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Review

Receptor and nonreceptor protein tyrosine phosphatases in the nervous system

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Abstract. Protein tyrosine phosphatases (PTPs) have emerged as a new class of signaling molecules that play important roles in the development and function of the central nervous system. They include both tyrosine-specific and dual-specific phosphatases. Based on their cellular localization they are also classified as receptor-like or intracellular PTP. However, the intracellular mechanisms by which these PTPs regulate cellular signaling pathways are not well understood. Evidence gathered to date provides some insight into the physiological function of these PTPs in the nervous system. In this review, we outline what is currently known about the functional role of PTPs expressed in the brain.

Key words. Receptor PTPs; intracellular tyrosine phosphatase; dual-specificity phosphatases; nervous system; intracellular signaling.

Introduction

Tyrosine phosphorylation is an important posttranslational modification that regulates fundamental biochemical processes in all cells. It is a dynamic process, governed by the opposing activities of protein tyrosine kinases (PTKs) that catalyze tyrosine phosphorylation, and protein tyrosine phosphatases (PTPs) that are responsible for tyrosine dephosphorylation. PTKs were originally regarded as an 'on' switch that activated a number of signal transduction pathways. Due to their initial role in oncogenesis, extensive studies have been carried out on PTKs to demonstrate their function and mechanisms of action [1, 2]. Several human diseases, including cancer and diabetes, are attributed to mutations in PTKs, and some of the latter have been selected as targets for drug discovery [3, 4].

PTPs were first recognized as biochemical entities in the early 1980s. They were initially considered nonspecific enzymes that functioned to reverse the action of PTKs. It became clear with the passage of time that this assumption was an oversimplification. With the sequencing of the genomes from various organisms as well as the completion of the first draft of the human genome, 113 distinct PTP catalytic domain sequences have been compiled [5]. Biochemical and genetic studies now indicate that PTPs exert both positive and negative effects on signaling pathways [6]. Moreover, deregulation of several PTPs contributes to the pathogenesis of human diseases [7]. As a result, substantial research over the last decade has focused on the structure and function of PTPs, and a number of these enzymes are now being tested as potential pharmaceutical targets [8]. This review focuses on a select group of PTPs that are expressed within the nervous system and for which a considerable amount of structural and/or functional information exists.

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The PTP family

PTPs have at least one highly conserved catalytic domain of ~280 amino acids that contains an active site with the consensus sequence (I/V)HCXAGXXR(S/T)G. They are characterized by their sensitivity to vanadate, ability to hydrolyze *p*-nitrophenyl phosphate, insensitivity to okadaic acid and lack of a requirement for metal ions during catalysis [9, 10]. PTPs generally display poor substrate specificity in vitro, as they are capable of dephosphorylating most phosphotyrosine-containing substrates. Therefore, PTP activity is tightly regulated in vivo to ensure effective signaling responses.

Regulation of PTP activity in vivo is accomplished by a number of mechanisms. These include alternative messenger RNA (mRNA) splicing, modulation of steady-state protein levels, posttranslational modification, dimerization and subcellular localization. Both the catalytic domain and the noncatalytic segments of PTPs contribute to substrate specificity. As will be discussed further below, the noncatalytic segments of PTPs possess amino acid sequences that target them to specific intracellular compartments in which the effective local concentration of a particular substrate is high.

The PTP family includes both tyrosine-specific and dual-specific phosphatases. The tyrosine-specific phosphatases hydrolyze only phosphotyrosine-containing proteins. In contrast, the dual-specificity phosphatases target proteins that contain both phosphotyrosine as well as phosphoserine or phosphothreonine residues. The tyrosine-specific phosphatases can be further subdivided into two groups: the receptor-like PTPs (RPTPs) and the intracellular PTPs.

Detailed enzymological studies and crystal structure analysis of several PTPs revealed that the active site contains a cysteine residue that is critically important for enzymatic activity, and mutation of this cysteine residue to serine completely inactivates the enzymes. The cysteine residue functions in nucleophilic attack on the substrate phosphotyrosine residue, forming a transient phosphoenzyme intermediate. The nearby arginine residue within the active site helps to stabilize the enzyme-substrate interaction. An upstream conserved aspartic acid facilitates this reaction by serving as a proton donor to the leaving phenolic oxygen. The reaction is terminated by the hydrolysis of the phosphoenzyme intermediate. Termination is also facilitated by the same aspartic acid through abstraction of a proton from the attacking water molecule [9–11].

Receptor-like PTPs

The structure of RPTPs suggests that they function as an interface between the extracellular environment of a cell and its intracellular signaling pathways. They usually possess two intracellular phosphatase domains, although some exceptions exist. Their extracellular domains are highly variable, but all of them contain motifs that are implicated in cell adhesion. Most of these molecules are orphan receptors, and their mode of action and functional ligands remain largely unknown. With the exception of type I RPTPs, all subclasses of RPTPs are expressed in the nervous system (fig. 1 and table 1). As is discussed below, the majority of those characterized to date are involved in the regulation of neuronal adhesion, axon growth and guidance during the central nervous system (CNS) development.

Type IIa RPTPs

Leukocyte antigen-related (LAR) protein is the founding member of a large subfamily of RPTPs that includes LAR, PTPδ and PTPσ (CRYPα in chick). They contain three immunoglobulin (Ig)-like domains and a variable number of fibronectin type-III (FN-III) repeats in their extracellular domain. The mammalian variants are closely related to Dlar, PTP-3 and HmLAR found in *Drosophila*, *C. elegans* and leech, respectively [12–14]. The presence of Ig-like or FN-III motifs characteristic of cell adhesion or extracellular matrix molecules suggests a role of these RPTPs in cell surface recognition or cell adhesion.

Support for this hypothesis has come mostly from research with *Drosophila* mutants. These studies indicate that Dlar modulates neurite path finding during development [15, 16]. Null mutant crosses indicate that Dlar influences signal transduction of Robo (Roundabout), netrin-1 receptor DCC (deleted in colorectal cancer), cadherin and several neurite-modulating receptors [17, 18]. Moreover, phosphorylation of Ena (enabled), a regulator of actin polymerization in growth cones, is controlled by the opposing actions of Dlar and the Abl tyrosine kinase [19–22]. *Drosophila* studies have also shown that Dlar and Abl interact with Trio, a regulator of the Rac and Rho GTP-binding proteins that in turn control actin assembly and neurite outgrowth [23–25]. Inhibition of HmLAR2, the leech ortholog of Dlar, leads to neurite navigational errors and growth cone collapse [13, 26, 27].

LAR, the first member of the type IIa RPTP family, is present within neurites and growth cones [28–30] and plays a role in neural development and regeneration [31–34]. LAR isoforms are produced by alternative splicing coordinated in a spatiotemporal manner during development [35]. Several studies indicate that the LAR family of RPTPs are prime candidates for regulating extracellular matrix (ECM)-mediated cytoskeletal reorganization and signal transduction. The role of mammalian LAR in the regulation of actin cytoskeleton has been sug-

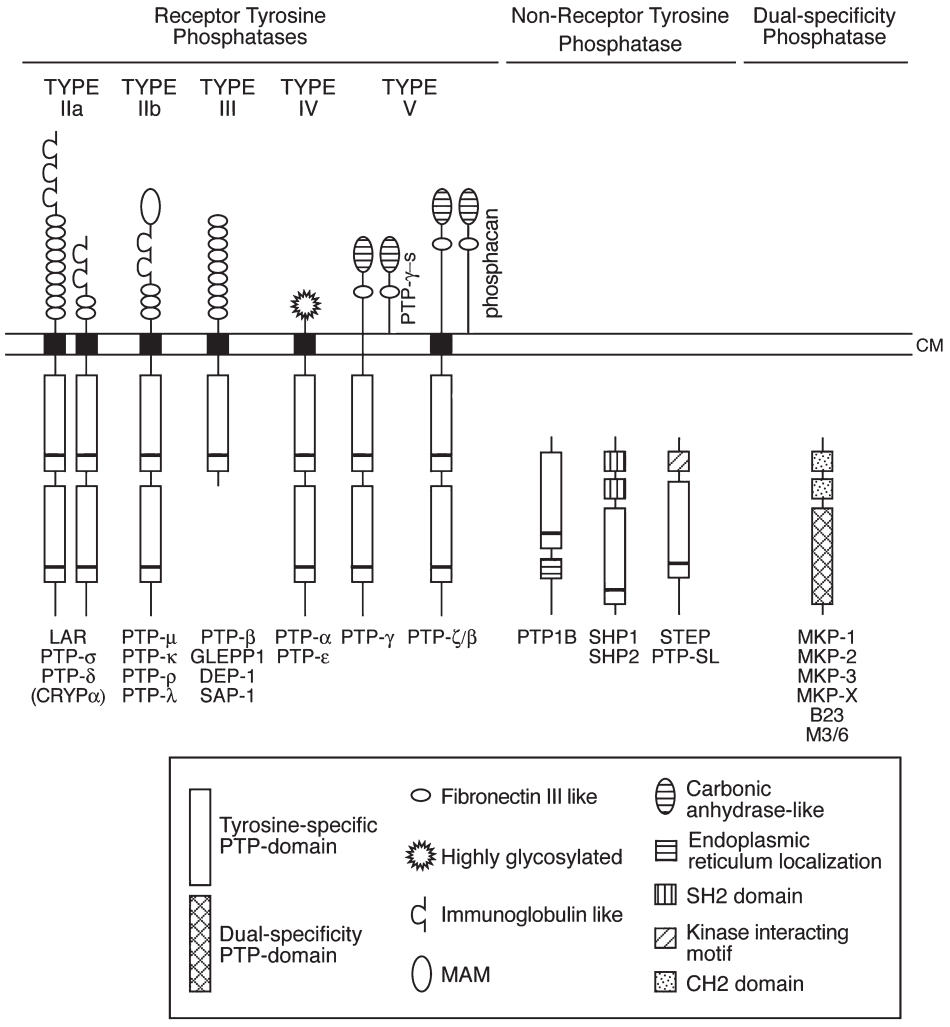

Figure 1. Schematic representation of major receptor PTPs, nonreceptor PTPs and DSPs expressed in the nervous system. CM, cell membrane. Phosphacan represents a secreted form that consists of the entire extracellular domain. CH2, Cdc 25 homology domain.

gested based on findings that LAR binds Trio in mammalian cells and that Mena, the mammalian ortholog of Ena, is concentrated at the tips of growth cones [36, 37]. Studies in two different models of transgenic LAR-deficient mice also revealed abnormalities in forebrain cholinergic neurons and a decrease in cholinergic fiber innervations of the hippocampus dentate gyrus [31, 32]. In addition, the laminin-nidogen complex, a major component of the ECM that modulates neurite outgrowth, proliferation and differentiation, has been shown to be a ligand for a splice isoform of LAR [38].

In dorsal root ganglion neurons, sciatic nerve crush resulted in increased LAR protein expression. The nerve injury also led to an increase in the proportion of LAR isoform known to have increased binding affinity to laminin-nidogen complex. Morphological analysis of distal nerve segments in LAR-deficient transgenic mice, 2 weeks after nerve crush, demonstrated significant decrease in axon area and the density of myelinated fibers. These findings suggest a role of LAR family of RPTPs in regulating neurite outgrowth during nerve regeneration in vivo [33].

PTPσ is also known as LAR-PTP2, PTP-P1, CRYPα, PTP-NU3, PTP-NE3 and CPTP1 [39–45] and is expressed in the nervous system in a developmentally regulated manner. In the chick retina, PTPσ is expressed in the axons and growth cones of retinal ganglion cell and promotes axon elongation as well as the formation of the growth cone lammellipodia [46]. The function of PTPσ in vertebrates remains largely unknown. Mutant mice that lack PTPσ exhibit stunted growth, delayed development, severe neurological defects and increased neonatal mortality [47, 48]. The phosphatase domains of PTPσ and PTPδ were shown to form heterodimers. The second catalytic domain of PTPδ binds to and inhibits the enzymatic activity of the first catalytic domain of PTPσ [49–51]. However, the biological significance of this association is still not known. PTPδ also undergoes homophillic inter-

Table 1. Overview of receptor PTPs expressed in the nervous system.

Receptor PTPs	Tissue distribution	Brain localization	Substrates and ligands	Ref.
LAR	brain, spinal cord, lungs, thymus, testes, ovary, skin	cortex, midbrain, brain stem, cerebellum	trio, liprin, laminin-nidogen	27, 28, 36, 38, 41
PTPσ	brain, heart, kidney, lung, pancreas, muscle	cortex, hippocampus cerebellum, olfactory tubercule	liprin	28, 40, 41, 43
PTPδ	brain, kidney, heart, thymus, spleen	hippocampus, thalamus piriform cortex	liprin	28, 50, 51, 59
PTPμ	brain, placenta, skeletal muscle, heart, lung,	striatum, cortex, thalamus, hypothalamus	cadherins, catenin, Rack 1	60, 64, 67
PTPκ	brain, kidney, liver, heart, intestine, placenta, skeletal muscle and lung	cortex, hippocampus, periform cortex, thalamus, cerebellum	cadherins, catenin	57, 60, 68
PTPϱ	brain	throughout brain and spinal cord	unknown	61
PTPλ	brain, lungs, kidney, heart, skeletal muscle and testis	cortex, midbrain, brain stem and spinal chord	unknown	58, 60
DEP-1	brain, kidney, spleen and lungs	unknown	p120-catenin	69–71
PTP-β	brain, lung, heart, testis, liver	unknown	VE-cadherin	72, 73
SAP-1	brain, liver, heart and stomach	unknown	$P130^{cas}$	74, 75
GLEPP-1 (CRYP-2)	developing CNS, peripheral nervous system	all regions	unknown	79, 83
PTPα	brain, lung, kidney, heart, ovary, liver, stomach	cerebrum, cerebellum	$pp60^{c\text{-}src}$, $p59^{fyn}$, Grb2, PSD-95, contactin	100, 114, 116, 118
PTPε	brain, testes, lung, spleen, lymph node, thymus	unknown	Grb2	101, 110
PTPβ (PTPζ)	brain specific	hippocampus olfactory bulb piriform cortex, striatum	contactin	122, 124
PTPγ	brain, lung, kidney, heart, muscle, ovary	cortex, thalamus, hippocampus	unknown	123

Abbreviations: Rack 1, receptor for activated C kinase-1; DEP-1, density-enhanced phosphatase-1; SAP-1, stomach cancer-associated PTP-1; GLEPP1, glomerular epithelial protein 1; Grb2, growth factor receptor binding protein 2.

actions and serves to promote neurite outgrowth and adhesion of forebrain neurons in vitro [52]. PTPδ mutant mice show altered learning and long-term potentiation (LTP) [53]. However, none of these defects are as severe as the homozygous lethal defects seen when Dlar is mutated in *Drosophila*, suggesting that in vertebrates loss of one LAR family member may be partially compensated for by the function of other LAR family members. It is also possible that a truncated gene product may still be expressed in the mutant mice, which interacts with other LAR subfamily members and is thereby responsible for the observed phenotype. Double and triple mutant mice will further clarify whether the type IIa RPTPs have overlapping functions in the development of the vertebrate CNS.

The LAR subfamily of RPTPs seems to recruit a group of scaffolding proteins called liprins that link LAR to a network of other proteins [54, 55]. Liprins are coiled-coil proteins that contain steryl α motif (SAM) repeats in the carboxy terminal and are divided into the α-liprins and β-liprins. α-Liprins bind to LAR, PTPσ and PTPδ, whereas β-liprins bind to α-liprins but not to LAR family members. The liprins are highly conserved from worm to fly to humans and are expressed in the developing nervous system. In *Drosophila*, loss of α-liprin results in a reduction in both synapse size and terminal branch complexity, an identical phenotype to Dlar loss of function at the synapse [56]. However, the function of liprins in vertebrates remains unclear, although it has been proposed that liprins function to localize the LAR family of PTPs at specific sites on the plasma membrane, possibly to regulate their interaction with the extracellular matrix proteins or their association with intracellular substrates.

Despite the fact that the LAR subfamily of RPTPs has 65–70% homology and interacts with common cytoplasmic effectors such as α-liprin, this group of RPTPs does not exhibit homologous functions. Some of them mediate homophilic binding, while others interact with heterotypic molecules. Some RPTPs mediate repulsion and defasciculation of growing neurites, while others mediate attraction and fasciculation. These data imply that the signaling pathways controlled by type IIa RPTPs are complex, and understanding the signaling events downstream of this group of RPTPs remains a major challenge for the future.

Type IIb RPTPs

The type IIb family of vertebrate RPTPs includes PTPρ, PTPμ, PTPκ and PTPλ. They are characterized by the presence of an amino-terminal meprin/A5/PTPμ (MAM) domain, one Ig domain and multiple FN-III repeats in the extracellular domain [57–61]. They are expressed in distinct patterns in the developing CNS, and PTPμ, PTPκ and PTPλ are also expressed in the adult brain.

The most extensively studied members of this family are PTPμ and PTPκ. Both are homophillic cell-adhesion molecules that promote neurite outgrowth and interact with the cadherin-catenin complex [62–64]. In retinal cells, PTPμ was found in a complex with N-cadherin, a calcium-dependent adhesion molecule that promotes neurite outgrowth [65, 66]. Downregulation of PTPμ expression using antisense oligonucleotides or expression of a dominant negative C-S mutant PTPμ significantly decreased neurite outgrowth on N-cadherin [65]. This suggests that PTPμ may play a dual role in the regulation of neurite outgrowth: it may promote neurite outgrowth by itself, presumably through homophillic interactions, and also by an indirect mechanism involving the regulation of N-cadherin function. In a more recent study, PTPμ was shown to interact in vitro with the scaffolding protein RACK1 (receptor for activated C kinase-1) [67]. The physiological significance of this binding remains unclear. PTPκ and PTPλ have also been shown to be associated with β-catenin and localized at cell-cell boundaries [58, 68]. The significance of this binding is still not clear, but it has been proposed that they control cadherin function during processes such as neurite outgrowth.

Type III RPTPs

The type III family of vertebrate RPTPs expressed in the nervous system include DEP-1 (also known as PTPeta/CD148/F-36-12 and Byp in mice) [69–71], PTP-β (VE-PTP in mouse) [72, 73], SAP-1 [74, 75] and GLEPP-1 (PTPU2/GLEPP1/PTProt in humans, RPTP-BK in rats, mGLEPP/mPTPRO/PTPphi in mice and CRYP-2/cPTPRO in chicks) [76–83]. PTPS31 (PTPGMC1/PTPRQ in rats) is the fifth member of this group and is not expressed in the nervous system [84]. Unlike other RPTPs, the PTPβ group contains only one catalytic domain and an extracellular domain composed entirely of FN-III repeats. Members of this group that are expressed in *Drosophila* include DPTP10D, DPTP52F and DPTP4E [85–86]. They are expressed selectively in the CNS of *Drosophila* and play a role in axon guidance during development. Mutant flies lacking DPTP10D or the related PTP, DPTP99A, have no effect on their own. However, a role for these molecules is revealed in multiple mutant combinations with DPTP69D or Dlar [87–88]. Axon guidance at the midline of the *Drosophila* CNS has been extensively studied, and it has been shown that attractive signals emanating from the midline are required to recruit growth cones into commissural pathways that cross over to the contralateral side of the embryo [89]. At the same time, repulsive signals from the midline repel growth cones and prevent longitudinal axons from crossing the midline [90]. Double mutation of DPTP69D/DPTP99A results in the inappropriate growth of longitudinal axons across the midline [16]. Triple or quadruple (DPTP69D/DPTP99A/DPTP10D/Dlar) RPTP mutations result in the conversion of all detectable longitudinal tracts into commissural pathways [16]. *Drosophila* studies also demonstrate that DPTP69D and DPTP10D interact with Robo, Slit and Comm (Commisureless), genes known to regulate axon guidance at the *Drosophila* midline [91, 92]. Mutations in DPTP52F lead to multiple CNS and motor axon guidance defects. However, Dlar mutations are able to rescue the DPTP52F CNS phenotype [86]. Taken together, these findings suggest that both competitive and cooperative interactions occur between the various *Drosophila* RPTPs to control different aspects of axon guidance during development.

The most extensively studied vertebrate type III RPTP is CRYP2. It is selectively expressed in neurons of the CNS during the period of axon growth and guidance [79]. In the retina, it is expressed in the axons and growth cones of the projection neurons (retinal ganglion cells) and the optic tectum, the major target of retinal projection neurons [93]. Recent studies indicate that in contrast to other RPTPs, the CRYP2 extracellular domain is antiadhesive and inhibits neurite outgrowth in vitro [94]. It is also a potent growth cone collapsing signal and acts as a repulsive guidance cue for retinal neurons [94].

Type IV RPTPs

The only known members of type IV family of RPTPs are RPTPα (also known as LRP) and RPTPε [95, 96]. They are murine homologs of HPTPα (also called HLPR) and HPTPε in humans [97, 98]. These PTPs are characterized by the presence of two phosphatase domains and a very short, highly glycosylated extracellular domain with no adhesion motifs [95, 98–100]. Extensive sequence similarities exist between both the molecules and extend beyond their conserved catalytic domains. PTPε is somewhat unique among PTPs in that the single PTPε gene contains two distinct promoters, each of which gives rise to a unique protein product: a transmembrane receptor-type protein (tm-PTPε) and a cytoplasmic protein (cyt-PTPε). They differ at their N-termini, which determine their subcellular localization and physiological roles [101–103]. Both RPTPα and RPTPε can undergo calpain-mediated cleavage in vivo to generate the

N-terminally truncated analogs, p65PTPε and p66PTPα [104].

RPTPα is expressed in most murine tissues and most abundantly in brain and kidney. RPTPα has been implicated in several signaling pathways, including cellular transformation [105], neuronal differentiation [106, 107], cellular adhesion and spreading [108, 109], downregulation of insulin receptor signaling [110] and activation of some voltage-gated potassium channels [111]. Structural studies indicate that dimerization of RPTPα negatively regulates its activity in vivo [112]. The intracellular mediators of PTPα signaling are not known. However, the tyrosine kinase $pp60^{c\text{-}src}$ and $p59^{fyn}$ are considered potential substrates of PTPα for a combination of reasons. Both $pp60^{c\text{-}src}$ and $p59^{fyn}$ share a similar expression pattern with PTPα [113], and endogenous PTPα associates with $p59^{fyn}$ in mouse brain [114]. Over-expressed PTPα leads to the C-terminal dephosphorylation and activation of Src and Fyn [106, 109, 114, 115]. Moreover, PTPα has been shown to bind to the PDZ2 domain of postsynaptic density-95 (PSD-95). Thus Src kinase, its activator PTPα and substrate NMDA receptors are all linked by the same scaffolding protein, PSD-95 [116]. Taken together, these data suggest that PTPα may play a critical role in the induction of LTP in the CNS. PTPα has also been shown to bind to the adapter protein Grb2 in vivo [117], as well as the glycosylphosphatidylinositol-linked protein contactin α in neuronal cells [118].

PTPε is strongly expressed in the nervous system; however, little is known about its physiological role. Both forms of PTPε bind to Grb2 [119]. tm-PTPε can also downregulate insulin receptor signaling [110]. In the nervous system, lack of cyt-PTPε expression in PTPε-deficient mice results in reduced myelination of sciatic nerve axons in the early stages of development. This is associated with increased activity of voltage-gated potassium channels (Kv) and hyper-phosphorylation of Kv-α subunit in sciatic nerve tissues and in primary Schwann cells [120]. However, myelination of sciatic nerve axons in adult PTPε-deficient mice was found to be normal. This suggests that lack of PTPε is compensated by the expression of another PTP, possibly PTPσ, as PTPσ-deficient mice exhibit reduced myelination of sciatic nerve axons caused by an undetermined molecular mechanism [48].

Type V RPTPs

The type V RPTPs have two identified family members: HPTPζ/RPTPβ and HPTPγ/RPTPγ. RPTPβ is restricted to the central and peripheral nervous system, while RPTPγ is expressed in the nervous system and in a variety of other tissues [121–125]. They have a carbonic anhydrase-like domain, a FN-III like domain and a large cysteine-free, glycine-rich region extracellularly, and two phosphatase domains intracellularly [123, 126]. RPTPζ/β are unusual among RPTPs in that they are expressed as a chodroitin sulfate proteoglycan [126, 127]. Alternative splicing produces three isoforms: a full-length form, a short form in which a part of the glycine-rich region is deleted, and a soluble form termed phosphacan, or 6B4 proteoglycan. Phosphacan consists of only the extracellular domain and is secreted independently of the transmembrane and intracellular domains. RPTPγ has four known isoforms, RPTPγ-A, B, C and S (a secreted form) [125]. The extracellular domain of RPTPζ binds to a number of neurite outgrowth-promoting cell adhesion molecules, as well as the tenascin extracellular matrix proteins, and some growth factor receptors [128–135]. The interaction between phosphacans and these molecules seems to have both stimulatory and repulsive effects on neurite outgrowth, depending on the particular neuron or binding molecule that is examined [136–138]. This is probably due to competition between phosphacan and the transmembrane forms for binding to CAMs and extracellular matrix components.

More recent findings indicate that the intracellular domain of RPTPζ can interact with the PSD-95/SAP90 family proteins, indicating its involvement in the regulation of synaptic function [139]. Both the intracellular and extracellular domains of RPTPβ are associated with voltage-gated sodium channels in brain neurons and modulate these channels through tyrosine phosphorylation [140]. In addition, one study found that multiple sclerosis lesions induce the expression of PTPRζ1, the human homolog of RPTPζ, and that the gene is specifically expressed in remyelinating oligodendrocytes within these lesions [141], implicating a role of RPTPζ in recovery from demyelinating diseases.

Intracellular PTPs

The intracellular PTPs expressed in the nervous system are further subdivided into two groups based on their substrate specificity. The first group includes those that are tyrosine specific phosphatases and include PTP1B, striatal enriched phosphatase (STEP), the STEP-like phosphatase (PTP-SL) and the src-homology 2 domain containing phosphatases (SHP1 and SHP2) (fig.1 and table 2). The second group includes those that dephosphorylate both phosphotyrosine and phosphoserine or phosphothreonine. These latter phosphatases are known as *d*ual *s*pecificity *p*hosphatases (DSPs) that include the mitogen-activated protein kinase phosphatases (MKPs) (fig.1 and table 3). In contrast to the receptor-like PTPs, members of the intracellular PTPs lack a transmembrane domain, possess a single phosphatase domain and have multiple variable domains either in the N- or C-terminus.

Table 2. Overview of nonreceptor PTPs expressed in the nervous system.

Nonreceptor PTPs	Tissue distribution	Brain localization	Substrates	Ref.
PTP1B	ubiquitous	hypothalamus, hippocampus, cortex and other areas of CNS	leptin, N-cadherin Jak-2, TYK2	146, 149–153
STEP	brain specific	striatum, hippocampus, cortex	ERK1/2, p38 (?)	161, 162, 168, 170
PTP-SL	brain specific	cerebellum, cerebrum	ERK1/2, ERK5, p38	159, 160, 168, 173
SHP1	liver, spleen, thymus, brain, spinal cord	cerebral cortex, hippocampus, cerebellum	$pp60^{c\text{-}src}$	189, 190
SHP2	brain, thymus, lung, heart, liver, muscle, stomach, pancreas, kidney, colon	hippocampus, cerebral cortex, striatum, thalamus, cerebellum	SHPS-1, PZR, Gab1, Gab2, IRSI, STAT5A, STAT1, NR2B	199, 200, 205, 222, 224, 225

Abbreviations: PTP1B, protein tyrosine phosphatase 1B; SHP1 and 2, *src* homology 2 domain containing protein tyrosine phosphatase-1 and -2; STEP, striatal-enriched protein tyrosine phosphatase; PTP-SL, STEP-like protein tyrosine phosphatase; IRS1, insulin receptor substrate 1; Jak-2, Janus tyrosine kinase-2; Tyk2, a nonreceptor protein tyrosine kinase; SHPS-1, SHP substrate 1; PZR, protein zero related; Gab1 and 2, Grb2-associated binder 1 and 2; STAT, signal transducers and activators of transcription; NR2B, NMDA-receptor subunit 2B; ERK, extracellular signal-regulated kinase.

PTP1B

PTP1B is the founding member of the family of PTPs and serves to illustrate several of the properties of PTPs. It was biochemically purified from human placental tissue [142, 143]. It is expressed ubiquitously (table 2) and localizes to the cytoplasmic face of the endoplasmic reticulum through the C-terminal 35 residues [144, 145]. PTP-1 is the rat homolog of PTP1B [146]. Since its discovery, PTP1B has been associated with two critical metabolic pathways. In muscle and liver, PTP1B negatively regulates the insulin-signaling pathway by directly dephosphorylating the insulin receptor. Mice lacking functional PTP1B exhibit increased sensitivity toward insulin and are resistant to obesity [147, 148]. In addition, PTP1B negatively regulates the leptin-signaling pathway in hypothalamic neurons. The peptide hormone leptin is widely accepted as an important regulator of obesity and is present in many tissues, but its effects on body mass are mediated through neurons in the mediobasal hypothalamus [149]. Loss of PTP1B attenuates weight gain in mice lacking normal hypothalamic leptin signaling, probably via dephosphorylation of Jak2 bound to the leptin receptor during signaling [150,151]. Thus, one might speculate that PTP1B coordinately regulates both insulin and leptin signaling to participate in homeostatic control of body weight.

PTP1B also regulates neurite extension mediated by cell-cell and cell-matrix adhesion molecules. PTP1B is localized at the tips of growing neurites and regulates both N-cadherin and β1-integrin, two adhesion receptor systems that play important roles in growth cone adhesion and guidance. It interacts with the cytoplasmic domain of N-cadherin that is adjacent to and partially overlapping with the binding site of β-catenin and may regulate cadherin function through dephosphorylation of β-catenin [152, 153]. It coimmunoprecipitates with β1-integrin and appears to mediate integrin-mediated adhesion through regulation of Src activation [154]. PTP1B has also been identified as the major PTP that dephosphorylates and activates c-Src in several human breast cancer cell lines [155], and downregulates signaling through epidermal growth factor receptor and the tyrosine kinase $p210^{bcr\text{-}abl}$ [156]. These results indicate that PTP1B participates in several signaling pathways. As a result, there is an intense effort to obtain specific and potent inhibitors of PTP1B for biological studies and possible therapeutic interventions.

STEP and PTP-SL

STEP and PTP-SL (also known as PC 12-PTP1) belong to a group of PTPases which currently have three members [157–159] expressed in vertebrates. STEP is a brain-specific phosphatase preferentially expressed in neurons of the basal ganglia, hippocampus, cortex and related structures (table 2) [160, 161]. STEP family members are produced by alternative splicing, and both cytosolic ($STEP_{46}$) and membrane-associated ($STEP_{61}$) variants exists [162, 163]. In addition, some STEP members are truncated isoforms that lack the catalytic phosphatase domain [164]. Diversity among STEP isoforms derive from either the absence or presence of specific amino acid motifs implicated in their subcellular localization, substrate specificity and regulation of catalytic activity [163, 164]. The functions of the truncated isoforms are not yet known, although they may serve analogous function to the tyrosine kinases that exist as truncated isoforms and bind to substrates to protect them from phosphorylation.

PTP-SL and PTPBR7 are two members of the same family that differ in the length of their N-terminal domain and are derived from a single gene (*Ptprr*) through developmentally regulated use of alternative promoters [165]. PTBR7 is expressed during early embryogenesis in spinal ganglia cells as well as in developing Purkinje cells. Postnatal PTBR7 is expressed in various regions of the adult brain, but expression in Purkinje cells ceases and is replaced by the PTP-SL-specific transcript (table 2). PTPBR7 is a type I transmembrane protein, whereas PTP-SL appears to be a cytosolic membrane-associated PTP, located at the perinuclear vesicular structures that partly belong to the endosomal compartment. The hematopoietic phosphatase, HePTP, is the third member of this group and is not expressed in the nervous system [166]. The only member of this group expressed in *Drosophila* is PTP-ER [167].

Both STEP and PTP-SL bind to and regulate the activity of mitogen-activated protein (MAP) kinase family members, ERK and p38, through a short motif termed the kinase interaction motif (KIM) located in their noncatalytic regulatory domains [168]. Binding of ERK1/2 to the KIM domain of STEP and PTP-SL inactivates the ERKs through dephosphorylation of the regulatory tyrosine residue and blocks nuclear translocation of the ERKs [169, 170]. This domain is also conserved in HePTP [171]. In addition, a region adjacent to the KIM of these three PTPs (the KIS, or kinase specificity sequence) has been identified that is involved in the differential recognition of ERK and p38 as substrates [172]. A role for PTP-SL in the regulation of ERK5 pathway and its downstream responses has also been reported [173]. Taken together, it appears that binding and regulation of MAP kinases is a common property of this subgroup of PTPs.

The binding of both STEP and PTP-SL to their substrates is regulated by cyclic AMP (cAMP)-dependent protein kinase-mediated phosphorylation of a serine residue within their KIM domain [168, 174]. Phosphorylation at the regulatory serine residue within the KIM domain sterically prevents interactions with ERKs, and dephosphorylation of this serine residue is required for PTP-ER associations. Additional findings show that the enzymatic activity of STEP in neurons is regulated through dopamine/D1 receptor-mediated phosphorylation and glutamate/*N*-methyl-D-aspartic acid (NMDA) receptor-mediated dephosphorylation of the serine residue within the KIM domain [170, 174]. STEP thus appears to act as a switch that is activated by glutamate and inactivated by dopamine signaling pathways. In this way, STEP is capable of regulating both the activity and duration of ERK signaling. A second study demonstrated that STEP regulates NMDA receptor channel activity and hippocampal long-term potentiation [175]. This occurs through either direct dephosphorylation of the receptor or through an indirect mechanism that leads to the dephosphorylation and inactivation of Src-family kinase members [176]. The fact that STEP regulates both the ERK cascade and LTP suggests that it may play an important role in aspects of learning and memory. Whether PTP-SL plays a similar role in the cerebellum remains to be established.

SHP1 and SHP2

SHP-1 and SHP-2 are members of a subfamily of PTPs that possess two src-homology 2 (SH2) domains at the N-terminus and one phosphatase domain at the C-terminus [177–180]. Deletion of the N-terminal SH2 domain, but not the C-terminal SH2 domain, results in strong activation of the enzyme, suggesting that the catalytic activity is suppressed by an intramolecular interaction involving the N-terminal SH2 domain [181, 182]. This conclusion is supported by the recently resolved crystal structure of both SHP-1 and SHP-2 [183, 184].

SHP-1 is also known as HCP, SHPTP-1, PTP1C or PTPN6 [177, 185, 186]. It is expressed predominantly in hematopoietic cells [177]. A loss of function mutation in the gene encoding SHP-1 in me/me (motheaten) mice has confirmed the integral role of SHP-1 in the negative regulation of cell signaling in hematopoietic cells [187, 188]. However, its role in the development and differentiation of the CNS is not well understood. In the mouse CNS, SHP-1 is expressed in the cortex, cerebellum and cervical spinal cord [189]. SHP-1 associates with synaptic vesicles and interacts with the vesicle-associated protein synaptophysin, suggesting its involvement in neurotransmission [190]. It has also been implicated in astrocyte proliferation and differentiation. In vivo studies show that lack of SHP-1 leads to a decrease in the number of astrocytes and microglia in me/me brains [191]. In vitro studies further reveal that in astrocytes, SHP-1 modulates cytokine activity through negative regulation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway and by controlling the expression of interferon (IFN)-inducible genes [192, 193]. Finally, motheaten mice also display reduced myelination in the CNS, suggesting that SHP-1 plays a role in oligodendrocyte differentiation, maturation and survival [189].

Mammalian SHP-2 was previously identified by several groups and is variably named SH-PTP2, PTP1D, SH-PTP3, PTP-2C and Syp, while its *Drosophila* homolog is known as Corkscrew [194–198]. SHP-2 is expressed ubiquitously [199, 200] and is activated by various growth factors, including platelet-derived growth factors, epidermal growth factor (EGF), insulin-like growth factor-1, cytokines, insulin and interferon [201–203]. SHP-2 is a positive effector for a number of intracellular signaling cascades that include the Ras-Raf-MAP kinase and phospatidylinositol 3 (PI3) kinase pathways [204, 205]. However, it plays a negative role in the JAK-STAT

Table 3. Overview of MAP kinase phosphatases expressed in the nervous system.

Dual-specificity phosphatases	Tissue distribution	Brain localization	Substrate specificity	Ref.
MKP-1	lung, heart, skeletal muscle, brain, spleen, liver, kidney	cortex, thalamus, striatum, cerebellum	p38 > JNK/SAPK >> ERK	234, 247, 256, 257
MKP-2	heart, lung, brain, spleen, testis, skeletal muscle	prefrontal cortex, hippocampus, cerebellum	ERK = JNK/SAPK > p38	234, 240, 248, 258
MKP-3	lung, brain, heart, spleen, liver, kidney	cerebral cortex, striatum, hippocampus	ERK >> JNK/SAPK = p38	242, 246, 256, 257
MKP-X (B59)	heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas	throughout the brain	ERK > p38	242, 243, 249, 256
B 23	brain, heart, lung, liver, pancreas, skeletal muscle, kidney, placenta	hippocampus, cerebellum	unknown	236, 256
M3/6	brain, eye, heart, skeletal muscle, lung	unknown	JNK/SAPK > P38 >> ERK	238, 239, 246

Abbreviations: MKP, mitogen-activated protein (MAP) kinase phosphatase; JNK/SAPK, c-Jun N-terminal kinase/stress-activated protein kinase; ERK, extracellular signal-regulated kinase.

signaling pathway initiated by IFN-α and -γ [205, 206]. The significance of SHP-2 in the mammalian CNS is not well understood, as mice homozygous for a SHP-2 mutation are embryonic lethal [207, 208]. Chimeric mice generated from homozygous mutant embryonic stem (ES) cells die at different stages of development, thereby giving us some information about the role of SHP-2 in neuronal survival and function [209]. Besides abnormal limb development, another striking observation in the chimeric mice is that 50% of them have open eyelids, a phenotype typical of EGF receptor knockout mice, suggesting a role of SHP-2 in the regulation of EGF receptor or its downstream effector molecules [209–211]. More recently, it has been shown that transgenic mice overexpressing a dominant negative form of SHP-2 are more susceptible to ischemia-induced brain damage and neuronal death than controls [212]. SHP-2 is involved in nerve growth factor (NGF)-mediated signaling in sympathetic neurons and PC12 cells and brain-derived neurotrophic factor (BDNF)-mediated signaling in cultured cerebral cortical neurons [213–215]. It has also been proposed that expression of the zinc finger transcription factor, Egr-1, in the hypothalamus of mice occurs via the activation of SHP-2 and the ERK pathways [216]. Substrates of SHP-2 identified to date include SHPS-1, PZR, Gab1, Gab2, IRSI, STAT5A and NR2B [217–223]. However, the functional significance of these interactions in the CNS is not clearly understood. Finally, recent findings indicate that SHP-2 may function as a dual-specificity phosphatase (DSP) involved in the dephosphorylation of STAT1 and STAT5A both in vitro and in vivo [224, 225].

DSPs

The first mammalian DSP identified was the mouse immediate early gene 3CH134 and its human ortholog, CL100 [226, 227]. Initial studies showed that 3CH134/CL100 specifically dephosphorylates ERK MAP kinase at its regulatory phosphothreonine and phosphotyrosine residues, when compared with a number of other phosphoproteins [228, 229]. This led to its renaming as MAP kinase phosphatase-1 (MKP-1) [230]. Since the initial cloning of MKP-1, eight additional mammalian MKPs have been identified. These include PAC1 [231, 232] MKP-2/TYP-1/hVH-2 [233–235], B23/hVH-3 [236, 237], M3/6/ hVH-5 [238, 239], MKP-3/PYST1/rVH6 [240–242], MKP-X/PYST2/B59 [242, 243], MKP-4 [244] and MKP-5 [245]. Expression of some MKPs is restricted to distinct subcellular compartments. MKP-1, MKP-2, B23 and PAC-1 are localized within the nucleus [231, 233, 237, 240], whereas MKP-3 appears to be exclusively cytosolic [242]. In contrast, MKP-4 is present in the cytosol as well as punctate nuclear bodies [244], and M3/6 may be either nuclear or cytosolic depending on the cellular environment [239].

Another important development in our understanding of MKP function came with the discovery that some MKPs can selectively inactivate different MAP kinases. MKP-3, at low concentration, can completely inactivate ERK1 and ERK2 but not JNK/SAPK or p38 MAP kinase [246]. In contrast, MKP-1 acts preferentially on JNK/SAPK and p38 MAP kinases [247]. Other MKPs such as PAC1, MKP-2, MKP-X and M3/6 have different specificities toward the various MAPKs [240, 246, 248, 249]. Substrate specificity of MKPs is ensured through protein-protein interaction and catalytic activation of the phosphatases. MKP-1 and MKP-2 are immediately early genes that are

induced upon activation of the ERK signaling pathway [250]. Furthermore, MKP-1 and MKP-2 proteins are stabilized by ERK phosphorylation [251]. Phosphorylation of MKP-1 on ser 359 and ser 364 by ERK reduces the rate of proteosome-dependent degradation and thereby stabilizes it. In contrast, MKP-1 and MKP-3 are catalytically activated only upon ERK binding to their noncatalytic amino-terminal domain [252, 253]. Examination of the gene structure of MKP-3 shows that the N-terminus of MKP-3 contains a specific ERK binding domain that confers tight association with ERK but not with other MAPKs [253, 254]. It is also likely that there is some redundancy in the expression and function of MKPs, since deletion of the MKP-1 gene in mice had no adverse effect on ERK activity or mouse physiology [255].

In situ hybridization and Northern blotting analysis demonstrated a highly localized and distinct pattern of expression of MKP-1, MKP-2, MKP-3, MKP-X and B23 in the brain (table 3) [234, 256]. However, the role of these MKPs in neuronal function and development is largely unknown. In a recent study, the role of MKP-1 and MKP-3 was investigated in the behavioral sensitization induced by methamphetamine treatment. The findings suggest that in the earlier induction process, MKP-1 and MKP-3 play important roles in neural plastic modifications that occur after drug exposure. These include synaptogenesis, neurite sprouting, neuritic elongation and activation of MAP kinase cascades throughout most of the brain. In the later maintenance phase of chronic drug exposure that results in lasting sensitization, the MKPs appear in restricted brain regions [257]. A second study has investigated the role of MKPs in human depressive disorders. The findings demonstrate that in the postmortem brains of suicide subjects with major depression there is a significant decrease in ERK1/2 activity and protein expression compared with nonpsychiatric normal controls. This is accompanied with an increase in protein expression of MKP-2. This suggests a possible role of MKP-2 in the disruption of ERK signaling in the postmortem brains of suicide subjects with major depression [258]. However, additional studies will be necessary to clarify the exact role of MKPs in normal brain functioning, as well as in different neurological disorders.

Conclusion

The coordinated and complex interaction between multiple signaling cascades is the key to the orderly formation of the CNS and requires proper function of both kinases and phosphatases. A vast array of literature has already established the role of kinases and serine/threonine phosphatases in proper CNS development. The involvement of PTPs in a variety of intracellular signal transduction pathways now adds a new dimension to our understanding of the CNS. It is quite evident that both receptor and nonreceptor PTPs play important roles in many aspects of neural morphogenesis, differentiation, maturation and functioning under normal and pathological conditions. Two recent articles [5, 259] have published a complete, nonredundant list of all vertebrate PTPs. For this review we have searched the database for the expression of each of these PTPs in the nervous system and included those for which substantial information exists. Additional PTPs with known expression in the nervous system, including PTPH1 [260], PTP-NP2 [261], and PRL-1 [262], have not been discussed in this article, since their physiological function and substrates are mostly unknown. Future research on PTPs should concentrate on clarifying how they are regulated, assessing their physiological and pathological roles using transgenic or knockout animals, and developing specific inhibitors. This will accelerate the process of developing drug targets that may prove useful for testing in disease models.

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