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Extracellular vesicles: interneural shuttles of complex messages

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A core function of neural cells is the exchange and integration of information. Extracellular vesicles such as exosomes and microvesicles recently entered the scene of neuroscience as novel vehicles transmitting complex signals between neural cells. Carrying a defined but mixed cargo of biomolecules, extracellular vesicles possess versatile biological activities with the ability to profoundly modulate the molecular configuration and behaviour of target cells. Extracellular vesicles are suggested to carry out functions during neural development and maintenance, they appear to spread neuropathology and furthermore, convey neuroprotection and regeneration. Understanding the molecular mechanisms of this sophisticated cellular crosstalk will fundamentally improve our insight in complex intercellular processes in the healthy and diseased nervous system.

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Introduction

Vesicles not only shuttle cargo within cells but also cross the extracellular space and enter target cells. These so-called extracellular vesicles (EVs) originate from different cellular sites and hence, comprise distinct types of vesicles: microvesicles (MVs) shed from the plasma membrane, while exosomes are released from the lumen of multivesicular bodies (MVBs) that, instead of maturing to lysosomes, fuse with the plasma membrane [1,2]. In contrast to intracellular transport vesicles (such as synaptic vesicles), EVs are filled with cytoplasmic cargo and the surrounding membrane shares the topology of the plasma membrane. This topology allows EVs to exchange cargo between cells that would normally not traverse membrane barriers, such as membrane proteins, lipids, cytosolic enzymes, and different species of RNAs. In particular the transfer of mRNAs and miRNAs to recipient cells turns EVs into a potentially powerful instrument of horizontal gene regulation. The content of EVs reflects the current molecular status of the cell from which they are derived and can vary in response to environmental signals such as stress. Thus, compared to other modes of cellular communication, EVs represent complex and versatile signalling entities, that simultaneously deliver an array of potential effectors to receiving cells.

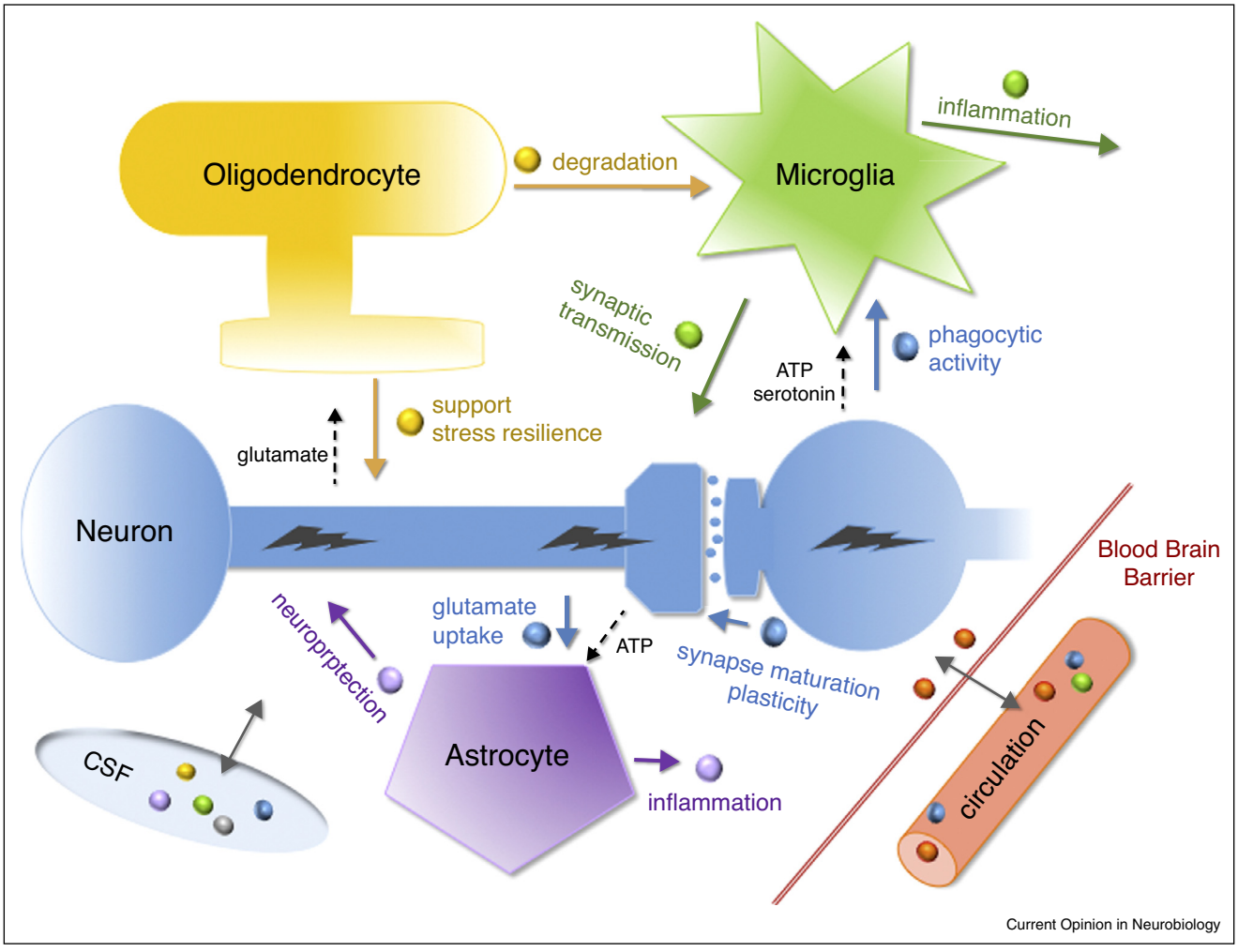
The biogenesis of MVs and exosomes is assisted by the ESCRT-complex or is driven by cone-shaped lipids, such as ceramide [3]. How cargo is selected during EV biogenesis is not entirely understood, but appears to depend on the interaction with tetraspanin-enriched and cholesterol-enriched microdomains and regulated by post-translational modifications, such as ubiquitination and sumoylation [4,5••]. Since MVs and exosomes share many features, including components of their biosynthesis machinery that are utilized as markers, their discrimination is challenging. A standardized classification performed on the basis of biochemical, morphological and biophysical arguments has been introduced [6•,7]. This definition and the typical EV marker profile clearly discriminates EVs from synaptic vesicles, the predominant pool of intracellular vesicles in the nervous system.

To date, EVs have established signalling functions in many tissues of the body [8] and seem to be used by tumours to manipulate their direct and remote environment [9••,10]. But how about the nervous system, which as an organ is built on connectivity and depends in performance on fine-tuned cell interactions? Apparently, all major cell types of the CNS appear to send and receive MVs or exosomes (Figure 1), which as a mix can be detected in the cerebrospinal fluid (CSF) [11–13]. In this article, we give a brief overview on the recent advances shedding light on the role of EVs in neuron–neuron and neuron–glia communication in the normal, degenerating and regenerating nervous system.

EVs in the healthy nervous system

The release of EVs by neural cells and their contents have been extensively characterized in tissue culture by analysis of vesicles that are contained in cell supernatants (reviewed in [14]). The presence of EVs in cerebrospinal fluid (CSF) underscores their relevance in neural tissue,

Figure 1



Communication among neural cells via EVs. All major cells types of the CNS send and receive EVs, establishing lines of intercellular trafficking in the CNS. The release of EVs is largely regulated by neuronal electrical activity and neurotransmitter signalling. EVs are depicted as small spheres, coloured arrows indicate the direction of EV-delivery, and the proposed functional relevance of the pathway is denoted along side. Dashed arrows indicate signals triggering EV release. EVs can cross the blood–brain barrier and enter the CNS (red spheres) and CNS-derived EVs are detected in the cerebrospinal fluid (CSF) and circulation.

although EVs from CSF might not exactly correlate with the EVs isolated from cultured cells. While isolation of EVs from the native CNS tissue has been achieved [15], caution should be taken as the lack of unique EV-markers challenges the discrimination of co-isolated tissue fragments generated during homogenization of the tissue.

Convincing evidence for a functional role of EVs *in vivo* derives from the use of invertebrate model systems. In the adult *C. elegans* worm, ciliated sensory neurons bud MVs from the ciliary base and are released into the environment, controlling male mating behaviour. By genetic screening, p38 MAPK PMK1 and myristoylated CIL-7 were identified as regulators of EV-biogenesis in this pathway [16,17]. A series of conclusive studies performed on the *Drosophila* larval neuromuscular junction (NMJ) revealed that exosomes mediate the transfer of the hydrophobic Wnt-signalling protein Wingless bound to the membrane protein Evi/Wntless and of Synaptotagmin 4 from presynaptic boutons to the postsynaptic muscle, functionally relevant for synapse maturation and plasticity [18••,19]. Exosome release at the NMJ was regulated by electrical activity and dependent on the GTPase Rab11 and the SNARE protein Syntaxin1A, which may be part of the machinery controlling maturation and fusion of secretory MVBs. These studies affirm the value of invertebrate model systems as effective tools to study evolutionary conserved aspects of EV-biology and function *in vivo*.