal lobe epilepsy (Vezzani *et al.*, 1999; Jabs *et al.*, 2008). Recurrent limbic seizures in rodents induce an activation of glial cells predominantly in the hippocampus and limbic cortex where seizures originate and spread. Glutamate released by astrocytes has been demonstrated to trigger ictal events in several models of experimental seizure (Tian *et al.*, 2005).

Although the role of glial cells in convulsive seizures has been widely investigated, little is known about the contribution of these cells in non-convulsive forms of epilepsy, particularly in absence epilepsy. Dutuit *et al.* (2000) demonstrated that the astrocyte-specific glial fibrillary acidic protein and its mRNA levels were increased in the cortex and thalamus of genetic absence epilepsy rats from Strasbourg (GAERS) before the development of absence seizures. These findings suggest that there is an age-related early impairment of the neuron–glia interactions in rats with genetic absence epilepsy. More recently, it was shown, by using nuclear magnetic resonance spectroscopy to study cerebral metabolism, that the level of astrocytic glutamate metabolism is enhanced in the cortex of adult GAERS (Melø *et al.*, 2006; Melo *et al.*, 2007). In addition, IL-1 β , a prototypical inflammatory molecule, is induced in activated astrocytes specifically in the somatosensory cortex of GAERS (Akin *et al.*, 2011). This age-related astrocytic activity accompanies the age-dependent development of spike-and-wave discharges in these rats. In fact, these findings raise the crucial question of whether the changes in astrocytes are caused by the spike-and-wave discharges or whether they contribute to this activity. In another well-validated absence epilepsy model, WAG/Rij rats, it was found that the number of glial cells was decreased and the glia-neuron index lower in the somatosensory cortex, a cortical area known to play a key role in triggering epileptic discharges and in the pathogenesis of absence epilepsy (Sitnikova *et al.*, 2011). The highly interconnected circuitry of the cortex and the thalamus is widely regarded as playing an important role in the pathophysiology of absence epilepsy (Onat *et al.*, 2012). The finding that GABA uptake by the GABA transporter GAT-1 is malfunctioning in the thalamus of GAERS has suggested that absence seizures may be astrocyte-specific because GABA uptake is governed exclusively by astrocytes in the thalamus (Cope *et al.*, 2009).

The study of Yamamura *et al.* focused on the regulation of glial transmission with a particular emphasis on network mechanisms in animal models of convulsive and non-convulsive seizures. This paper significantly advances our understanding of the modulation of spike-and-wave discharges of absence seizures with the use of ONO-2506, but considerable work remains before one can determine the relative importance of the several mechanisms involved in the action of ONO-2506 on glial transmission. Future studies on the effectiveness of ONO-2506 on absence epilepsy in well-validated non-convulsive models are essential to clarify it as a therapeutic option for absence epilepsy. In addition, ONO-2506 is not only a viable candidate for absence epilepsy treatment, but also seems to be a potential tool to investigate mechanisms underlying epilepsy and the modulation of seizures through glial transmission. Furthermore, one of the most important future advances in epilepsy research will be the understanding of the communication between the astrocytic functions and neuronal signalling in epileptogenesis.

Conflict of interest

I have no conflict of interest to report.

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