# PERSPECTIVES

## The action is at the terminal

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The magnocellular neurons of the supraoptic nucleus have been intensively studied because of their unique bursting and phasic activity patterns. While these can be explained in part by intrinsic membrane conductances, it is now also apparent that afferent inputs are important in sculpting and initiating the activity patterns. Modulation of these inputs, therefore, provides a powerful way to regulate magnocellular neuronal activity.

The paper by Oliet & Poulain in this issue of *The Journal of Physiology* provides evidence that adenosine may be such a modulator in that it acts presynaptically in the supraoptic nucleus (SON) to inhibit both excitatory and inhibitory synaptic currents onto magnocellular neurons. Furthermore, the authors were able to demonstrate an action of endogenous adenosine in the slice by blocking, with an $A_1$-type antagonist, a progressive synaptic depression brought about by continuous afferent stimulation at 1 Hz over 2 min or more. This paper therefore adds to a compelling body of evidence that adenosine has transmitter action in the central nervous system (Dunwiddie, 1985). Several aspects of this study deserve comment and raise questions amenable to experimentation.

Adenosine was equipotent in inhibiting IPSCs and EPSCs, thereby raising questions as to the consequences of adenosine action on the output of the nucleus. While it could be argued that intense excitatory inputs would be attenuated, the same would be true for inhibition, making the net effect rather minor. One possible effect could be to stabilize activity levels of the postsynaptic cell at levels conducive for the generation of intrinsic voltage-dependent activity patterns. Another possibility is that adenosine is simply acting to reduce overall metabolic activity; since the metabolic consequences of activity in the presynaptic terminal would be similar in excitatory and inhibitory terminals, it may be irrelevant as to the nature of the transmitter.

It is also interesting that the maximum inhibition attained in response to adenosine is only 60% for either excitatory or inhibitory inputs. This is in contrast to such presynaptic modulators as baclofen, acting at $GABA_B$ receptors, where there is 100% attenuation of afferent evoked potentials (Pittman *et al.* 1998). Whether this is due to a distribution of adenosine receptors on only a limited number of afferent terminals, or whether it reflects a mechanism of action that is only partially effective in reducing the transmitter release is not known. For example, if adenosine receptors were coupled to only a subset of the calcium channels engaged in transmitter release, one might predict that only part of the transmitter release would be inhibited. However, data from the Oliet & Poulain paper indicate that miniature EPSCs and miniature IPSCs are inhibited by adenosine; as most evidence indicates that TTX-resistant spontaneous currents in magnocellular neurons are calcium insensitive, this suggests that adenosine acts downstream of the calcium influx, perhaps by interfering with the transmitter release machinery (reviewed in Wu & Saggau, 1997). It would also be interesting to determine whether the presynaptic $A_1$ receptors identified here display a sensitivity to pertussis toxin pretreatment. While such receptors are known to be G-protein coupled, presynaptic receptors are often insensitive to inhibition by pertussis toxin.

The identification of an action of endogenous adenosine required repetitive stimulation, perhaps because reuptake mechanisms at lower frequencies efficiently removed adenosine. The source of this endogenous adenosine is still unknown. While it could be released by a nucleoside transporter from either glial cells or neurons, another possibility is that it may be produced by metabolic breakdown of ATP (Cunha *et al.* 1998). ATP is known to be released in the SON from noradrenergic afferents (Buller *et al.* 1996) and there is also some evidence that it may be released from the magnocellular neurons themselves (Troadec *et al.* 1998). It would be of interest to determine whether the synaptic depression evoked by endogenous adenosine could be blocked by an inhibitor of the extracellular nucleotidases responsible for metabolism of ATP to adenosine.

Adenosine can thus be added to a growing list of substances that act presynaptically to modulate supraoptic neuronal activity. It is apparent that an understanding of the synaptic pharmacology of this nucleus will require a fully differentiated, synaptically intact preparation such as that presented either by the *in vivo* brain or by an acutely isolated slice or explant.

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