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Review

Astrogliopathology: Could nanotechnology restore aberrant calcium signalling and pathological astroglial remodelling?☆

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ABSTRACT

Pathology of the brain is caused by the deficiency in tissue homeostasis. As the main homeostatic element of the mammalian nervous system is represented by astrocytes, these glial cells are involved in many, if not all, brain disorders. Diseased astrocytes undergo a variety of morphological and functional changes, including deregulation of calcium dynamics. To rectify undesirable changes in astrocytes and/or neurones that occur in disease, we postulate the future use of nanotechnology-based therapeutics. Carbon nanotubes emerged as one of the most promising advanced nanomaterials for use in neuroprosthesis. Recently, they have been used to affect morpho-functional characteristics of astrocytes. This article is part of a Special Issue entitled: 12th European Symposium on Calcium.

1. Introduction

Neuroglia was initially described by Rudolf Virchow as a connective tissue that binds nervous elements together [1] before its cellular nature was established by Camillo Golgi [2,3]. Astrocytes, a subset of glial cells that represent the main subject of this review, were named by Michael von Lenhossek [4]. In the vertebrates, astrocytes are the main homeostatic element of the nervous system. Thus, unsurprisingly, they represent a substrate of many if not all neurological and psychiatric disorders, which in general terms all occur as a consequence of homeostasis gone bad. A prominent component of astrocytic contribution to the brain homeostasis and signalling present itself in variations of intercellular calcium levels. This signalling leads to a bidirectional dialogue between astrocyte and neurones, which is endowed by the intimate structural associations between these two principal cells of the brain. Of note, these neural cellular components can undergo morphological and functional changes in health and disease. In this review, we discuss the above aspects of the astroglial role in disease. We indicate a possible novel nanotechnology-based therapeutic approach to treat diseased brain. Namely, we discuss carbon nanotubes, which emerged as one of the most promising advanced nanomaterials for use in neuroprosthesis. Although this could be considered as a somewhat premature and provocative approach, there is palpable evidence that this class of nanomaterials deserves such an expose.

2. General pathophysiology of neuroglia

The origin of neurological diseases lies in the deficient tissue homeostasis; regardless the aetiology all diseases of the nervous system can be considered as homeostatic failures. In the vertebrates the main homeostatic element of the nervous system is represented by neuroglia that, in the course of evolution, assume the main role in housekeeping and stability of the nervous tissue. Neuroglia, by definition, cover highly heterogeneous cellular populations that include cells of neural (astroglia, radial glia, oligodendroglia, NG2 cells, and various types of peripheral glia, which include for example enteric glia, Schwann cells and satellite cells) and non-neural (microglia that develops from foetal macrophages) origins (see [5–10] for comprehensive recent reviews).

Damage to the nervous system, regardless of the aetiology, generally triggers defensive reactions of the glia, which are broadly represented by astrogliosis, Wallerian degeneration and activation of microglia (Fig. 1 and [11]). All these defensive programmes are multi-staged often

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reversible and are at their core neuroprotective. Reactive astrogliosis, for example, represents complex remodelling of astrocyte biochemistry associated with the release of many neurotrophic and neuroprotective factors that assist neuronal survival and facilitate post-lesioned nervous tissue remodelling [12]. At the same time severe insults may drive reactive glia into a neurotoxic state in which they release multiple deleterious factors that exacerbate damage of the nervous tissue. All in all, neuroglial cells represent an important pathogenetic factor, are critical for the progression of virtually all neurological disorders and instrumental in defining the outcome of a neuropathological process [11,13–16].

3. Astroglial calcium signalling in neurological diseases

It is universally accepted that intracellular calcium signalling provides a substrate for astroglial excitability [17–19]. Indeed multiple receptors expressed by astrocytes *in vitro* and *in situ* are linked to generation of transient fluctuations of Ca^{2+} concentration in the cytosol and in the intracellular organelles. Astroglial calcium signals originate from both Ca^{2+} release from intracellular organelles and plasmalemmal Ca^{2+} entry, with these two processes being mutually regulated. Global Ca^{2+} signals, cytosolic Ca^{2+} oscillations and intercellular Ca^{2+} waves (the latter integrate astroglial syncytia) are mainly associated with Ca^{2+} release from the endoplasmic reticulum (ER) intracellular store. The ER is well developed in astrocytes and acts as their principal dynamic Ca^{2+} store. Activation of ER Ca^{2+} release in astrocytes is primarily associated with opening of inositol-1,4,5 trisphosphate ($InsP_3$)-gated channels or $InsP_3$ receptors ($InsP_3Rs$) localised in the endomembrane. $InsP_3$ is produced by phospholipase C coupled to a multitude of astroglial metabotropic receptors located at the plasma membrane of which the most abundant are metabotropic glutamate receptors, metabotropic purinoceptors (of both P2Y and adenosine subtypes) and possibly adrenoceptors [20,21]. These $InsP_3$-dependent Ca^{2+} signals developed following activation of metabotropic receptors have been observed in astroglia *in vitro*, *in situ* and *in vivo* (see e.g. [22–27]).

Plasmalemmal Ca^{2+} entry pathway in astrocytes has been investigated in less detail; nonetheless, it plays an important role for fast and local Ca^{2+} signals that are critical for fast signalling in astroglial perisynaptic processes that follow synaptic transmission. Calcium influx into astrocytes occurs through several plasmalemmal routes represented by store-operated pathways, ionotropic receptors and sodium–calcium exchangers. The store-operated entry, activated following depletion of the ER store in astrocytes, occurs through TRPC1 containing channels which have substantial Ca^{2+} permeability [28]. Similarly, Ca^{2+} can be carried into astrocytes through ionotropic glutamate receptors mainly of the N-methyl D-aspartate (NMDA) type differentially expressed by astrocytes in different brain regions and through purinergic P2X receptors [29–31]. Calcium permeability ($P_{Ca}/P_{monovalent}$) of astroglial NMDA receptors has been determined at about 3, while that of P2X receptors varies between 2 for $P2X_{1/5}$ receptors and >10 for P2X7 receptors [32,33]. Finally Ca^{2+} can enter astrocytes through a sodium–calcium exchanger (NCX) operating in the reverse mode. Due to the relatively high cytosolic Na^+ concentration in astrocytes, the reversal potential of NCX lies close to a resting membrane potential [34], and hence even small depolarisations of moderate increases in intracellular Na^+ concentration switch astroglial NCX into the reverse mode [35].

Various neuropathological conditions are associated with aberrant astroglial Ca^{2+} signalling and failures of astroglial Ca^{2+} homeostasis. For example, in stroke, increased glial Ca^{2+} signals and pathological glial Ca^{2+} waves are likely responsible for spreading the cell death through the infarction penumbra. These intercellular Ca^{2+} waves can trigger a distant release of glutamate and/or ATP from astroglia that may assume excitotoxic proportions [36]. Pathological astroglial Ca^{2+} signalling may also increase following oedema and cell swelling

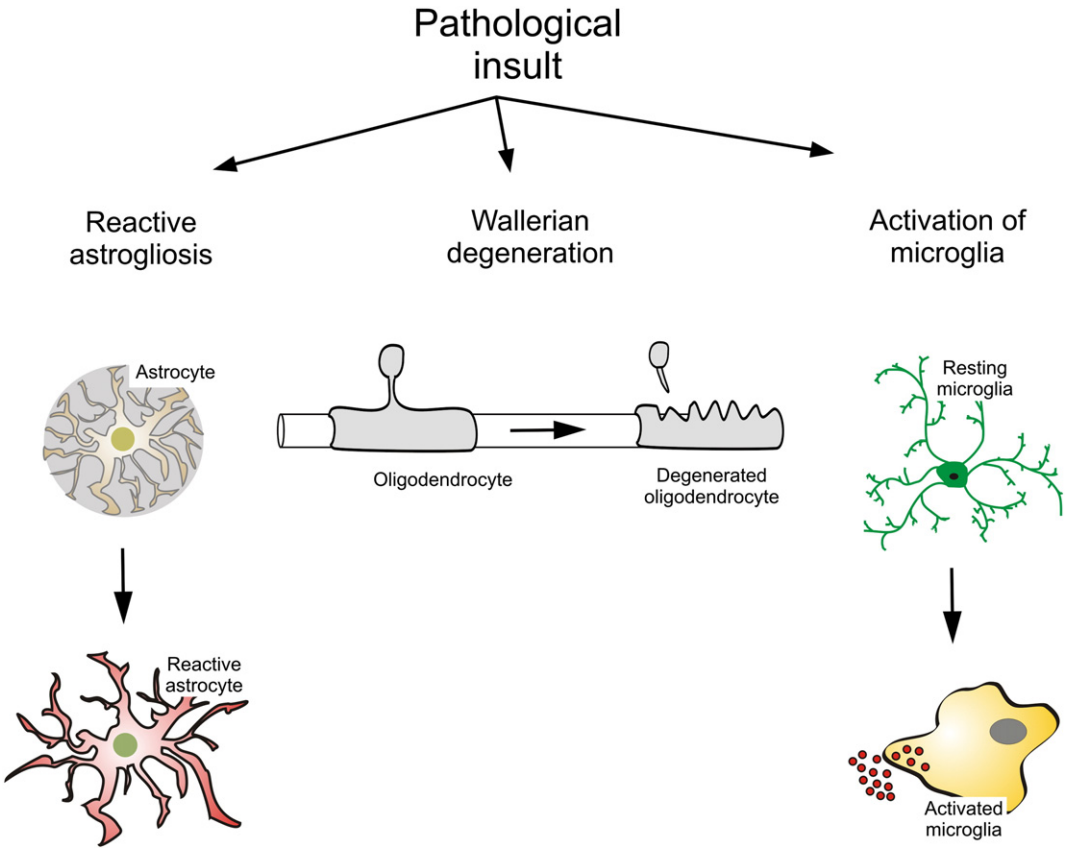

Fig. 1. General pathophysiology of neuroglia. Lesions to the brain trigger evolutionary conserved neuroglial defensive programmes represented by reactive astrogliosis, Wallerian degeneration and activation of microglia.