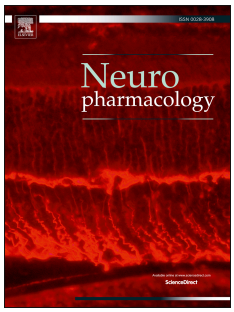
Accepted Manuscript



ATPergic signalling during seizures and epilepsy

Tobias Engel, Ph.D., Mariana Alves, Caroline Sheedy, David C. Henshall

PII: S0028-3908(15)30165-9

DOI: 10.1016/j.neuropharm.2015.11.001

Reference: NP 6067

To appear in: *Neuropharmacology*

Received Date: 31 July 2015

Revised Date: 1 November 2015

Accepted Date: 2 November 2015

Please cite this article as: Engel, T., Alves, M., Sheedy, C., Henshall, D.C., ATPergic signalling during seizures and epilepsy, *Neuropharmacology* (2015), doi: 10.1016/j.neuropharm.2015.11.001.

ATPergic signalling during seizures and epilepsy

Authors: Tobias Engel[1*], Mariana Alves[1], Caroline Sheedy[1] and David C. Henshall[1]

[1]Department of Physiology & Medical Physics, Royal College of Surgeons in Ireland, Dublin 2, Ireland

Abstract:

Much progress has been made over the last few decades in the identification of new anti-epileptic drugs (AEDs). However, 30% of epilepsy patients suffer poor seizure control. This underscores the need to identify alternative druggable neurotransmitter systems and drugs with novel mechanisms of action. An emerging concept is that seizure generation involves a complex interplay between neurons and glial cells at the tripartite synapse and neuroinflammation has been proposed as one of the main drivers of epileptogenesis. The ATP-gated purinergic receptor family is expressed throughout the brain and is functional on neurons and glial cells. ATP is released in high amounts into the extracellular space after increased neuronal activity and during chronic inflammation and cell death to act as a neuro- and gliotransmitter. Emerging work shows pharmacological targeting of ATP-gated purinergic P2 receptors can potently modulate seizure generation, inflammatory processes and seizure-induced brain damage. To date, work showing the functional contribution of P2 receptors has been mainly performed in animal models of acute seizures, in particular, by targeting the ionotropic P2X7 receptor subtype. Other ionotropic P2X and metabotropic P2Y receptor family members have also been implicated in pathological processes following seizures such as the P2X4 receptor and the P2Y12 receptor. However, during epilepsy, the characterization of P2 receptors was mostly restricted to the study of expressional changes of the different receptor subtypes. This review summarizes the work to date on ATP-mediated signalling during seizures and the functional impact of targeting the ATP-gated purinergic receptors on seizures and seizure-induced pathology.

Corresponding author:

**Correspondence:* Tobias Engel, Ph.D., Dept. of Physiology & Medical Physics, Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Ireland. Telephone number: +35314022122 Fax: +35314022447, *Email:* tengel@rcsi.ie

Keywords: Epilepsy, seizures, status epilepticus, ATP, P2 purinergic receptors