ANNEXINS AS MEDIATORS IN INTRACELLULAR SIGNALLING PATHWAYS – ARE THEY INTRACELLULAR GTP BIOSENSORS?

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Mammalian annexins (annexin A1-11 and A13) belong to a ubiquitous family of Ca²⁺-, pH-, and nucleotide-regulated membrane binding proteins, exhibiting a high level of expression in specific cell types such as endothelial cells. Intracellularly, they are localized either in the cytosol, or in association with organelles participating in calcium homeostasis and energy transduction (the endoplasmic reticulum, the mitochondria), various compartments involved in vesicular traffic (early and late endosomes, the prelysosomal compartment), the nuclear envelope, and last but not least, the lipid microdomains of the plasma membrane (the caveolae). Such an intracellular localization of annexins and their potential ligands (including various protein kinases, nucleic acids, precursors of signal transduction molecules, etc.) is consistent with the postulated role of these proteins in the maintenance of intracellular calcium homeostasis, in specific gene transcription, in vesicle-mediated processes, in membrane microdomain assembly, in targeting some proteins into specific membrane compartments, and in signal transduction pathways in which various GTP-binding proteins participate. Recently, it was reported that annexin A6 is able to interact with various GTP-binding proteins and binds GTP \textit{in vitro} with a high affinity (K_D \approx 10^6 M^{-1}). Moreover, GTP in a millimolar concentration range specifically induces the formation of voltage-dependent ion channels by annexin A6 molecules in planar lipid membranes. The GTP-induced ion channel activity of annexin A6 was found associated with the structural flexibility of the protein. This was characterized by changes in its secondary and tertiary structure, suggesting that such structural flexibility could contribute to a molecular mechanism of annexin A6 acting as an intracellular GTP biosensor, or as an atypical G protein, responsible for detecting the Ca²⁺/GTP signals in some cell types. As an alternative, it can be proposed that annexin A6/nucleotide binding may participate, directly or indirectly, in the regulation of functions of other GTP-binding or GTPase-activating proteins and, therefore, in the modulation of the intracellular signalling pathways mediated by these proteins.

This research is supported by grant No. 3 PO4A 007 22 from the State Committee for Scientific Research and by the Nencki Institute of Experimental Biology.