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Internodal Ca permeable channels: implications for axon degeneration

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Central myelinated axons are injured in a variety of conditions including ischemia, trauma and neuroinflammation. Failure of ion pumping in compromised axons leads to depolarization and dysregulation of ionic homeostasis within the axon and supporting myelinating glia. This in turn promotes toxic Ca overload in these elements via a number of Ca transporters and Ca-permeable membrane channels, together with Ca release from intra-axonal Ca stores. Under the myelin sheath, the intermodal axon expresses a variety of “signaling nanocomplexes” consisting of L-type Ca channels, AMPA/kainate glutamate receptors and nNOS. These is turn are physically and/or functionally linked to intra-axonal Ca stores containing ryanodine and IP3-sensitive Ca release channels. Depolarization of the axolemma is sensed by Cav 1.2 and 1.3 channels, which in turn are coupled to RyR1 and 2 receptors on subjacent “axoplasmic reticulum”, leading to Ca release from these stores, in a manner similar to "excitation-contraction coupling" in skeletal muscle. This arrangement is under additional control of GluR6 kainate receptors that form part of these macromolecular complexes. Axonal AMPA receptors in turn permeate small amounts of Ca to release additional Ca from ryanodine-dependent stores in a cardiac type “Ca-induced Ca release” fashion. GluR5 kainate receptors operate in a non-canonical metabotropic manner to generate IP3 via activation of PLC, releasing Ca from IP3 stores. In contrast to the intermodal axolemma, the overlying myelin sheath expresses NMDA receptors. During injury, Na-coupled glutamate and glycine transporters, driven in the transmitter efflux mode, promote excessive activation of these receptors and Ca entry into the cytosolic spiral of myelin (the major dense line). Thus, excessive glutamate and glycine release, leading to receptor over-activation, represents a novel and potentially very important mechanism of injury to oligodendrocytes and the myelin sheath; excessive activation of these myelinic receptors may represent one of the most proximal events leading to demyelination.