LUPINE PUBLISHERS

Online Journal of Neurology and Brain Disorders

DOI: 10.32474/OJNBD.2020.05.000202

ISSN: 2637-6628

Mini Review

Prosaposin and Its Receptors, GRP37 and GPR37L1, Protects Neurons Against *In Vivo* Neuropathological Disorders

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Received: December 08, 2020 **Published:** December 22, 2020

Abstract

Prosaposin (PSAP) is both a precursor protein of saposin A–D and a neuroprotective factor. In response to neuropathological disorders such as ischemia, neurotoxins, and nerve transection, PSAP is up-regulated such that both PSAP immunoreactivity and PSAP mRNA levels in neurons increase significantly. PSAP and an 18-mer peptide (PS18) derived from its neurotrophic region were shown to significantly protect damaged neurons. Meyer et al. [1] characterized the PSAP receptors GPR37 and GPR37L1, both of which are involved in neuronal protection, although their expression and their interactions with PSAP have not been fully elucidated (see the review of Smith [2]). However, the increased expression of PSAP and its receptors in damaged neurons and the surrounding glia points to a role for these proteins in protecting damaged cells in the nervous system. This mini-review examines the neuro- and glio-protective functions of PSAP and its receptors, based mainly on data from neuropathological in vivo models. Additional information can be found in the review by Meyer et al. [3].

Keywords: Prosaposin; Neuroprotection; Kainic Acid; Parkinsonism; Nerve Transection; Dystrophin-Deficient Mdx

PSAP Protects Against Ischemic Damage

Prosaposin (PSAP) is a precursor protein of saposin A–D [4,5]. Unprocessed PSAP is found in cerebrospinal fluid [6,7], and PSAP mRNA is strongly expressed in the choroid plexus [8], which together suggest that PSAP is a secretory neurotrophic factor. O'Brien et al. [9] were the first to identify PSAP as a potent neurotrophic factor. Both PSAP and peptides containing the PSAP neurotrophic activity domain exhibit neuro- and glio-protective functions *in vitro* [9-15]. The enhanced expression and release of PSAP following ischemia

suggest that it protects cells from ischemic damage [16-18]. In a study by our group, PSAP infusion into the lateral ventricles of gerbils prevented learning disabilities and ischemic neuronal death [19]. Similar results were obtained with PS18 [20,21]. These effects were accompanied by the protection of cells from apoptotic death [19,21]. Similar protective effects were observed in the thalamus following occlusion of the middle cerebral artery [22,23].

PSAP Rescues Neurons from Damage Induced by Neurotoxic Agents

Kainic acid (KA) is a glutamate analogue whose injection causes neurotoxicity in animals. At a dose of 5 mg/kg, a subcutaneous injection of KA stimulates neurons without causing cell death [24]. Following KA injection, PSAP expression in hippocampal pyramidal neurons and interneurons increased (Figure 1a-d). After KA injection (12 mg/kg), injured and healthy pyramidal neurons in the hippocampal CA1 region in rats with/without PS18 injection were counted (Figure 1e-g). The presence of fewer injured neurons and more healthy neurons in the PS18-injected rats indicated that PS18 rescues CA1 neurons from KA-induced degeneration. The detection of higher levels of PSAP in PV-positive GABAergic inhibitory interneurons and their axons around pyramidal neurons suggested the axonal transport of PSAP [24,25] (Figure 1h-i). Similarly, PSAP was strongly expressed in the Purkinje cells and interneurons of the cerebellum of KA-injected rats [26]. These findings provide insights into the role of PSAP in alleviating the neural damage caused by KA. PSAP is up-regulated in the substantia nigra of patients with Parkinson's disease [27]. The ability of a PSAP-derived peptide to protect dopaminergic neurons from the neurotoxins MPP+ and MPTP in *in vitro* and *in vivo* models of Parkinson's disease, respectively, was reported [28,29]. In the latter study, PSAP was shown to inhibit the MPTP-induced cleavage of caspase-3, down-regulate the pro-apoptotic factor BAX, and up-regulate the anti-apoptotic factor Bcl-2, consistent with an inhibition of apoptosis by PSAP [29].

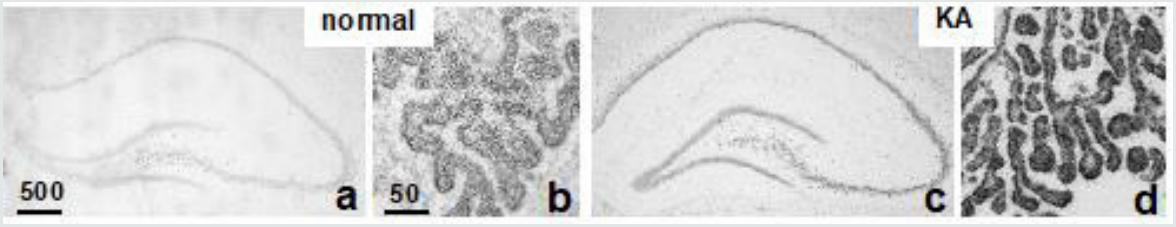

Figure 1a-d: In situ hybridization of PSAP mRNA expression. Compared with normal control (a, b), the signals of the antisense probe in the hippocampus (a, c) and the choroid plexus (b, d) were significantly more intense after KA injection (c, d). The numbers on the bar indicate μm. Figures reproduced with permission from PLoS One [24].

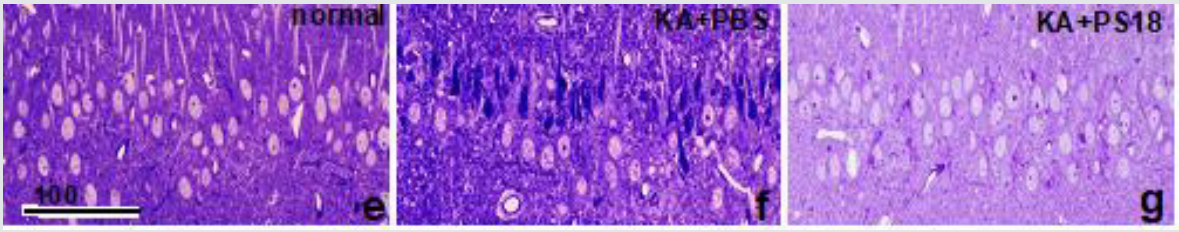

Figure 1e-g: Light microscopic analysis of hippocampal CA1. Photomicrographs of toluidine blue-stained hippocampal CA1 neurons in a normal control rat (e) and rats that received an injection of PBS (f), or 2.0 mg/kg PS18 (g) after a 12 mg/kg KA injection. Injured CA1 neurons were rescued by a PS18 treatment (g). Figures reproduced with permission from PLoS One [39].

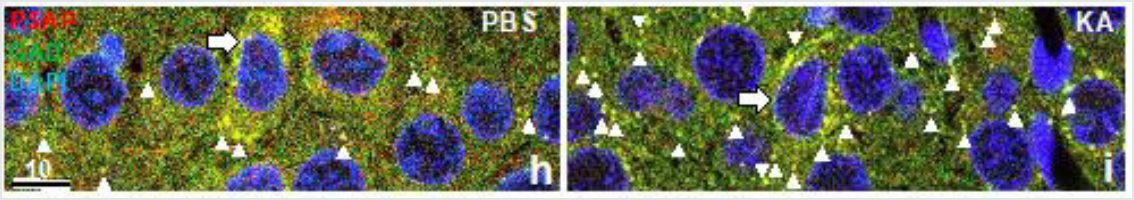

Figure 1h-i: Immunofluorescence light micrographs of the hippocampal CA1 neurons stained with anti-PSAP IgG, anti-GAD, and DAPI showing the PSAP-IR 3 days after PBS (h) or 5 mg/kg KA (i) injection. The arrows indicate interneurons with slender nuclei and very intense immunoreactivity both of PSAP and GAD. Note that the GAD-PSAP double positive axon terminals (arrowheads) are observed around almost all CA1 neurons after KA injection (i), but only some after PBS injection (h). Nuclei are stained with DAPI (blue), PSAP is shown red, and GAD is shown green. Figures reproduced with permission from IBRO Reports [24].

PSAP Shows Neuro- and Glio-Protection After Nerve Transection

PSAP and an PS18 facilitate regeneration following sciatic nerve transection [20]. A PSAP-derived peptide was shown to increase both the expression and enzymatic activity of GALT, an enzyme predominantly found in myelinating Schwann cells [15], and sulfatide concentrations in the brain and sciatic nerve of developing rats [30]. Our group similarly found an increase in the levels of intrinsic PSAP and its mRNA in the facial nerve nucleus after nerve transection [31,32].

In rats, PSAP gene transcription generates two alternative splicing forms of PSAP mRNA: Pro +9, containing a 9-base insertion, and Pro +0 without the insertion. In the rat facial nucleus after facial nerve transection, a peak in Pro +0 mRNA levels was detected after 5–10 days whereas Pro +9 mRNA levels remained unchanged. Moreover, during facial nerve regeneration PSAP mRNA expression increased not only in facial motoneurons but also in microglia [32].

Meyer et al. [1] characterized the PSAP receptors GPR37 and GPR37L1, both of which are involved in neuronal protection [33,34], although their expression and their interactions with PSAP have not been fully elucidated (see the review of Smith [2]). We also examined changes in the immunoreactivity of the PSAP receptors GPR37 and GPR37L1 in the rat facial nucleus after facial nerve transection. Strong GPR37L1 immunoreactivity was detected in many of the microglia (Figure 1j-k) and astrocytes (Figure 1l-m) on the operated side whereas GPR37 expression was mainly observed in neurons [35].

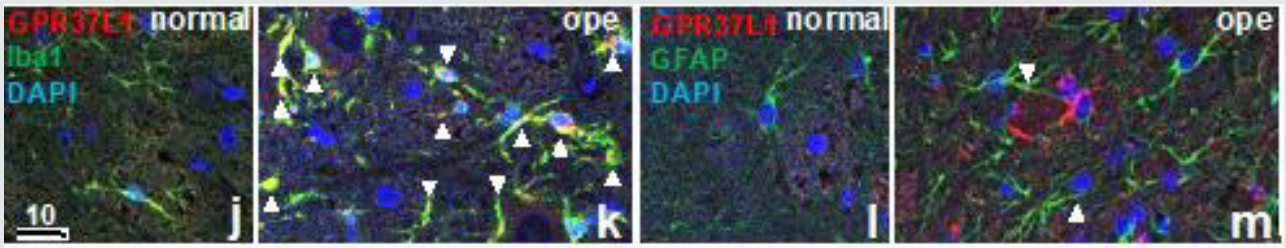

Figure 1j-m: Double-immunofluorescence staining in the facial nucleus 7 days after facial nerve transection. Double-staining images for GPR37L1 (red) with glial markers (Iba1, GFAP, green) and DAPI (blue) are shown.

These images show that cells with a high GPR37L1-IR signal were located predominately on the operated (ope) side (k, m). Double-staining with GPR37L1 and Iba1 (j, k) showed that GPR37L1-IR and Iba1-IR also increased on the operated side, and high co-localization of GPR37L1 with Iba1 (arrowheads) was observed in many cells (k). Double-staining with GPR37L1 and GFAP (l, m) showed that GPR37L1-IR and GFAP-IR increased intensely on the operated side, but co-localization of GPR37L1 with GFAP (arrowheads) was not frequent (m).

PSAP and Its Receptors in the Dorsal Root Ganglion (DRG)

We examined the distribution of PSAP and its receptors in the developing DRG. PSAP colocalized with two receptors in the satellite cells and made very characteristic ring-shaped image around 8 weeks after birth, a period of intense growth of DRG (Figure 1n-q). This ring-shaped image suggests that several satellite cells are synchronously activated.

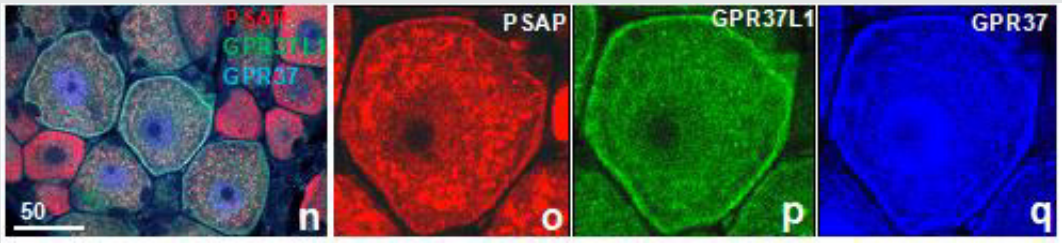

Figure 1n-q: The immunofluorescence light micrographs of the rat DRG at 8 weeks clearly show the colocalization of PSAP and its receptors.

Decreased PSAP Expression in A Duchene Muscular Dystrophy Model

The dystrophin-deficient mdx mouse is a model of human Duchene muscular dystrophy, a disease characterized by disorders of the central nervous system, including mental retardation and metabolic damage, and damage to the neuromuscular system. However, whether PSAP is related to the loss of dystrophin and/or to the brain abnormalities of the disease remains unclear. In a study of mdx mice, we found decreased levels of intrinsic PSAP and

its mRNA in the brain [36], consistent with a report of low levels of PSAP in the muscles of these animals [37].

Decreased PSAP Expression in the Lacrimal Glands of Adult Female Mice

Lacrimal glands produce growth factors whose expression increases during ocular injuries, suggesting that they respond to pathological conditions. We showed that in young male and female mice the expression of colocalized PSAP and its receptors did not differ whereas in older females a decrease was determined. Whether this result reflects cross-talk between lacrimal PSAP and gonadal secretion, particularly in response to aging, when the levels of sex hormone decline, remains to be explored in further studies [38].

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DOI: 10.32474/OJNBD.2020.05.000202