Marine Toxins Potently Affecting Neurotransmitter Release

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1 This chapter is dedicated to honour the memory of Professor André Ménez (1943–2008)
Abstract  Synapses are specialised structures where interneuronal communication takes place. Not only brain function is absolutely dependent on synaptic activity, but also most of our organs are intimately controlled by synaptic activity. Synapses are therefore an ideal target to act upon and poisonous species have evolved fascinating neurotoxins capable of shutting down neuronal communication by blocking or activating essential components of the synapse. By hijacking key proteins of the communication machinery, neurotoxins are therefore extremely valuable tools that have, in turn, greatly helped our understanding of synaptic biology. Moreover, analysis and understanding of the molecular strategy used by certain neurotoxins has allowed the design of entirely new classes of drugs acting on specific targets with high selectivity and efficacy. This chapter will discuss the different classes of marine neurotoxins, their effects on neurotransmitter release and how they act to incapacitate key steps in the process leading to synaptic vesicle fusion.

1 Introduction

Neurotoxins have paved the way of modern neurobiology by providing indispensable tools to unravel pre- and post-synaptic mechanisms. In particular, marine neurotoxins have been very useful in determining the role played by calcium, sodium and potassium channels in mediating neurotransmitter release and controlling excitability in various synaptic preparations. The exquisite specificity of certain neurotoxins facilitated the identification of various channel subtypes and their functional roles. The mode of action of neurotoxins has not been only centred on presynaptic mechanisms: the post-synaptic machinery has also greatly benefited from their use. Neurotoxins targeting muscular nicotinic receptor were the first to be characterised (see review by Terlau and Olivera 2004) but the interest soon shifted to CNS transmission and novel categories of marine neurotoxins blocking nicotinic (Cartier et al. 1996), glutamate (Haack et al. 1990) receptors and other important synaptic targets were discovered (Terlau and Olivera 2004). In this chapter, we will first summarise the mechanism of quantal neurotransmitter release in order to set the scene for the examination of marine neurotoxins and their presynaptic actions.

Quantal transmitter release depends on the controlled fusion of neurotransmitter-containing synaptic vesicles with the presynaptic plasma membrane at specialised sites called active zones. There are two major types of quantal acetylcholine (ACh) release taking place at motor nerve terminals:

- Spontaneous neurotransmitter release which is asynchronous in nature and result from the random fusion of synaptic vesicles normally occurring at a low frequency. This can be detected post-synaptically as small amplitude depolarisations called miniature endplate potential (MEPP).
- Ca$^{2+}$-dependent phasic neurotransmitter release which results from the mobilisation and synchronised fusion of 40–200 synaptic vesicles. The postsynaptic depolarisation resulting from this ACh release called endplate potential (EPP) is of much larger amplitude and normally capable of triggering a post-synaptic action potential (Van der Kloot and Molgó 1994). Both types of quantal release can be affected by