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COMMENTARY

Heteroexchange of purines in the hippocampus: mixing-up or messing-up ATP and adenosine

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Interest in adenosine as a neuroactive substance in the CNS is based on its ability to modulate synaptic transmission through the control of neurotransmitter release (Cunha, 2001). In parallel, interest in ATP as a neurotransmitter in the CNS stemmed originally from its action in the ANS – although, unlike the ANS, ATP transmission in the brain still remains an ill-defined notion (Cunha & Ribeiro, 2000). In the past, these two branches of purine research have evolved in parallel yet separately, and only the study of ecto-nucleotidases – those enzymes converting extracellular ATP into adenosine – seems to be of common interest to researchers of ATP and adenosine pharmacology.

Considerable effort has been devoted to the characterization of responses mediated by extracellular ATP and adenosine, as well as to the location and molecular characterization of ATP and adenosine receptors mediating these responses. This effort contrasts with the sparse and arguably inconclusive work on how ATP and adenosine actually appear in the extracellular milieu. Since ATP is present in synaptic vesicles, it is generally assumed that ATP is released by exocytosis – in a Ca^{2+}-dependent vesicular manner – from electrically stimulated nerve terminals (Zimmermann, 1994). However, it is now realized that a number of postsynaptic sites and non-neuronal cells can also release ATP, most often without any evidence for conventional exocytotic processes (Bodin & Burnstock, 2001).

Likewise, it is generally assumed that adenosine is formed either by ecto-nucleotidases acting on released ATP or is released as such through bidirectional nonconcentrative nucleoside transporters (Cunha, 2001). Some studies have shown that ecto-nucleotidase inhibitors can actually decrease the extracellular accumulation of adenosine, although it must also be said that other studies have failed to show any such effects (Cunha, 2001; Latini & Pedata, 2001). Likewise, inhibitors of nucleoside transporters have been reported to either inhibit or enhance the extracellular accumulation of adenosine (Cunha, 2001; Latini & Pedata, 2001) and, so, it is far from clear to what degree transporters can bring about the bidirectional movement of purines in the CNS.

Confusion over the source(s) of extracellular ATP and adenosine is probably because of the failure to recognize two important aspects of purinergic signaling, namely: (i) the release of purines is different under stressful and nonstressful situations and rarely controlled (Cunha, 2001; Latini & Pedata, 2001); (ii) purines not only act synaptically, but also have important trophic roles, which, for instance, is accepted in angiogenesis but, only now, is recognized in the CNS (Rathbone *et al*., 1999). Thus, it is likely that purines may be recruited from different metabolic sources and/or from different compartments according to the different functions they subserve (Cunha, 2001).

The present paper of Sperlagh *et al*. (2003) in this present issue of *BJP* – describing a homo- and heteroexchange of adenine nucleotides and nucleosides through nucleoside transporters – defines one more avenue of interplay between the ATP and adenosine modulatory systems. Miras-Portugal's group has already provided strong evidence indicating that both ATP and adenosine receptors can control adenosine transporters – either by direct action (Casillas *et al*., 1993) or indirectly *via* protein kinase A and protein kinase C activation (Sen *et al*., 1993) – although the physiological relevance of this control remains to be fully explored. Furthermore, Stone's group has pioneered the notion that P2 receptor activation can trigger adenosine release (Nikbakht & Stone, 2000) but, again, the physiological rationale for this process remains unclear. The present work of Sperlagh and co-workers has ruled out the involvement of receptor-mediated processes in the hippocampus and, instead, implicates a direct ATP – adenosine exchange pathway through nucleoside transporters. Several questions remain to be answered fully from this study, namely: (i) can ATP truly be a substrate of adenosine transporters, or is it first broken down; (ii) what type of nucleoside transporter is involved here, given that only compounds with adenine moieties triggered purine release in the hippocampus, yet uridine is known to be a preferred substrate of nucleoside transporters; (iii) in what cell type or compartment does the exchange of ATP and adenosine occur? But clearly, the most pressing question might be the physiological relevance of this process.

As pointed out by the authors, it is unlikely that this ATP/adenosine exchange process is involved in the control of those ATP and adenosine levels that normally play a modulatory role at the synapse. Instead, a more plausible role may involve such structures as astrocytes, where purine-evoked purine release is instrumental in the propagation of calcium waves (Cotrina *et al*., 2000). This ATP/adenosine exchange process might also allow the extracellular concentration of purines to be sustained at critically important, yet elevated, levels where both ATP and adenosine can act as trophic/survival/differentiation factors in the CNS (Rathbone *et al*., 1999). In this

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respect, it will be interesting to re-evaluate the long-term effects of nucleoside transport inhibitors in terms of CNS cell survival, metabolism and circuitry plasticity. However, irrespective of these proposed physiological roles, this ATP/adenosine exchange process further stresses the need to keep in mind that the study of one of these two purines cannot be carried out without keeping in mind the other – an issue too often overlooked.

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