Adenosine and epilepsy—thinking beyond A₁ receptors

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Roseti C, Palma E, Martinello K, Fucile S, Morace R, Esposito V, Cantore G, Arcella A, Giangaspero F, Aronica E, Mascia A, Di Gennaro G, Quarato PP, Manfredi M, Cristalli G, Lambertucci C, Marucci G, Volpini R, Limatola C, Eusebi F. (2009) Blockage of A_{2A} and A₃ adenosine receptors decreases the desensitisation of human GABA(A) receptors microtransplanted to *Xenopus* oocytes. *Proc Natl Acad Sci U S A*. 106: 15927–1531

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Combined summary

In these two tightly related papers, the authors analysed the influence of adenosine upon human GABA_A receptor instability, assessed by the rundown of the GABA_A currents (I_{GABA}) that occurs upon repeated application of GABA. I_{GABA} were recorded from oocytes injected with membranes extracted from human epileptic brain, including pharmacoresistant mesial temporal lobe epilepsy, focal cortical dysplasia and perigloma epileptic tissues. For

comparison, data were also obtained from epileptic slices obtained from neurosurgical resection in patients suffering from some of the aforementioned diseases, as well as from cortical slices of pilocarpine-treated epileptic rats and A₁ or A_{2A} receptor-deficient mice.

Rundown (desensitisation) of GABAergic currents is pro-excitatory in mature neurons since it reduces the efficacy of the GABAergic signal. Accordingly, exacerbated I_{GABA} rundown together with slow recovery is characteristic of epileptic tissue. The well-established antiepileptic action of adenosine could allow the anticipation that if any, adenosine would attenuate I_{GABA} rundown and that A₁ receptors would be involved. Surprisingly and, in my view, refreshing in the field, it was found that adenosine A₁ receptors are not involved in the effect of this endogenous purine receptor agonist. Indeed, the most consistent finding throughout the two papers is that adenosine A₁ receptors do not modulate I_{GABA} rundown, irrespectively of the model (human vs. rats or mice, type of epilepsy, injected oocytes vs. brain slices) or the approach (pharmacological vs. receptor knockout) used. All sets of data are fully consistent in what concerns the absence of modulation by A₁ receptors of GABA_A receptor instability.

Contrasting with the absence of effect of a selective A₁ receptor antagonist, a blanket adenosine receptor antagonist and adenosine deaminase reduced I_{GABA} rundown, indicating that adenosine present in the extracellular space is exacerbating GABA_A receptor desensitisation, therefore highlighting a putative proconvulsant action of adenosine. Whilst trying to dissect out the types of receptors involved, no clear-cut conclusions could be drawn. The most striking case was with A_{2A} receptor antagonists or A_{2A} knockout mice. Indeed, not all A_{2A} receptor antagonists tested had effects in all models used, and when they did, opposite actions were often observed in subsets of cell populations.

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No clear association with disease type or experimental model could be identified to explain discrepant results. Within the most extensively used model, injected oocytes, the same A_{2A} receptor antagonist had opposite effects in different cell subsets. In a majority of cells and models tested, A_{2A} receptor antagonism reduced I_{GABA} rundown, suggesting that A_{2A} receptor activation by endogenous adenosine exacerbates $GABA_A$ receptor desensitisation. This could be expected since receptor desensitisation often occurs through phosphorylation (frequently mediated by cAMP and PKA, the well-known transduction pathways of A_{2A} receptors). However, in a minority of cells, the selective A_{2A} receptor antagonists exacerbated I_{GABA} rundown and, surprisingly, data from A_{2A} receptor knockout mice corroborated the results obtained in this minority of cells— I_{GABA} rundown was more pronounced in mice lacking A_{2A} receptors. The A_3 receptor antagonists mostly reduced the I_{GABA} rundown but increased it if tissue was from dysplastic neocortices. The A_{2B} receptor was not extensively studied, but its antagonism also reduced I_{GABA} rundown.

Combined commentary

Summarising, in what concerns a relevant dysfunctional characteristic of epileptic tissue, $GABA_A$ receptor instability, adenosine tonically exacerbated it. For sure, this action does not involve A_1 receptors. It may, however, involve any other adenosine receptor. The trend is that selective

antagonists of non- A_1 receptors attenuate $GABA_A$ receptor desensitisation. One should, however, keep in mind that the same antagonist may have opposite effects in different cell populations within the same pathological model. Furthermore, it still remains to be understood why data from A_{2A} receptor knockout mice and data obtained with the A_{2A} receptor antagonists in the majority of cells lead to opposite conclusions. Indeed, data from A_{2A} receptor knockout mice would fit to the idea that A_{2A} receptors could have an anticonvulsant role. Irrespectively of the adenosine receptor subtype(s) involved in the modulation of $GABA_A$ receptor desensitisation in epileptic tissue and the mechanism(s) operated by them, these two papers highlight the need of thinking beyond A_1 receptors whilst aiming at a full understanding of the role of adenosine in epilepsy.

About the author

Ana M. Sebastião is at present Associate Professor at the Faculty of Medicine, University of Lisbon. Her research interests relate to purines since 1983. She has been interested in the characterisation of adenosine receptors as well as in the role played by endogenous adenosine in the nervous system, especially at the neuromuscular junction and hippocampus. More recently, she has been concentrating on the mechanisms by which adenosine receptors interact with other neuromodulatory systems, including neuropeptides, cannabinoids and neurotrophic factors.