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HIGHLIGHTS IN PURINERGIC SIGNALLING

Neurabin: a key factor in the specific neuroprotection mediated by Adenosine

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Yunjia Chen, Yin Liu, Christopher Cottingham, Lori McMahon, Kai Jiao, Paul Greengard and Qin Wang (2012) Neurabin Scaffolding of Adenosine Receptor and RGS4 Regulates Anti-seizure Effect of Endogenous Adenosine J. Neurosci. 32(8):2683–2695

Summary of the article

In this article, it is shown that the A1 Adenosine receptor (A1R) is a G-protein coupled receptor (GPCR) that is regulated by the activity of Regulator of G-protein Signaling (RGS4), which functions as a GTPase-activating protein to terminate G-protein signaling [5]. The possible role of RGS4 in adenosine-evoked signaling neuroprotection has been investigated, and it is shown that a new interacting protein, neurabin, forms a scaffold between A1R and RGS4, thus regulating the activity of A1R. It is also demonstrated that inhibiting neurabin or deleting its gene in mice provides a mean to enhance the neuroprotective effects of endogenous adenosine released during brain ischemia or during kainate induced seizures. Thus, neuroprotection can be achieved through a mechanism that does not require administration of A1R agonists, which would have important peripheral side effects. Indeed, it has already been shown that molecules inhibiting RGS4 functional activity, like CCG-4986 [4], reduce kainate-induced seizure activity in mice in vivo.

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Commentary

Neurabin is specifically expressed in neural tissues with special reference to cortex, hippocampus and cerebellum [3]. This protein belongs to a family of scaffolding proteins and its homolog, spinophilin, has been shown to interact with a number of GPCRs like the Dopamine D2 [7], α1 and α2 adrenaline [9], and M2 and M3 muscarinic actylcholine [2] receptors. Neurabin has been also shown to sequester RGS2 from binding to α_1AR, thus enhancing α_1AR mediated signaling [10]. Moreover, deleting the gene of spinophilin reduces the analgesic effects of acute morphine administration, but enhances adaptation to sub-chronic morphine exposure, including increased morphine dependence, place-conditioning and analgesic tolerance [1].

However, the direct interaction of neurabin or spinophilin with these GPCRs had never been shown before. By studying the interaction of neurabin with A1R at molecular level, this article fills this gap. The interaction neurabin-A1R occurs at the third intracellular loop of A1R and the C-terminal tail of neurabin (amino acids 146 and 453).

Neurabin interacts with A1R only when the agonist binds to its receptor and its binding attenuates receptor signaling: therefore inhibition of neurabin enhances the effect of A1R agonists, like R-PIA, and its sedative effects. It is important to note that modifications in the activity of neurabin occurs always in the absence of any modification of A1R numbers or affinity.

It has always been suggested that adenosine could serve as an important neuroprotectant and anti-seizure compound [6,8] via A1Rs, but its therapeutic efficacy has always been questioned by the potential side effects of A1 agonists at different peripheric organs and systems. By showing that adenosine induced neuroprotection can be achieved by a

direct interaction with neurabin that does not require administration of adenosine A1R agonists, this article opens up the possibility to exploit the adenosinergic system to obtain molecules able to show therapeutic efficacy specifically at the level of CNS.

Future directions of research

It will be interesting to find novel compounds able to suppress neurabin functional activity. By knowing neurabin gene structure, it should be possible to design new molecular entities able to disrupt or prevent the formation of the A1R/neurabin/RGS4 complex. It should be pointed out, once again, that this should result in a specific effect at the level of CNS and therefore make possible to exploit the adenosinergic system for selective therapeutic interventions in the field of neurodegenerative diseases, an area in a tremendous need of new and effective drugs.

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