Targeting the Pleiotrophin/Receptor Protein Tyrosine Phosphatase β/ζ Signaling Pathway to Limit Neurotoxicity Induced by Drug Abuse

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Abstract: This review compiles the scientific basis to propose the pleiotrophin/receptor protein tyrosine phosphatase β/ζ signaling pathway as a new therapeutic target to prevent drug of abuse-induced toxicity. In addition, potential guidelines are provided for the development of new therapeutic compounds derived from that knowledge. This approach may be relevant since efficient therapeutic strategies are currently lacking in this field, even when drug-induced neurotoxicity seems to underlie the neurodegenerative disorders diagnosed in drug addicts.

Key Words: Neurodegeneration, cocaine, Parkinson´s disease, drug discovery, pleiotrophin, midkine, RPTPβ/ζ, drug development.

INTRODUCTION

The neurotoxic effects of cocaine and other drugs of abuse underlie not only drug seeking behaviours but neurodegeneration processes associated to chronic drug consumption (see for example [1]). The addictive and neurotoxic effects of psychostimulants and other drugs of abuse have been previously related to an increase in dopaminergic activity and damage of dopaminergic neuronal bodies and terminals in substantia nigra and striatum, respectively [2,3]. Different types of drugs of abuse promote the intracellular accumulation of dopamine [4-6] and this could elicit neuronal death by blocking mitocondrial complex 1, as it happens for example with parkinsonian agents [7,8]. In addition, cocaine has been shown to cause significant increases of α-synuclein levels in dopaminergic neurons [9-11]; as it is widely known, α-synuclein contributes to the formation of Lewy bodies, a pathological hallmark of Parkinson´s disease [12], depletes tyrosine hydroxylase (TH, the rate-limiting enzyme of dopamine synthesis), and is partially responsible for the degeneration of dopaminergic neurons in this disease [13].

Besides dopamine, other neurotransmitters (notably noradrenaline) seem to be deeply involved both in the addictive and neurotoxic effects of psychotropic drugs. For instance, opioid drugs decrease central noradrenergic activity, thereby affecting neuronal survival and neurogenesis in brain areas such as the hippocampus [14]. Moreover, this same effect triggers neuroadaptations that underlie the development of opioid dependence (see review [15]). Taking into account this prominent role of catecholaminergic systems in neurotoxicity and addiction, any survival or differentiation factor for catecholaminergic neurons whose expression levels are significantly regulated by drugs of abuse emerges as a potential therapeutic target in drug abuse. This review focuses on one of these factors, pleiotrophin (PTN), in an effort to broadcast the need of novel therapeutic strategies to limit the neurotoxic effects induced by drugs of abuse. As discussed below, the evidence available recommends the initiation of drug discovery studies targeting the PTN signaling pathway for this indication. This may be very important since, if the current tendency is confirmed during the years to follow, we are facing increasing numbers of chronic consumers of drugs of abuse in many countries which, potentially, may develop neurodegenerative disorders early in their lives. Therefore, any attempt to discover new drugs to prevent or diminish the impact caused by drugs of abuse within the brain should be encouraged.

PLEIOTROPHIN, A CYTOKINE WITH CRITICAL FUNCTIONS IN NEURONAL REPAIR PROCESSES.

Pleiotrophin, initially cited as heparin binding growth factor-8 (HBGF-8) [16] and heparin binding-growth associated molecule (HB-GAM) [17] is a secreted, highly conserved 136-amino acid cytokine [16, 18, 19] that shares over 50% identity in amino acid sequence with midkine (MK), the only other member of the PTN/MK developmentally regulated gene family [16]. Pleiotrophin is expressed in a temporal and cell type-specific pattern in neuroepithelial and mesenchymal cells during development [18, 20-22] but its expression is limited to neuronal and glial cell populations in adults and different lining cells including pleura, peritoneum and dura [23, 24]. The PTN gene is induced by platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) [25]; its levels of expression peak 1-2 days after those of PDGF in late embryonic development [18, 25, 26]. During development, in the central nervous system, PTN expression is found in discrete loci that correspond at the same time to peaks of growth and early differentiation of neurons and glia [18]. The pattern of expression of PTN strongly suggested that PTN could play a physiological role in neuronal differentiation, which was subsequently confirmed in primary cultures of neonatal neurons [17, 18], neural stem cells [27] and embryonic stem cell-derived cells [28].

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Besides differentiation, PTN and MK seem to participate in cell survival and repair of damaged tissues. Both cytokines are upregulated in different cells at sites of injury and during repair processes [23, 29-32]. In the brain, PTN was found to play a significant role in injury-induced and activity-dependent hippocampal plasticity [33] and to be part of the supportive environment to regenerate axons after injury [34]. Recently, endothelial-derived pleiotrophin has been found to be a source of trophic support for neurons in the brain [35]. Furthermore, accordingly to the ability of PTN to promote the survival and neurite outgrowth of dopaminergic neurons *in vitro* [28, 36-38], PTN has been shown to exert key trophic effects on donor cells in neural transplantation *in vivo* to achieve functional recovery of nigrostriatal pathways [39]. In addition, fetal striatum- and ventral mesencephalon-derived neurospheres grafted into the mouse midbrain has served to identify PTN as one of the factors that critically mediates the rescue of nigral dopaminergic neurons from degeneration [40].

Pleiotrophin has been shown to exert neurotrophic effects on spinal motor neurons [41]. In this study, the PTN repair functions were also found to be efficient in the periphery, where PTN promotes regeneration of peripheral nerve axons after sciatic nerve transection [41]. Accordingly, PTN has been also found to be significantly upregulated in the dorsal root ganglia after chronic constriction injury of the sciatic nerve, circumstance that correlated with the rate of recovery from neuropathic pain [31]. Interestingly, the ability of PTN to induce formation of functional neovasculature *in vivo* has been proven to be important in PTN-induced repair processes [42].

MECHANISM OF ACTION OF PLEIOTROPHIN

Pleiotrophin was the first soluble active ligand identified for any of the receptor protein tyrosine phosphatases (RPTPs) [43, 44]. Most RPTPs exhibit an extracellular domain, a single transmembrane domain and one or two catalytic PTP domains. In the case of RPTPβ/ζ, also known as RPTPβ [45], PTPζ [46] and Ptprz, the membrane proximal domain (D1) has the PTP activity whereas the distal domain (D2) has little or no catalytic activity [47]. Three splicing variants of RPTPβ/ζ are known: the full length form Ptprz-A, the short receptor form Ptprz-B with a deletion in the extracellular region and the secretory variant of the full length form Ptprz-S (also known as 6B4 proteoglycan/phospacan) [48].

Pleiotrophin signals through a unique mechanism. After high affinity binding to RPTPβ/ζ [43], PTN inactivates the intrinsic tyrosine phosphatase activity of this protein and hence prevents dephosphorylation of its substrates (see a scheme of this mechanism of action in Fig. (**1**)). RPTPβ/ζ inactivation presumably involves an interference with the access of substrates to the active site in the D1 domain, as a consequence of PTN-enforced dimerization of this receptor (Fig. (**1**)) [43]. The crystallographic analysis of the remarkably homologous D1 (active) domain of RPTPα [49-52] suggested this mechanism of ligand-enforced inactivation of the transmembrane class of tyrosine phosphatases. This hypothesis was later confirmed by Fukada and colleagues [53] that succeeded inducing the oligomerization of RPTPβ/ζ by an artificial dimerizer, polyclonal antibodies against the extracellular region of RPTPβ/ζ, and by PTN.

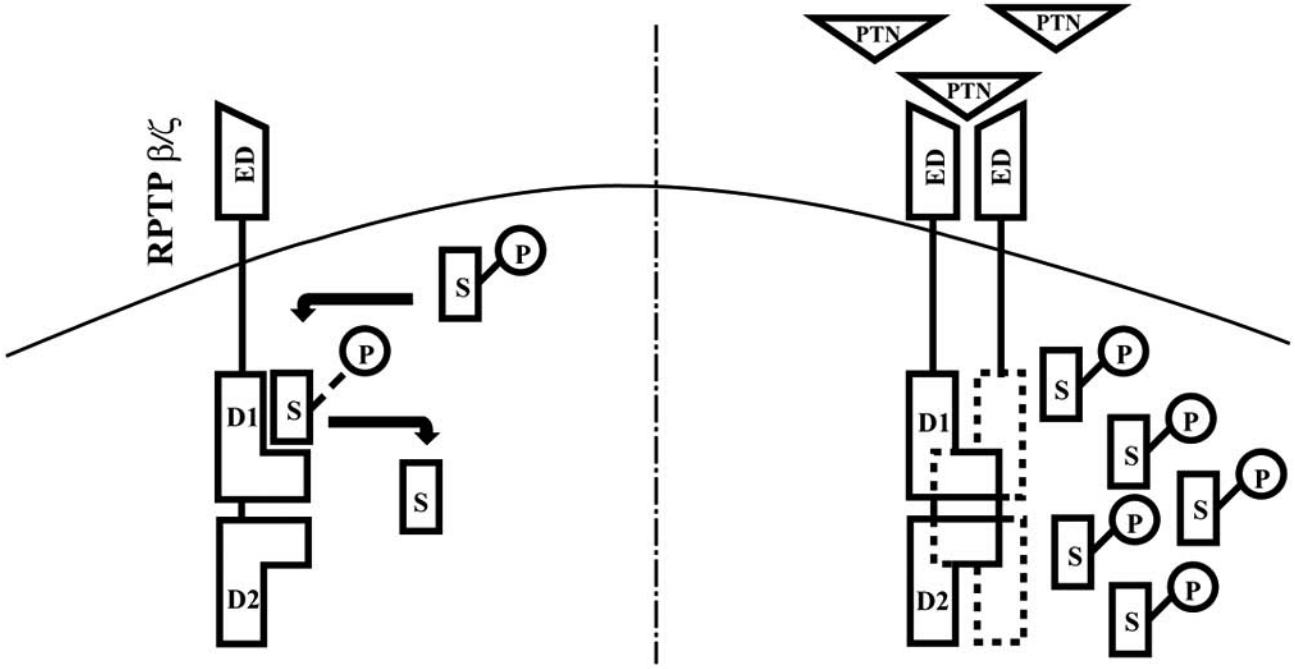

Fig. (1). Pleiotrophin mechanism of action. The PTN receptor RPTPβ/ζ has an extracellular domain (ED), a transmembrane domain, a catalytic intracellular domain (D1) and an inactive intracellular domain (D2). Left side: RPTPβ/ζ is found in monomeric form in the cell membrane in absence of PTN. In this form, RPTPβ/ζ exerts its phosphatase activity dephosphorylating its substrates (S) β-catenin, Git1, p190 RhoGAP, Magi 1, Fyn, β-adducin and ALK. Right side: When PTN is present, it induces the dimerization of RPTPβ/ζ inactivating its phosphatase activity, presumably by denying substrate access to the catalytic domain (D1). As a result, increases in the phosphorylation levels of the different substrates of RPTPβ/ζ are found in PTN-stimulated cells.

When PTN inactivates RPTPβ/ζ, the substrates of RPTPβ/ζ are no longer dephosphorylated and thus tyrosine phosphorylation of these substrates is increased by disruption of the balanced contribution of RPTPβ/ζ and protein tyrosine kinases (PTKs). The downstream targets of the PTN/RPTPβ/ζ signaling pathway thus far identified include β-catenin [43], G protein-coupled receptor kinase interactor 1 (Git1) [54], p190 RhoGAP and membrane-associated guanylate kinase, WW, and PDZ domain containing 1 (Magi 1) [55]; Fyn [56] and β-adducin [57, 58]. Interestingly, anaplastic lymphoma kinase (ALK) has also been proposed as a receptor for PTN [59], however it has been recently determined that ALK is also a substrate of RPTPβ/ζ [60]. In this sense, it has to be noted that N-Syndecan (Syndecan-3) has also been proposed as a receptor for PTN [61]. Although N-syndecan functions as a functional coreceptor mediating some of the PTN-induced neurite outgrowth effects [33], its role in the PTN neuroprotective effects against drug of abuse-induced toxicity remains to be studied. In contrast, PTN signaling through inactivation of RPTPβ/ζ and increase of the phosphorylation levels of RPTPβ/ζ substrates significantly support the role of PTN in drug-induced toxicity and is discussed in depth in the next point of this review.

Similarly to PTN, the pattern of expression of RPTPβ/ζ is restricted to the central nervous system in adults whereas during development high levels of expression of RPTPβ/ζ are found in the ventricular and subventricular areas of the embryonic mouse brain [62], thus suggesting critical roles for the PTN/RPTPβ/ζ signaling pathway in brain development.

A wide transcriptional profiling study has been recently performed in different organs of PTN and MK genetically deficient mice (PTN -/- and MK -/-) in order to find new signaling pathways triggered by both cytokines. It was found that PTN and MK regulate the renin-angiotensin system and catecholamine synthesis *in vivo* [63-66]. These data also suggest that PTN and MK are highly redundant in function confirming further evidence reported in other contexts [67, 68]. Interestingly, it was also found that PTN -/- and MK -/- mice exhibit lower TH mRNA levels in different brain areas [69], suggesting that PTN and MK regulate dopamine synthesis, which is highly interesting when dealing with neurotoxicity and addiction as it has been previously explained.

ROLE OF PTN IN NEUROTOXICITY INDUCED BY DRUG ABUSE

Interestingly, the data just introduced correlate with the ability of PTN to induce TH expression in cultures [28]. Furthermore, PTN has been shown to exert trophic effects on dopaminergic neurons *in vitro* [38], to be a survival factor for the catecholaminergic PC12 cell line [70] and to induce the differentiation of catecholaminergic neurons from embryonic stem cell-derived nestin-positive cells [28]. Accordingly, some of these findings were consistently linked with PTN overexpression in the striatum of patients with Parkinson´s disease [37], leading the authors to suggest a trophic effect of PTN on dopaminergic neurons in this neurodegenerative disease. It is also reasonable to think that this "protective" role of PTN could be extendable to other kind of cellular damage, i.e. drug-induced toxicity. Interestingly, PTN is upregulated in the nucleus accumbens after acute administration of amphetamine [71] and in the cingulate cortex, frontoparietal cortex and caudate-putamen after delta-9-tetrahydrocannabinol injection [72]. Midkine, the PTN-related cytokine, has been also found to be upregulated in the hippocampus of morphine-treated rats [73] and prefrontral cortex of alcoholics and smokers [74, 75]. Remarkably, the administration of yohimbine, an alpha-2 adrenergic antagonist known to prevent opioid-induced gliosis in the rodent brain, consistently increases MK expression, thus suggesting a possible role of MK in the prevention of opioid-induced long-term alterations in the brain [73, 76].

The available evidence strongly suggests that PTN and/or MK could provide neuroprotection against the toxic effects of drug abuse. We have recently tested this hypothesis in NG108-15 neuroblastoma x glioma cells and in PC12 cells, a catecholaminergic line widely used to evaluate drug toxicity [77] that is known to express high levels of dopamine transporter, the pharmacological target of cocaine [78]. Pleiotrophin significantly prevented cocaine-induced toxicity in both cell lines, as measured by the neutral red test [70]. We have now confirmed this protection using the MTT test (Invittox IP-17, European Center for the Validation of Alternative Methods database); in these experiments, a low concentration of PTN (3 μM) which did not affect cell proliferation by itself significantly prevented the antiproliferative effect of cocaine in NG108-15 cell cultures (Fig. (**2**)).

The molecular mechanisms involved in the repair processes led by PTN in the central nervous system remain to be established, but they probably involve an interaction with RPTPβ/ζ and the subsequent increase of the phosphorylation levels of RPTPβ/ζ substrates. Increased tyrosine phosphorylation of these substrates by PTN contributes to disrupt homophilic cell-cell adhesion and cytoskeletal stability, facilitating as a result an epithelial mesenchymal transition [79] that is characteristic in repair processes. Some of the proteins downstream of the PTN/RPTPβ/ζ have already been shown to have critical functions within the dopaminergic system and in the control of mechanisms involved in neurotoxicity processes:

a) β-Catenin

Pleiotrophin has been found to increase the phosphorylation levels of β-catenin to initiate downstream signaling pathways [43]. Interestingly, high β-catenin levels have been found in Nurr1+ precursor cells in the mouse ventral midbrain region [80]. β-catenin binds Nurr 1 and acts as a transcriptional cofactor regulating the development of Nurr 1+ precursor cells *in vivo* [81], a preliminary step in the expansion and differentiation of dopaminergic neurons. These results fit perfectly with recent data demonstrating that downregulation of β-catenin levels could be part of the mechanisms involved in the neuronal loss characteristic of neurodegenerative diseases such as Parkinson´s disease [82]. Very interestingly, one of the few genes significantly downregulated in dorsal striatum in response to repeated cocaine self-administration is β-catenin [83], suggesting cocaine and other drugs of abuse may cause degeneration of dopaminergic neurons by disrupting Wnt signaling. Once again, the existing data strongly suggest common molecular mecha-

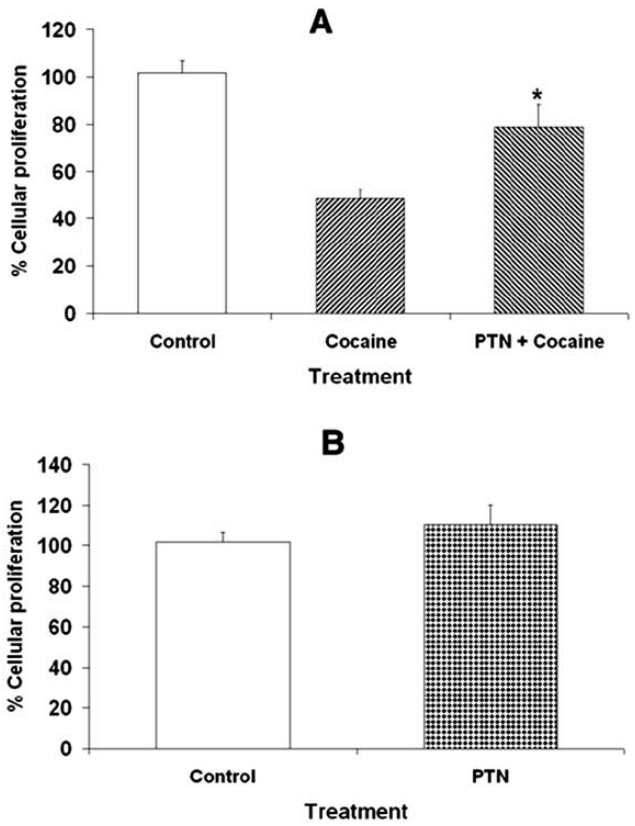

Fig. (2). Effects of pleiotrophin on cocaine-induced toxicity in NG108-15 cells. (A) NG108-15 cells cultured with media supplemented with cocaine (5 mM) and pleiotrophin (PTN; 3 μM) for 24 hours. (B) NG108-15 cells cultured with media supplemented with pleiotrophin (PTN; 3 μM) for 24 hours. Results are expressed as mean ± S.E.M. * $P < 0.05$ *vs* Cocaine.

nisms underlying the damage of dopaminergic neurons observed in Parkinson´s disease with that induced by chronic administration of drugs of abuse.

b) Protein Kinase C and Fyn

Pleiotrophin has been shown to activate protein kinase C (PKC) and, through this mechanism, to regulate the pattern of phosphorylation of β-adducin [58] and the cellular distribution of β-adducin that is key in the cytoskeletal rearrangement characteristic of cell differentiation processes. Interestingly, robust evidence suggests a direct link between PKC activation and modulation of drug seeking behaviours (see review [84]). The remaining challenge is to define the role of every PKC isoform in drug addiction since different PKC isoforms seem to have different (even contrary) effects on drug seeking behaviours and drug-induced toxicity. For example, ethanol-induced abnormal behaviours and ethanol-potentiation of gamma amino butyric acid (GABA) are significantly reduced in PKCγ knockout mice while increased in PKCε knockout mice [85-87]. Studies directed to elucidate which PKC isoforms are activated by PTN and the roles of the remaining PKC isoforms in drug addiction and neurotoxicity will possibly serve to establish (or discard) another potential molecular mechanism by which PTN exerts its effects on drugs of abuse-induced toxicity.

Interestingly, it has been recently shown that PKC and Fyn, another confirmed downstream molecule of PTN/RPTPβ/ζ signaling pathway [56], are both required for neural cell adhesion molecule (NCAM)-induced neurite outgrowth and neuronal survival, suggesting the involvement of Fyn and PKC in the survival effects of PTN on dopaminergic neurons and PC12 cells.

TARGETING THE PTN/RPTPβ/ζ SIGNALING PATHWAY TO TREAT DRUG OF ABUSE-INDUCED TOXICITY

The data discussed so far strongly suggest that the PTN/RPTPβ/ζ signaling pathway represents a potential target to limit the neurotoxic consequences of drug abuse. Since this is a relatively novel pathway, to the best of our knowledge, no current therapies targeting PTN or RPTPβ/ζ for this or any other indication are available in humans. Drug discovery studies in this field could be orientated by previous experience with other PTN-like growth factors or protein tyrosine phosphatases (PTPs), therefore we propose the following strategies as initial steps:

a) Pleiotrophin

The evidence available highly recommends testing PTN as a new potential therapy for neurotoxic disorders associated with drug abuse. However, there is an obvious and significant problem with the route of administration. As many other substances with potential therapeutic actions within the central nervous system, local administration of PTN is recommended to avoid side effects in other tissues. Even when this approach seems problematic, there is already wide experience concerning intracerebral administration of cytokines to humans in similar conditions to those proposed here. This is the case of glial cell line-derived neurotrophic factor (GDNF), which has been infused in the putamen of patients with Parkinson´s disease in several clinical trials [88-90].

Nevertheless, given the complexity of this route of administration, a profound evaluation of the balance benefits/risks for this therapy is required, and a comparative evaluation with the effects of systemic injection of PTN should be performed. In this sense, it is important to note that PTN acts as a tumor promoter and an angiogenic factor in tumors of diverse origin [20] recommending that oncogenic effects of PTN should be studied as potential side effects. Although these possible side effects of PTN should be definitely considered when studying PTN to treat drug-induced toxicity, it is important to note as well that significant upregulation of PTN levels in different injured organs such as the brain of patients with Parkinson´s disease [37] did not correlate with increases in the possibilities to develop tumors in these patients. In addition, an eventual systemic administration of PTN may not increase the possibility to suffer side effects in other tissues since intracellular phosphorylation balance in non-injured cells will prevail, being the effects of PTN still of critical importance in the injured cell. This is strongly supported by studies in RPTPβ/ζ genetically deficient mice. In normal condition, these mice do not exhibit gross abnormalities suggesting other PTPs are compensating for the absence of RPTPβ/ζ [91]. However, the important problem of blood brain barrier (BBB) penetration could

decisively influence the utility of systemic injections of PTN, and therefore deserves further attention.

b) RPTPβ/ζ

Since the balanced contribution of PTPs and protein tyrosine kinases (PTKs) on tyrosine phosphorylation is key in intracellular signaling, and disruption of this balance underlies different diseases [92-94], PTPs (including the receptor-like class) are currently being considered as main targets for drug design by the pharmaceutical industry [95]. Selective and potent PTK inhibitors have been developed and approved for clinical use [96]. Unfortunately the development of pharmaceutically suitable PTP inhibitors remains a challenge. The hydrophilic and charged phosphate group of their natural substrates is difficult to mimic without compromising the membrane permeability and BBB penetration of the inhibitor. Thus, PTPs inhibitors usually need a highly charged active site with electrostatic properties optimized for binding the phosphate moiety [97]. It seems however that membrane-permeable phosphatase inhibitors can be produced, although their poor availability after oral administration is another problem to overcome [98].

PhosphoTyr (pTyr) residue isostere mimetics have been incorporated in the design of different PTPs inhibitors since it was determined that over 50% of the binding free energy is provided by interactions with this residue [99]. Both pTyr and phosphate isostere mimetics have been reviewed recently [100] and they include **i)** compounds containing a hydrolytically stable phosphonate group obtained by replacing the bridging oxygen atom with methylene moiety, **ii)** phosphinate isosteres with reduced charge and greater membrane permeability, **iii)** α,α-difluoro-β-ketophosphonic acids to try to mimic a bound water molecule in the active site and **iv)** carboxylate-based isosteres, including combinations of a carboxylate group and a polar group, to try to capture phosphate-like electrostatic interactions in a functional group composite more cell-permeable than phosphate [97].

The success attained with the development of selective PTK inhibitors was greatly based on structure-based drug design, and helped to understand the mechanism of the enzymatic activity of PTPs which was key for early attempts at inhibitor development. For example, the profound study of the interaction of PTP-1B with the diphosphorylated activation loop of the insulin receptor [101] was critical to elucidate the molecular mechanism of receptor dephosphorylation. Besides, these efforts joined to X-ray crystallography have significantly helped to understand and optimize the potency and selectivity of PTP-1B inhibitors [97,102-104] that reached clinical use [100].

Clearly, this kind of studies seems a reasonable strategy to improve our knowledge of the PTP family of enzymes. In any case, the development of RPTPβ/ζ inhibitors may be achieved based on small molecule inhibitors developed for other PTPs, such as those recently developed to target the catalytic intracellular domain of these enzymes [95, 100]. It is important to note, however, that the high diversity of extracellular domains of RPTPs represent a diversification of epitopes available for ligand binding, which provides an interesting opportunity for the development of more specific inhibitors. Other strategy is the design of antisense oligonucleotides targeting RPTPβ/ζ, following the path opened by ISIS-113715, a 20-mer antisense oligonucleotide against PTP-1B currently in phase II clinical trials for the treatment of type 2 diabetes.

Xie and colleagues [105] have developed another strategy to inhibit PTP function based in the wedge-shaped helix-loop-helix region just N-terminal of the catalytic active D1 domain that, upon dimerization, may inhibit the phosphatase activity by blocking the entrance to the catalytic domain [50, 52]. This group demonstrated the specific inhibition of the phosphatase activity after administration of cell-permeable wedge-domain peptides, providing a very interesting alternative strategy to inhibit PTPs. In addition, engineering the extracellular and catalytic domains of RPTPβ/ζ based on its structure will allow to crystallyze inhibitor complexes and, thus, to identify new small inhibitors. This form of rational peptide design has proven to be very useful to optimize the ability to rapidly generate multiple ligand-bound structures of pharmaceutically relevant PTPs, enhancing the efficiency of structure-guided inhibitor optimization in this important new area of drug discovery [98].

Despite more than 20 years of research in the field, ligands capable to bind any of the RPTPs and, more importantly, to induce an effect on the catalytic activity of these receptors, still remain a challenge. In fact, to the best of our knowledge, binding and ligand-induced effects have been only demonstrated in the case of PTN and RPTPβ/ζ [43]. Thus, current efforts are consistently directed towards the identification of additional RPTP functional ligands (see for example [106]). Recent structural work is also providing important insights into the ectodomain-dependent mechanisms that regulate RPTPμ and RPTPκ [107], which may significantly help the rational drug design targeting the extracellular domains of other RPTPs.

CONCLUSION

In this review, we summarize for the first time the scientific basis available to strongly consider the novel PTN/RPTPβ/ζ signaling pathway as a main target to develop new drugs to efficiently treat drug of abuse-induced neurotoxicity. This is considered critically important since therapeutics for this indication do not exist and the number of patients with neurodegenerative diseases originated or aggravated by chronic drug of abuse consumption is yearly increasing. The novelty of the PTN/RPTPβ/ζ signaling pathway and the absence of any prototype molecule targeting this pathway at the moment makes of the rational drug design to target this pathway an imposing task. A medical breakthrough could be achieved from the combination of specific neuroprotective drugs with substitutive pharmacological and psychological therapies to help drug addicts to abandon drug consumption habits.

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ABBREVIATIONS

PTN = Pleiotrophin

MK = Midkine

RPTP = Receptor Protein Tyrosine Phosphatase

PTP = Protein Tyrosine Phosphatase

ALK = Anaplastic Lymphoma Kinase

Git 1 = G protein-coupled receptor kinase interactor 1

Magi 1 = Mmembrane-associated guanylate kinase, WW, and PDZ domain containing 1

PDGF = Platelet-Derived Growth Factor

bFGF = basic Fibroblast Growth Factor

TH = Tyrosine Hydroxylase

PTK = Protein Tyrosine Kinase

PKC = Protein Kinase C

GABA = gamma amino butyric acid

NCAM = Neural Cell Adhesion Molecule

BBB = Blood Brain Barrier

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