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Review

The axon as a physical structure in health and acute trauma

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ABSTRACT

The physical structure of neurons – dendrites converging on the soma, with an axon conveying activity to distant locations – is uniquely tied to their function. To perform their role, axons need to maintain structural precision in the soft, gelatinous environment of the central nervous system and the dynamic, flexible paths of nerves in the periphery. This requires close mechanical coupling between axons and the surrounding tissue, as well as an elastic, robust axoplasm resistant to pinching and flattening, and capable of sustaining transport despite physical distortion. These mechanical properties arise primarily from the properties of the internal cytoskeleton, coupled to the axonal membrane and the extracellular matrix. In particular, the two large constituents of the internal cytoskeleton, microtubules and neurofilaments, are braced against each other and flexibly interlinked by specialised proteins. Recent evidence suggests that the primary function of neurofilament sidearms is to structure the axoplasm into a linearly organised, elastic gel. This provides support and structure to the contents of axons in peripheral nerves subject to bending, protecting the relatively brittle microtubule bundles and maintaining them as transport conduits. Furthermore, a substantial proportion of axons are myelinated, and this thick jacket of membrane wrappings alters the form, function and internal composition of the axons to which it is applied. Together these structures determine the physical properties and integrity of neural tissue, both under conditions of normal movement, and in response to physical trauma. The effects of traumatic injury are directly dependent on the physical properties of neural tissue, especially axons, and because of axons' extreme structural specialisation, post-traumatic effects are usually characterised by particular modes of axonal damage. The physical realities of axons in neural tissue are integral to both normal function and their response to injury, and require specific consideration in evaluating research models of neurotrauma.

Contents

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1. The axon

In the mature nervous system, the primary purpose of the axon is to propagate and regenerate action potentials at a consistent speed, and secondarily to this, to provide support for the energetic and signalling needs of its distal processes. Accordingly, its interior is structured to maintain its shape and calibre, and permit rapid internal transport along its length, while remaining compliant across the range of everyday movements. In large part this is attributable to the physical qualities of the axoplasm, which resembles a structured gel or liquid crystal (Weiss and Mayr, 1971; Mukhopadhyay et al., 2004; Jones and Safinya, 2008) due to the packed array of loosely interacting cytoskeletal proteins aligned with the main axis of the fibre (Berthold and Rydmark, 1995; Hirano and Llena, 1995). In addition to the passive mechanical properties of the individual elements, many are coupled by motor proteins capable of using ATP-derived energy to generate physical force, adding an active element to the properties of the network (Goriely et al., 2015). The axon cytoskeleton consists of microtubules, which stiffen the axon and provide transport scaffolding; packed arrays of neurofilaments filling the axoplasm; actin microfilaments and spectrins, forming a cortex just inside the axolemma, and proteins which link these elements (Fig. 1; Schnapp and Reese, 1982; Berthold and Rydmark, 1995; Lasiecka et al., 2009).

1.1. Cytoskeleton

1.1.1. Microtubules

Microtubules (MTs) are the largest cytoskeletal element, consisting of spiral tubular polymers 22–23 μm in diameter, made from α- and β-tubulin heterodimers (see reviews by Fukushima, 2011; Kapitein and Hoogenraad, 2015). The microtubule-associated proteins (MAPs) facilitate microtubule assembly and transport mechanisms, and bind to microtubules to form side-arms which interact with the surrounding environment, promoting complexing and stability; the principal types employed in axons are MAP1A, MAP1B, MAP3, MAP5 and tau, whereas MAP2 is found in the soma and dendrites (Mandlekow and Mandlekow, 1995; Fukushima, 2011). Although MTs are vital for structure, growth, the transport of organelles and proteins (Gardel et al., 2008; Kapitein and Hoogenraad, 2015) and extending and organising growing axons during development (Haynes and Kinney, 2011), in mature axons they are primarily transport conduits and bracing structural elements (Brangwynne et al., 2006; Gardel et al., 2008; Ouyang et al., 2013).

Early in the initial polarisation of developing neurons, characteristic MT modifications (e.g. detyrosination and acetylation at specific residues) are enriched in the nascent axon, recruiting the transport proteins and MAPs appropriate for the structural and regulatory challenges of this extraordinary structure (Fukushima, 2011; Janke and Bulinski, 2011). In mature axons, further dynamic post-translational modifications such as acetylation, tyrosination, glutamylation and glycylation regulate MT stability on the local scale, alter MAP binding, and probably alter the movements of the microtubule motors kinesin and dynein (Janke and Bulinski, 2011).

1.1.2. Neurofilaments

Neurofilaments (NFs) are the only major cytoskeletal element unique to neurons, and are correspondingly unique among intermediate filaments (Leterrier et al., 1996; Parry, 2011). Although not all axons contain NFs, the axons which do are largely filled by them (Schnapp and Reese, 1982; Berthold and Rydmark, 1995). Mature NFs are heteropolymers consisting of a 10nm-wide core of protofilament dimers arranged in coiled coils, with their carboxy-terminal tail domains extending as perpendicular side-arms in a bottle-brush configuration (Fuchs and Cleveland, 1998; Leermakers and Zhulina, 2010; Parry, 2011).

NFs assemble from five structurally related subunits: neurofilament light (NFL), medium (NFM) and heavy (NFH) (66, 95-100 and 110–115 kDa respectively; Lee and Cleveland, 1996; Janmey et al., 2003) and α-internexin (INT; 66 kDa; Yuan and Nixon, 2011); peripherin also contributes to NFs in peripheral and some central axons (58 kDa; Parry, 2011). The amino-terminal rod domain is highly conserved between all subunits, but the tail domain is extended and structurally complex in NFM and NFH compared to NFL, INT and peripherin (Pant and Veeranna, 1995; Leermakers and Zhulina, 2010; Parry, 2011).

A series of lysine-serine-proline repeats in NFH and NFM tail domains provides multiple sites for phosphorylation (Elder et al., 1998a; Jones and Safinya, 2008), making NFs, particularly NFH, the most phosphorylated proteins in the nervous system (Pant and Veeranna, 1995). This phosphorylation alters inter-filament interaction (sometimes called “bridging”, although this term is misleading; Leterrier et al., 1996; Guadano-Ferraz et al., 1990; Mukhopadhyay et al., 2004; Leermakers and Zhulina, 2010), prevents premature assembly prior to entering the axon (Nixon, 1993; Lee and Cleveland, 1996), and alters interactions between NFs and microtubules (Hisanaga and Hirokawa, 1990). In the axon, phosphorylation of NFM and NFH creates linearly aligned, spaced lattices of NFs (Schnapp and Reese, 1982; Eyer and Leterrier, 1988; Gotow et al., 1994; Janmey et al., 2003) whereas dephosphorylation favours collapsed meshes and fascicles in the soma and dendrites (Hirokawa et al., 1984; Pant and Veeranna, 1995). This process is locally regulated, since individual NFs can have phosphorylated and dephosphorylated domains at different points along their length (Brown, 1998).

Axonal NFs, which become phosphorylated near the axon initial segment (Nixon et al., 1994; Schlaepfer and Bruce, 1990) form a tough, elastic network, capable of bearing considerably more elastic strain than other cytoskeletal elements (Kreplak and Fudge, 2007). Within the arrays, filaments have characteristic spacing (Elder et al., 1998a; Kumar et al., 2002; Jones and Safinya, 2008) but are otherwise distributed randomly (Price et al., 1988) or semi-randomly (Hsieh et al., 1994a; Mukhopadhyay et al., 2004), suggesting that the interactions between them are not fixed.

1.1.3. Actin and the axon cortex

The subsurface structure of the axolemma, the axon cortex, is largely composed of a meshwork of actin microfilaments linked by ankyrins and spectrins (Schnapp and Reese, 1982; Thi et al., 20043). These filaments provide a substrate for motor proteins such as myosin, and are pinned to the axolemma at adherens junctions, connected by catenins to cadherins in the membrane (Salzer, 1995; Thi et al., 2004, 2013). Motor proteins permit the actin cortex to locally modulate stiffness and compliance, in ways which may be linked to signalling mediated by extracellular attachments (Gardel et al., 2008).

At the axon initial segment, spectrins and ankyrins, assisted by transmembrane neurofascin, regulate the structured array of