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ATP Receptor/Channels: Their Contribution to Calcium Regulation and Modulation by Neurotransmitters

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A concept that extracellular ATP plays a role as a neurotransmitter is now widely accepted. ATP released from nerve terminals transmits both excitatory and inhibitory signals to postsynaptic neurons, muscle cells, and non-excitable cells. ATP-activated channels are effectors that convert the binding of ATP into the opening of ion channel pores in postsynaptic membrane. The channels are permeable to cations, but the selectivity among cation species is rather poor. Under physiological conditions, the opening of the channels results in the inflow of extracellular cations, and this inward current consists of mainly Na^+ and partly Ca^{2+}. As a consequence, two types of excitation occurs to postsynaptic cells: 1) depolarization of plasma membrane, and 2) direct entering of Ca^{2+} into cells. The former leads to the activation of voltage-gated channels including Na^+ and Ca^{2+} channels, and the latter directly leads to cellular responses such as secretion, muscle contraction and, presumably, synaptic plasticity.

ATP-activated channels are modulated by various substances including other neurotransmitters. Dopamine, 5-hydroxytryptamine and adenosine facilitate ionic currents permeating through the channels. Zn^{2+}, which is known to be present and thought to modulate cellular functions in the central nervous system, and Cd^{2+}, an exogenous substance, also exert a similar facilitatory modulation. On the other hand, trivalent cations including La^{3+} inhibit the ATP-activated channels. Agonists for nicotinic acetylcholine receptors also inhibits these channels, but the mode of the channel inhibition is rather puzzling. Recently, cDNAs encoding ATP-activated channels have been cloned by several groups.

The cloned channels are termed P2x purinoceptors, and seven subclasses have been cloned to date. The proposed structure of P2x purinoceptor/channels deduced from amino acid sequences are quite distinct from those of other ligand-gated channels. In addition to agonist selectivity and kinetics, different subclasses of the channels also differ in their sensitivities to the modulators listed above. The clarification of mechanisms underlying various properties of the channels will dramatically be progressed by applying molecular biological techniques to the cloned channels.