CHAPTER 5

The Synapsins and the Control of Neuroexocytosis

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Abstract

The synapsins have been the first synaptic vesicle-associated proteins to be discovered thanks to their prominent ability to be phosphorylated by a variety of protein kinases. At present, the synapsin family in mammals consists of at least 10 isoforms encoded by three distinct genes and composed by a mosaic of conserved and variable domains. The synapsins are highly conserved evolutionarily and synapsin homologues have been described in invertebrates and lower vertebrates. The synapsins are implicated in multiple interactions with synaptic vesicle proteins and phospholipids, actin and protein kinases. Via these interactions, the synapsins play multiple roles in synaptic transmission, including control of synapse formation, regulation of synaptic vesicle trafficking, neurotransmitter release and expression of short-term synaptic plasticity phenomena. This chapter tries to summarize the main functional features of the synapsins that have emerged in the last 20 years, in order to provide a framework for interpreting the complex role played by these phosphoproteins in synaptic physiology.

Introduction

The release of classical neurotransmitters (NTs) occurs at specialized sites of the plasma membrane, named active zones, by exocytotic fusion of small synaptic vesicles (SVs). The uniform loading of SVs with a discrete amount of NT is reflected by the reproducibility in the size of the postsynaptic response elicited by each exocytotic event referred to a NT quantum. At variance with nonneuronal cells, neuroexocytosis is characterized by: (1) an "explosive" rate of NT release, many orders of magnitude faster than that of nonneuronal cells; (2) the ability to operate at various levels of efficiency depending on the microenvironmental conditions and the previous "history" of the neuron; and (3) the ability to sustain repetitive high frequency NT release over a long period of time with strong reliability. The molecular features that confer such properties to neuroexocytosis in neurons are: (i) the high colocalization of Ca^{2+} channels with fusion competent SVs which allows an extremely rapid Ca^{2+}-dependent exocytosis, (ii) the existence of a strategically localized reserve pool of SV buffering the depletion of the readily released pool during sustained repetitive release and (iii) the presence of efficient recycling mechanisms active at the presynaptic membrane that prevent the rapid depletion of SVs during a sustained repetitive release. Such recycling mechanisms are contributed by a fast and direct endocytotic pathway operating at the active zones ("kiss & run" mechanism) and by a slower clathrin-mediated endocytosis active at periactive zones.

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The remarkable properties of neurotransmitter release are generated by the activity of a number of proteins that are localized within the presynaptic terminal and participate in synapse formation, maintenance and function. Among many presynaptic actors which have been identified in the last 20 years, the most abundant phosphoproteins are the synapsins, a highly conserved multigene family of neuron-specific, SV-associated phosphoproteins.

Synapsins exist in all organisms endowed with a nervous system and, in mammals, are encoded by three distinct genes (SYNI, SYNII and SYNIII) located in chromosome X, 3 and 22, respectively. They are composed of a mosaic of individual and shared domains, the latter of which are highly conserved during evolution (Fig. 1). Synapsins I and II are stably expressed at synapses of mature neurons, where they associate with the cytoplasmic surface of small SVs, whereas the expression of synapsin III is developmentally controlled and not strictly confined to synaptic terminals (Fig. 2). Synapsins are excellent substrates for a large array of protein kinases including protein kinase A, Ca\(^{2+}\)/calmodulin-dependent protein kinases (CaMK) I, II and IV, mitogen-activate protein (MAP) kinase and cyclin-dependent kinase-1, that phosphorylate them on distinct serine residues. Synapsins interact in vitro with lipid and protein

![Figure 1. Evolutionary conservation of the synapsins. Synapsins have been cloned from a variety of species, from invertebrates to man. Synapsins are composed of a mosaic of conserved and individual domains that are schematically represented in blocked color form and indicated by letters A-J. The length of the polypeptide chains is shown at the top in number of amino acid residues. Different shades or colors depicted within domains represent different sequences (e.g., within domain C of Aplysia synapsin). In the figure, highly conserved domains are shown as thick colored boxes. Domains A, C, and E are defined by significant homology to their mammalian counterparts. While in mammals, synapsins are coded by three distinct genes, in lower vertebrates and invertebrates one single gene gives rise to multiple synapsin isoforms.](image-url)