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Review

Communication breakdown: The impact of ageing on synapse structure☆

Ronald S. Petralia[a,1], Mark P. Mattson[b], Pamela J. Yao[b,*]

[a] Advanced Imaging Core, NIDCD/NIH, Bethesda, MD 20892, United States
[b] Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD 21224, United States

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ABSTRACT

Impaired synaptic plasticity is implicated in the functional decline of the nervous system associated with ageing. Understanding the structure of ageing synapses is essential to understanding the functions of these synapses and their role in the ageing nervous system. In this review, we summarize studies on ageing synapses in vertebrates and invertebrates, focusing on changes in morphology and ultrastructure. We cover different parts of the nervous system, including the brain, the retina, the cochlea, and the neuromuscular junction. The morphological characteristics of aged synapses could shed light on the underlying molecular changes and their functional consequences.

Contents

1. Introduction

One inevitable part of ageing is a decline in the functions of our nervous system, a decline that can affect everything from learning and memory to hearing and vision. The proper function of the nervous system depends on the underlying structure of neuronal networks, which includes the morphology of their axons, dendrites and synapses. Over one hundred years ago, Sir Charles Sherrington first coined the word synapse to connote the

* Corresponding author at: Laboratory of Neurosciences, NIA/NIH Biomedical Research Center, 251 Bayview Boulevard, Baltimore, MD 21224, United States. Tel.: +1 410 558 8586.
E-mail addresses: petralia@nidcd.nih.gov (R.S. Petralia), yaopa@grc.nia.nih.gov (P.J. Yao).
[1] 50 South Drive, Room 4142, Bethesda, MD 20892-8027, United States.

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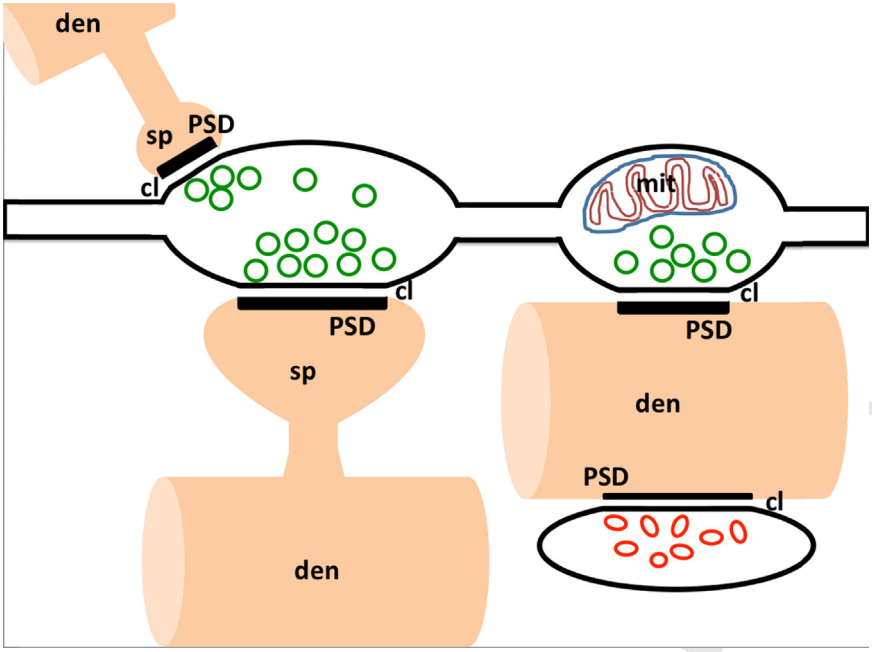

Fig. 1. Generalized diagram of typical synapses of the vertebrate brain. Presynaptic terminals can be a terminal bouton or *en passant* along the axon. Common examples include excitatory ones with round vesicles (green) containing the neurotransmitter, glutamate, and inhibitory ones with pleomorphic vesicles (red) containing the neurotransmitter, GABA, and they can form on dendrite spines (sp) or directly on the dendrite shaft (den). The area of vesicle release along the presynaptic membrane is called the active zone. The space between the pre- and postsynaptic processes is the synaptic cleft (cl) and the postsynaptic membrane, which contains the receptors, has an associated region of dense material called the postsynaptic density (psd) that is thick (asymmetric synapse) in excitatory and thin (symmetric synapse) in inhibitory types. A terminal can sometime form synapses on more than one postsynaptic process (multisynaptic bouton; left bouton in figure) and typically contains mitochondria (mit) and various reticular and vesicular structures (not shown). During ageing, changes are seen in the shape, size and number of all of these various components of synapses in animals, as described in the text.

physical relation – or the connection – between neurons (Foster and Sherrington, 1897). Since then, we have learned a great deal about how the synapse performs its role, connecting neurons via electrochemical neurotransmission and serving as the focal point of cell–cell signaling in the nervous system. A synapse, in the simplest sense, is typically composed of two main parts: a presynaptic compartment or terminal from the signal-sending neuron and a postsynaptic terminal from the signal-receiving neuron (Fig. 1; see Stewart et al., 2014). The presynaptic terminal harbors clusters of neurotransmitter-filled synaptic vesicles that are stunningly uniform in their size and shape. The acceptor postsynaptic terminal contains neurotransmitter-specific receptors, arranged on the membrane surface in a position to respond to neurotransmitter released from the presynaptic terminal.

The maintenance of this precise arrangement of the synaptic terminals requires a complex protein network. In the presynaptic terminal, there is an expansive array of proteins. These presynaptic proteins are expressed in precise amounts, situated at specific locations, and designated for specific functions (Takamori et al., 2006; Siksou et al., 2011). Similarly, in the postsynaptic terminal, there is a compendium of proteins (Sheng and Kim, 2011; Chen and Sabatini, 2012). Some of these proteins serve as neurotransmitter receptors and their downstream signaling molecules, whereas others function as the anchor for the receptors or the scaffold for the construction of the postsynaptic terminals. Together, these synaptic protein components constitute a dedicated system to ensure accurate, efficient and reliable synaptic transmission.

Age-related abnormalities of synaptic transmission have been documented in ageing studies of animal models and humans subjects (Peters et al., 2008; Dumitriu et al., 2010; Luebke and Chang, 2007; Luebke and Amatrudo, 2012). In this review we focus on structural changes that occur in synapses during ageing, i.e., the period that is considered normal old age for a particular animal. We discuss the morphological and structural alterations observed in the synapses of the ageing vertebrate nervous system, taking into account commonalities in the brain and several other parts of the nervous system. We also compare age-related changes in the synapses of several invertebrate model systems. We refer the reader to Morrison and Baxter (2012) and Yeoman et al. (2012) for comprehensive reviews of synaptic functions in ageing neurons, and Sheng et al. (2012) and Picconi et al. (2012) as examples of reviews of abnormal synapses observed in age-related diseases (see Section 9).

2. Vertebrate forebrain

2.1. Synapse number and distribution

Two approaches are often used to study synapse number and distribution in the nervous system. One approach is focused on the overall level of a synapse-specific protein, inferring the number or the state of the synapses from a given brain area. For example, when assessed by immunoblot analysis, the levels of synaptic vesicle proteins such as synaptophysin and SNAP-25 are significantly reduced in the hippocampus of 14–24 month-old rats compared to 2 month-old rats (Canas et al., 2009). Because synaptophysin and SNAP-25 are expressed in the presynaptic terminal, this finding implies an age-related decrease in the number of presynaptic terminals and may also point to a decrease in the amount of these proteins in the terminals. Another study using a combination of proteomic and immunoblot analysis, finds that the level of postsynaptic proteins, in addition to several presynaptic proteins, is also decreased in the hippocampus of older (26 months) rats (VanGuilder et al., 2010). This observation suggests that both presynaptic and postsynaptic terminals are affected in the ageing hippocampus.

The second approach is to study individual synaptic terminals using light or electron microscopy. This approach is useful for revealing spatial information of affected synapses in a specific

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