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The expression of syntaphilin is down-regulated in the optic nerve after axonal injury

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ABSTRACT

The impairment of mitochondrial function is an important pathogenic factor in glaucoma and other optic neuropathies in which retinal ganglion cell (RGC) death is the fundamental pathology. Syntaphilin was recently discovered as a docking protein that affects mitochondrial mobility. However, no reports have investigated the involvement of syntaphilin in the visual system. We investigated the expression of syntaphilin in the rat retina, optic nerve and brain. The expression of syntaphilin exhibited varying patterns in the visual system. Syntaphilin was expressed in retinal ganglion cells in the retina, in the cell bodies of neurons in the superior colliculus and was abundant in the astrocytes of rat optic nerves (similar to the findings that syntaphilin is expressed in human optic nerves). After optic nerve transection, which caused RGC death and axonal degeneration, quantitative real-time RT-PCR was used to assess changes in gene expression in the rat retina and optic nerve. Syntaphilin gene and protein expression in the optic nerve was downregulated 3 and 7 days after optic nerve transection. Our study suggests that syntaphilin expression in astrocytes at the optic nerve might be involved in axonal injury.

1. Introduction

The impairment of axonal transport is an important pathogenic factor in glaucoma (Anderson and Hendrickson, 1974; Pease et al., 2000; Quigley et al., 2000; Vrabec and Levin, 2007), a degenerative disease of retinal ganglion cells (RGCs) and the second highest cause of blindness worldwide (Quigley and Broman, 2006). Recently, deficits in axonal transport have been reported in rat and mouse glaucoma models (Salinas-Navarro et al., 2010; Chidlow et al., 2011) and in human high-pressure secondary glaucoma (Knox et al., 2007). Other optic neuropathies causing RGC death are also characterized by early breakdown of the axonal transport system (Crish et al., 2010; Haenold et al., 2012).

A characteristic feature of neurons is the axon, which can be several orders of magnitude longer than the cell body. To maintain cellular functions in remote areas of the axon, a transport system is required to carry various cargos, such as proteins and membrane-encapsulated vesicles, from the soma to the axon ending (anterograde) or in the opposite direction (retrograde) (Hirokawa et al., 2010). Mitochondria are transported along microtubules in an axon to peripheral locations of the neuron (Hollenbeck and Saxton, 2005). A balanced delivery of mitochondria helps them serve multiple functions inside neurons, including energy provision, regulation of calcium homeostasis, neuronal apoptosis, synaptic transmission and plasticity (Li et al., 2004; Chan, 2006). Motor proteins such as kinesin and dynein are known to play a role in mitochondrial transport. Syntaphilin was recently discovered to be a mitochondria docking protein (Kang et al., 2008). Complex mobility patterns have suggested that axonal mitochondria might be coupled to two opposing motors (kinesin and dynein) and docking machinery. The mechanism underlying the regulation of these motor proteins with respect to axonal transport is still unknown.

It was first reported that syntaphilin is prominently expressed in the rat brain but not in other tissues, such as the heart, kidney, lung, spleen and muscle (Lao et al., 2000). Later, *in vitro* studies demonstrated that syntaphilin was expressed in axonal mitochondria of neurons (Kang et al., 2008; Chen et al., 2009; Zhu and Sheng, 2011). Only one report has investigated the expression of syntaphilin *in vivo*. Syntaphilin was found to be expressed in neural fibers of chronic multiple sclerosis lesions in the human brain (Mahad et al., 2009). Evidence suggesting that mitochondrial dysfunction is involved in the development and progression of

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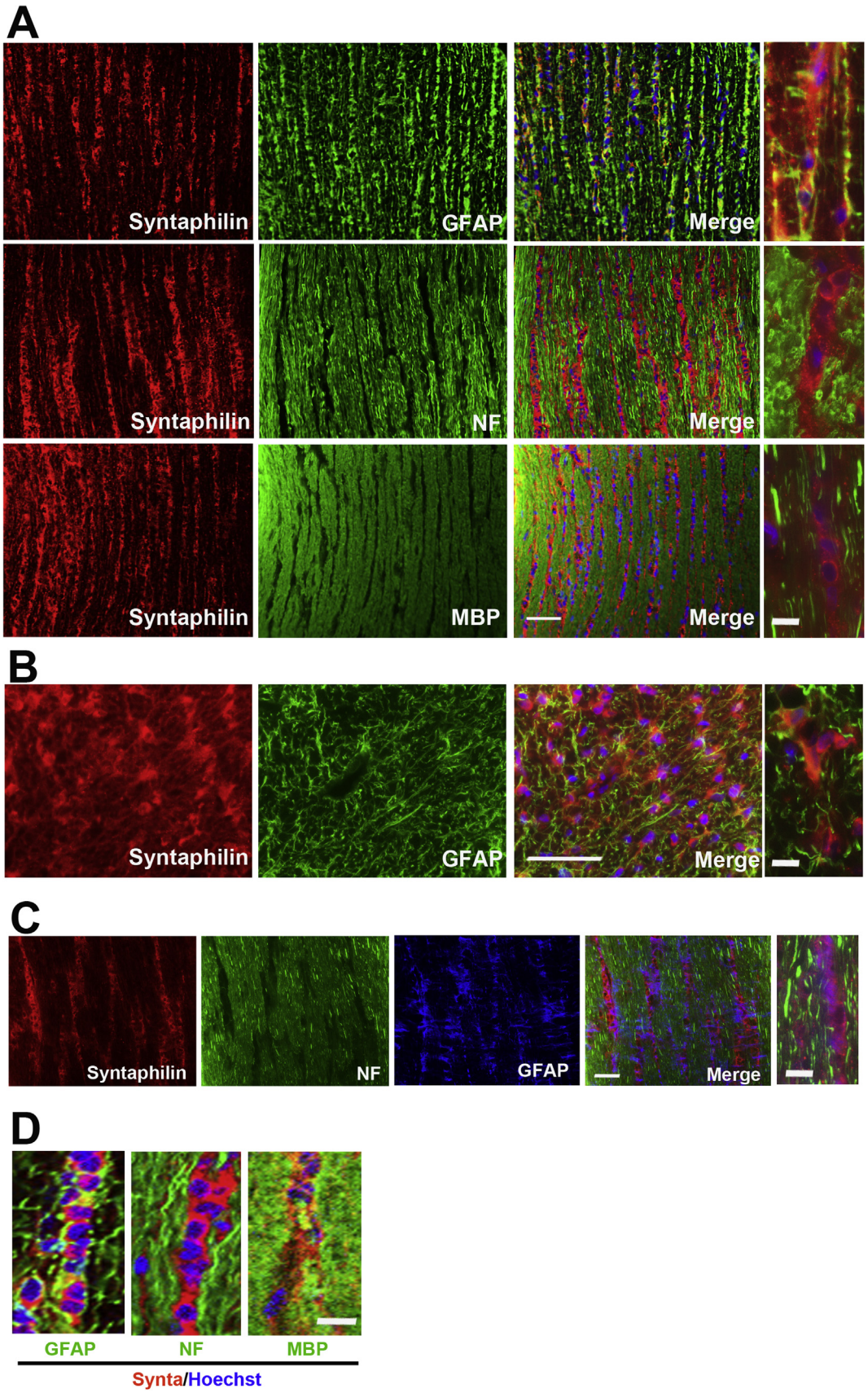

Fig. 1. Immunofluorescent localization of Syntaphilin in rat optic nerve. (A) The longitudinally sectioned rat optic nerve by double-label, fluorescent immunohistochemistry with antibodies against syntaphilin (red) and GFAP, NF or MBP (green). Nuclei are marked with Hoechst (blue). (B) Localization of syntaphilin in the cross section of rat optic nerve by double-label immunohistochemistry with antibodies against syntaphilin (red) and GFAP (green). The image in the third column is a merged image of those in the left two columns. The image in the right column is a image captured with the highest magnification. Nuclei are marked with Hoechst (blue). (C) Triple immunohistochemical staining for longitudinally sectioned rat optic nerve with antibodies against GFAP (blue), syntaphilin (red) and NF (green). The image in the fourth column is a merged image of those in the left three images. The image in the right column is a magnified image of the merged image. The merged image shows the concordant staining of syntaphilin and GFAP. (D) Confocal merged images of rat optic nerve stained with antibodies against syntaphilin (red) and GFAP, NF or MBP (green). Nuclei are marked with Hoechst (blue). Scale bar = 200 μm (A), 50 μm (B,C), 10 μm (the magnified images in A–C, D).