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Review

Astrocytic role in synapse formation after injury

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ABSTRACT

In 1969 a paper entitled *Neuronal plasticity in the septal nuclei of the adult rat* proposed that new synapses are formed in the adult brain after injury (Raisman, 1969). The quantitative electron microscopic study of the timed responses to selective partial denervation of the neuropil of the adult rat septal nuclei after distant transection of the hippocampal efferent axons in the fimbria showed that the new synapses arise by sprouting of surviving adjacent synapses which selectively take over the previously denervated sites and thus restore the number of synapses to normal. This article presents the evidence for the role of perisynaptic astrocytic processes in the removal and formation of synapses and considers its significance as one of the three major divisions of the astrocytic surface in terms of the axonal responses to injury and regeneration.

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1. Introduction

The decade following 1969 saw a gradual erosion of the previous entrenched view that the CNS was incapable of a positive response to injury. Inexorably the field was opening and plasticity after loss of synapses has broadened into a more general view that plasticity is an intrinsic core function of the brain and spinal cord. Plasticity occurs not only after injury (e.g. (Bareyre et al., 2004) and during development (e.g. Allen, 2013) but also throughout adult life (e.g. Kaas et al., 1983). Plasticity is the ongoing, everyday function of the CNS; it lies at the heart of learning, of memory and of forgetting. Plasticity is a characteristic of all

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systems, sensory, motor, autonomic and cognitive. It is the core function that enables the individual to adapt to a constantly changing environment.

What has become clear in the years since 1969 is that the glial connectome (Douglas, 2013), whose main representative is the astrocyte, is essential for the plasticity of the neuronal connectome (Clarke and Barres, 2013; Allen and Barres, 2005; Fields et al., 2015; Perea et al., 2014; Han et al., 2013; Heller and Rusakov, 2015). The involvement of astrocytes in synapse formation (Clarke and Barres, 2013) and synapse removal (Chung et al., 2013) has largely come from situations with confrontation of neurons and astrocytes in culture. However, it is only electron microscopy that can afford the resolution needed to study the behaviour of the very thin perisynaptic astrocytic processes (PAPs; Heller and Rusakov, 2015). In this article we will review some of our electron microscopic evidence for the role of the PAPs in the formation of new synapses after injury.

2. Observations

2.1. *Astrocytes in removal and formation of synapses*

Fig. 1, taken from the material of the 1969 study, illustrates the PAPs associated with what much later came to be called the tripartite synapse (Haydon, 2001; Perea et al., 2009). In 1973 we showed the PAPs to be an essential intermediary mediating both synapse removal and new synapse formation (Raisman and Field, 1973; Field and Raisman, 1983) in partially denervated neuropil. Fig. 2 shows how rapid and precisely targeted is the localised astrocytic hypertrophy to degenerating neuronal material (Cf. Watts et al., 2004). Fig. 3 shows how the phagocytosis of degenerating terminals leads the astrocytic processes to come into contact with the denervated ('vacated') postsynaptic thickenings. The vacated postsynaptic sites are not lost. They remain identifiable, and marked by the astrocyte-apposed postsynaptic thickenings (s, in Figs. 1–3)

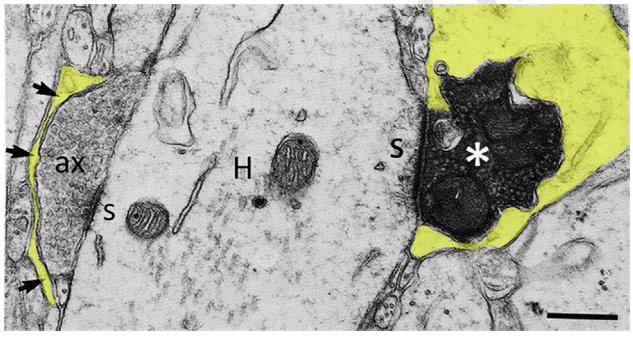

Fig. 1 – A dendritic shaft (H) receives a synapse from a normal axon terminal (ax, on the left). On the right the electron density and collapse indicates an axon terminal (*) degenerating as a result of transection of its parent axon in the fimbria. The PAPs (yellow highlight): compare the very thin (50 nm) PAP around the normal synapse with the swollen process invaginating (arrows) the degenerating synapse. s, Postsynaptic thickenings. From Figs. 2 and 3 in Raisman (1985). From the neuropil of the adult rat septal nuclei 2 days after transection of the hippocampal afferents in the fimbria. Scale bar 0.5 μm. Astrocytic processes are recognised in the electron microscope by their watery clear cytoplasm and sinuous irregular outlines (Peters et al., 1976).

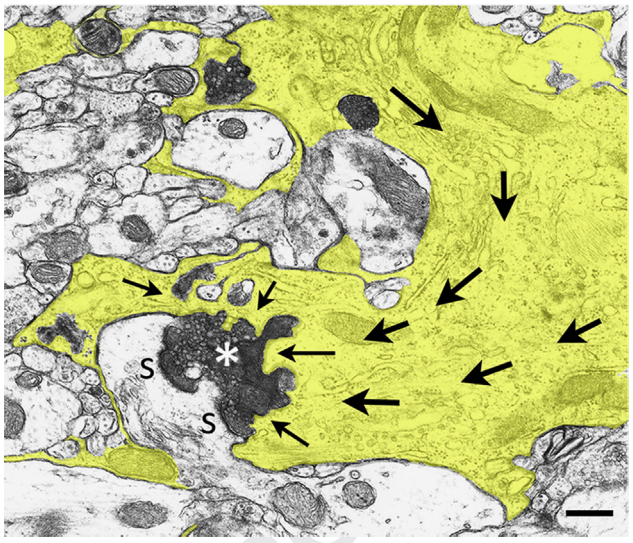

Fig. 2 – Major astrocytic hypertrophy directed (arrows) towards a degenerating axon terminal (*). From Fig. 25 in Raisman and Matthews (1972). From the neuropil of the adult rat septal nuclei 2 days after transection of the hippocampal afferents in the fimbria. Scale bar 0.5 μm. Astrocytic processes are recognised in the electron microscope by their watery clear cytoplasm and sinuous irregular outlines (Peters et al., 1976).

The removal of the degenerating terminals and the apposition of the phagocytic astrocytic processes to the vacated postsynaptic thickenings are transient events. Within days the vacated thickenings are re-occupied by re-apposition of new presynaptic terminals formed by extension of local undamaged presynaptic terminals (Raisman, 1969). As reinnervation occurs there is an orchestrated withdrawal of the astrocytic processes and an ingrowth of newly formed axon terminals (Fig. 4). The original sites are precisely re-occupied and the number of synapses is restored to normal (Raisman and Field, 1973). The importance of astrocytic involvement in this process is shown by the fact that synaptogenesis is much delayed and reduced in areas of neuropil where the density of degeneration seems to have overwhelmed the phagocytic capacity of the local astrocytes (Field and Raisman, 1983).

3. Discussion

Over the years PAPs have become recognised as a distinct astrocytic region which is involved in synapse formation. Confocal and laser scanning microscopy of brain slices has shown that astrocytic processes are rapidly motile (e.g. Hirrlinger et al., 2004; Haber et al., 2006) via mechanisms which include IP_3, Ca^{2+}, and an ezrin link from the actin cytoskeleton to the cell membrane (Tanaka et al., 2013;