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Review Article

The structure and function of presynaptic endosomes

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ABSTRACT

The function of endosomes and of endosome-like structures in the presynaptic compartment is still controversial. This is in part due to the absence of a consensus on definitions and markers for these compartments. Synaptic endosomes are sometimes seen as stable organelles, permanently present in the synapse. Alternatively, they are seen as short-lived intermediates in synaptic vesicle recycling, arising from the endocytosis of large vesicles from the plasma membrane, or from homotypic fusion of small vesicles. In addition, the potential function of the endosome is largely unknown in the synapse. Some groups have proposed that the endosome is involved in the sorting of synaptic vesicle proteins, albeit others have produced data that deny this possibility. In this review, we present the existing evidence for synaptic endosomes, we discuss their potential functions, and we highlight frequent technical pitfalls in the analysis of this elusive compartment. We also sketch a roadmap to definitely determine the role of synaptic endosomes for the synaptic vesicle cycle. Finally, we propose a common definition of synaptic endosome-like structures.

Contents

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Introduction

Endosome-like structures have been observed in the synapse since the very first papers on synaptic vesicle (SV) recycling [12]. Since these days, they have been subject of controversy. Heuser and Reese, who observed the appearance of large membrane-bound structures after strong electrical stimulation of frog neuromuscular junctions (NMJs), hypothesized a functional role for these organelles in SV recycling. This view was contested, especially based on the observation that low-frequency stimulation, which may be closer to the physiological levels of activity of the particular frog NMJs, does not trigger the formation of such organelles [4]. This implied that Heuser and Reese's endosome-like structures were mainly plasma membrane infoldings, appearing in response to excessive incorporation of SV membrane into the plasma membrane, after non-physiological levels of exocytosis [10,11]. Many studies have afterwards tried to deal with the question of whether recycling of SVs proceeds via endosome-like structures or not. Instead of a conclusion, many contradicting views have emerged, ranging from the non-existence of synaptic endosomes, to endosomes as part of the machinery that mediates membrane retrieval, and finally to endosomes implicated in the sorting of vesicle proteins, in a fashion similar to that in which sorting endosomes prune trafficking organelles in other cell types (Fig. 1; [4,5,8,12]). One additional problem is that there is no unitary definition of the synaptic endosome, and no clear molecular description. How can we define the synaptic endosome? Can it be characterized by a distinct set of molecules? Is it a protein and membrane sorting compartment? Or is it an endocytosed infolding which has just severed from the plasma membrane?

In this review, we will discuss several studies that describe the morphology, molecular composition, and function of synaptic endosome-like structures. We try to find common features, to identify experimental drawbacks, and finally to propose a definition that can serve to reconcile the contradicting observations.

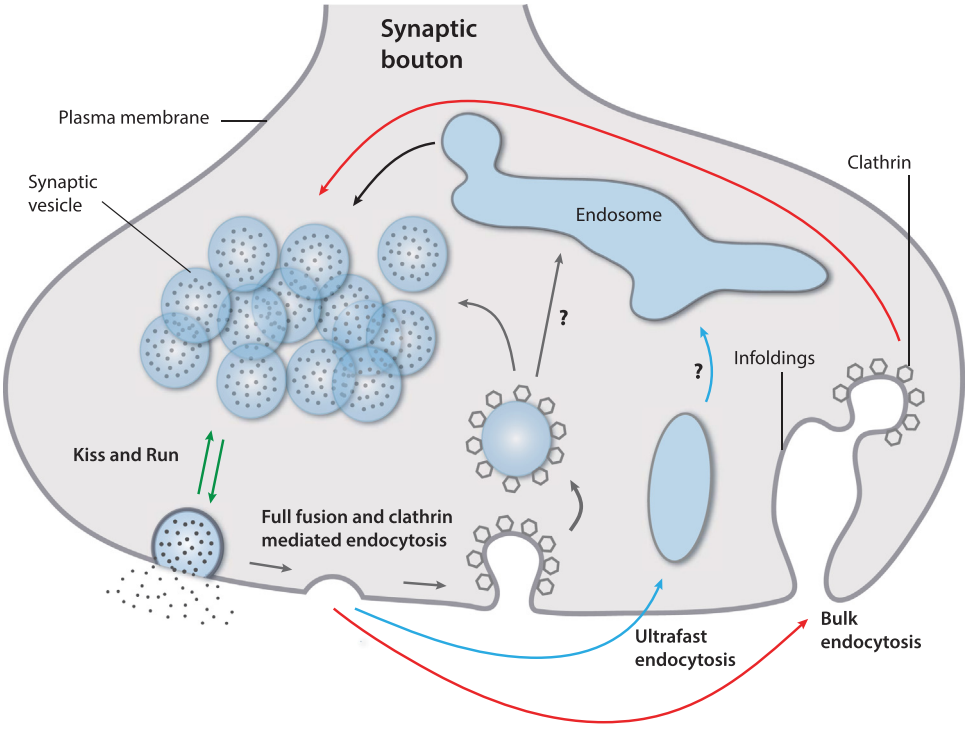

Fig. 1 – The position of endosome-like structures in the main models of synaptic vesicle recycling in the synapse. The schematic shows the four main models of SV endocytosis, including full fusion and clathrin-mediated endocytosis (gray), kiss and run (green), bulk endocytosis (red), and ultrafast endocytosis (blue). Except for kiss and run, endosome-like structures have been described in all of these models. They have been implicated in the sorting of SV proteins during the recycling process and in the degradation of old SV proteins [8,15]. Though also visible at resting conditions, endosome-like structures have mainly been associated to strong stimulation of nerve terminals, where large infoldings are forming at the plasma membrane. Clathrin-mediated endocytosis was observed from these infoldings. Occasionally, the infoldings were described to bud off the plasma membrane, a process termed bulk endocytosis. Bulk endocytosis has mainly been associated with the retrieval membrane after excessive stimulation [5]. Recently, endosome-like structures have been linked to a fast recycling model, called ultrafast endocytosis [36].