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PSA modification of NCAM supports the survival of injured retinal ganglion cells in adulthood

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ABSTRACT

Neural cell adhesion molecule (NCAM) is known as the cell surface glycoprotein, and it belongs to the immunoglobulin superfamily of adhesion molecules. Polysialic acid (PSA) is a carbohydrate attached to NCAM via either of two specific sialyltransferases: ST8SiaII and ST8SiaIV. Polysialylated neural cell adhesion molecule (PSA-NCAM) mediates cell interactions, plays a role in axon growth, migration, synaptic plasticity during development and cell regeneration. Some evidence has shown that PSA-NCAM supports the survival of neurons. It was demonstrated that PSA-NCAM is present in abundance in the retina during development and in adulthood. The aim of this study was to investigate whether PSA-NCAM promotes retinal ganglion cell (RGC) survival in transgenic mice with deficiencies in sialyltransferases or NCAM or after the administration of endoneuraminidase (Endo-N). RGC injury was induced by intravitreal administration of kainic acid (KA). These studies showed that injection of Endo-N after 14 days enhances the toxicity of KA to RGCs in wild-type (WT) mice by 18%. In contrast, in knockout mice (ST8SiaII−/−, ST8SiaIV−/−, NCAM−/−), survival of RGCs after KA injury did not change. Deficiencies of either ST8SiaII or ST8SiaIV did not influence the level of PSA-NCAM in the adult retina, however, in neonatal animals, decreased levels of PSA-NCAM were observed. In knockout ST8SiaII−/− adults, a reduced number of RGCs was detected, whereas in contrast, increased numbers of RGCs were noted in NCAM−/− mice. In conclusion, these data demonstrate that PSA-NCAM supports the survival of injured RGCs in adulthood. However, the role of PSA-NCAM in the adult retina requires further clarification.

1. Introduction

NCAM is expressed on the membranes of neurons and glial cells. The extracellular fragment of NCAM contains five Ig-like modules followed by two fibronectin type III modules (Cunningham et al., 1987). NCAM is considered to be a mediator of cell-cell interactions that can promote cell adhesion through a homophilic binding mechanism (rev. by Edelman, 1986). NCAM functions may be regulated by the addition of long linear homopolymers of alpha 2-8-linked

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sialic acids (PSA). PSA has a large hydrated volume and a high negative charge density and thus, reduced adhesion forces (Rougon, 1986; Rutishauser and Landmesser, 1996). Two transferases, called ST8SiaII and ST8SiaIV, synthesize PSA on NCAM. ST8SiaII functions primarily during embryogenesis, and its expression decreases shortly after birth. In contrast, ST8SiaIV is the primary in adulthood, and is almost absent during development (Livingston and Paulson, 1993; Eckhardt et al., 1995). PSA is widely expressed in the central nervous system during embryogenesis and is remarkably down-regulated after birth (Rothbard et al., 1982; rev. by Seki and Arai, 1993). However, its expression persists in brain regions with ongoing plasticity and neurogenesis, such as the olfactory bulb, piriform cortex, hippocampus, hypophysis and hypothalamus (rev. by Seki and Arai, 1993; Eckhardt et al., 2000). During development, PSA-NCAM is expressed abundantly in the retina, and it continues to be expressed in the adult optic nerve and retina by astrocytes and Müller cells (Bartsch et al., 1990; Sawaguchi et al., 1999; Canger and Rutishauser, 2003; Murphy et al., 2009). Müller cells are a type of glial cell, which extend processes throughout the retina. During embryogenesis, Müller cells promote the growth of RGCs axons towards the optic disk, which subsequently remains in close contact with the endfeet of Müller glia (Stuermer and Bastmeyer, 2000). PSA-NCAM has been shown to play a role in cell migration (Wang et al., 1994; Rousselot et al., 1995), synaptic plasticity (Lüth et al., 1994; Muller et al., 2000), is implicated in the regulation of axon growth, guidance, and fasciculation (Doherty et al., 1990; Tang et al., 1992; Rutishauser, 1996), and promotes the survival of cortical (Vutskits et al., 2001), subventricular zone neurons (Gascon et al., 2007), and RGCs (Murphy et al., 2009). Previously, it was shown that PSA on the surface of cultured neonatal RGCs supports the survival of these cells and that removal of PSA from the retina in vivo reduced RGC density following optic nerve transection by a further 27% (Murphy et al., 2009). In NCAM−/− mice, RGC loss following optic nerve transection occurs earlier than in WT mice (Murphy et al., 2007).

Knockout mice missing the sialyltransferases ST8SiaII, ST8SiaIV and NCAM−/− are used widely to explore PSA-NCAM functions (Murphy et al., 2007; Aonurm-Helm, 2010). Transgenic ST8SiaII−/− and ST8SiaIV−/− animals have normal NCAM, but lack PSA during the prenatal period and in adulthood, respectively. NCAM−/− mice do not have any NCAM or PSA during life. Knockout animals exhibit a number of morphological and functional abnormalities in the central nervous system and also behavioral abnormalities (Wood et al., 1998; Weinhold et al., 2005; Hildebrandt et al., 2007; Aonurm-Helm, 2010). In previous studies, PSA was removed from the eye via the application of Endo-N (Murphy et al., 2009). In this current study we wanted to explore the impact of retinal PSA-NCAM on the survival of injured and uninjured RGCs in vivo using transgenic animals or via the intravitreal administration of Endo-N.

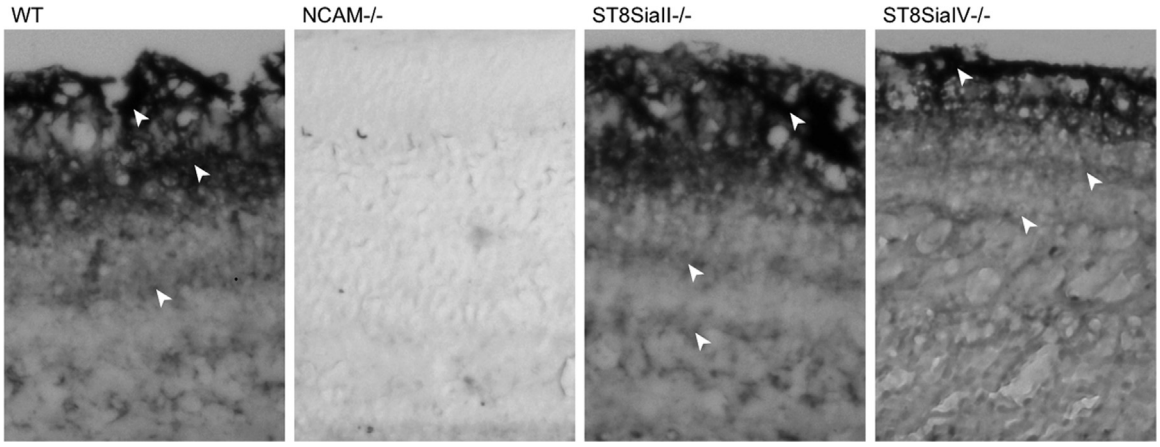

Fig. 1 – Representative microphotograph of PSA-NCAM expression in retinal sections from WT, NCAM−/−, ST8SiaII−/− or ST8SiaIV−/− mice. Arrowheads show PSA-NCAM expression. Magnification ×200.

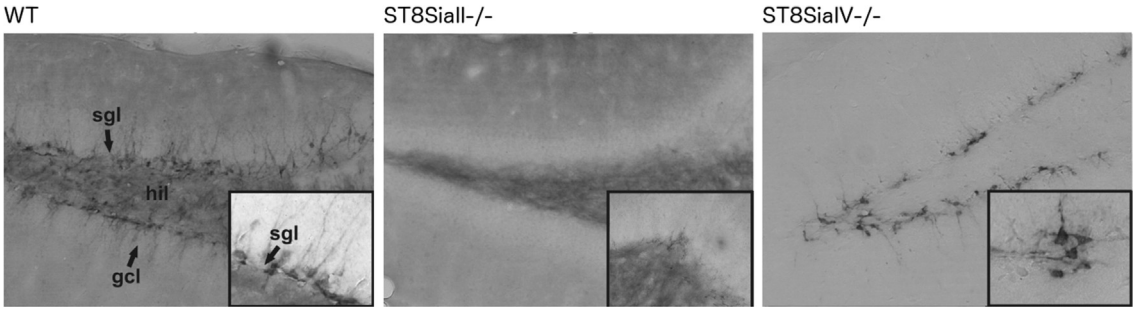

Fig. 2 – Representative microphotograph of PSA-NCAM expression in hippocampal sections from WT, ST8SiaII−/− or ST8SiaIV−/− mice. Abbreviations: gcl – granular cell layer; sgl – subgranular layer; hil – hilus. Magnification: ×200 (inset: ×400).