BLOCKING RECEPTOR PROTEIN TYROSINE PHOSPHATASEβ/ζ: A POTENTIAL THERAPEUTIC STRATEGY FOR PARKINSON´S DISEASE.

Running header: RPTPβ/ζ in Parkinson´s disease

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Abstract

Pleiotrophin (PTN) is a recently discovered cytokine which has been found highly upregulated in the substantia nigra and striatum of rodents in experimental models of Parkinson´s disease. Interestingly, immunohistochemical studies have shown increased levels of PTN expression in the substantia nigra of patients with Parkinson´s disease. Since, in other contexts, PTN has been shown to be critical in repair processes in the injured nervous system, the antecedents suggest that PTN could exhibit protective effects in Parkinson´s disease. This hypothesis was confirmed when PTN was shown to support survival of dopaminergic neurons and to promote the differentiation of neural stem cells to dopaminergic neurons. These findings suggest a new therapeutic approach in the treatment of Parkinson´s disease based on the molecular mechanism of action of PTN. Pleiotrophin receptor, receptor protein tyrosine phosphatase (RPTP) β/ζ, is found active in monomeric form in neurons and glia within the central nervous system. Pleiotrophin induces dimerization of RPTPβ/ζ inactivating its phosphatase activity, thus increasing the phosphorylation levels of its substrates such as β-catenin, Fyn and β-adducin. These substrates have been shown to be critical for the proliferation of dopaminergic progenitors and the survival and differentiation of dopaminergic neurons. This review summarizes the strong scientific basis to consider blocking RPTPβ/ζ as a potentially novel therapeutic strategy in the treatment of Parkinson´s disease and discusses various starting points to design antagonists of this receptor.

Keywords: pleiotrophin, midkine, receptor protein tyrosine phosphatase, dopamine, Parkinson's disease, survival, differentiation, neurodegeneration.

INTRODUCTION

Different cellular processes required for normal development of the nervous system, including proliferation, survival, differentiation, synaptogenesis and maturation, are stimulated by specific neurotrophic factors [1-4]. Typically, the expression levels of these neurotrophic factors within the central nervous system are significantly diminished after development, but, in areas where neurodegeneration occurs, significant increases of expression of these neurotrophic factors are found. This may be seen as an opportunity to develop new therapeutics that could mimic the neuroprotective actions of these endogenous neurotrophic factors under pathological conditions.

In Parkinson´s disease, a significant loss of dopaminergic neurons in the substantia nigra and, thus, of their projections in the striatum is observed. Alpha-synuclein aggregates, responsible for the formation of Lewy bodies within this type of neurons, seem to contribute greatly to neuronal degeneration. Thus, the identification of survival factors for dopaminergic neurons that are highly upregulated in these brain areas of patients with Parkinson´s disease has been considered of critical importance in the development of new therapeutic approaches to Parkinson´s disease.

Pleiotrophin, a cytokine with multiple repair functions within the central nervous system.

Pleiotrophin (PTN), initially cited as heparin binding growth factor-8 (HBGF-8) [5-7], and heparin binding-growth associated molecule (HB-GAM) [8] is a secreted, highly conserved cytokine [5-7] which shares over 50% identity in amino acid sequence with midkine (MK), the only other member of the PTN/MK developmentally regulated gene family [7].

The PTN gene is induced by platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) [9]; its expression levels peak 1-2 days after those of PDGF in late embryonic development [6, 9, 10]. During development, in the central nervous system, PTN expression is found in discrete loci that correspond at the same time to growth peaks and early differentiation of neurons and glia [6]. The expression pattern of PTN strongly suggests that PTN may function in vivo in the differentiation of these cells. This hypothesis was confirmed when PTN was found to stimulate neuronal differentiation responses in neonatal neuronal cells in primary culture [6, 8], to enhance differentiation of neural stem cells [11] and to induce neuronal differentiation from embryonic stem cell-derived cells [12].

Pleiotrophin (and MK) expression is upregulated in different cells at injury sites and during repair processes in the nervous system [13-17], suggesting that PTN is upregulated at injury sites to repair the damaged tissue. This hypothesis was strongly supported when PTN was found to play a significant role in injury-induced and activity-dependent plasticity in the rat hippocampus [18], to be part of the supportive environment to regenerate axons in the injured brain [19], and to be a source of trophic support for neurons in the brain [20].

Pleiotrophin Receptor: Interaction of PTN with receptor protein tyrosine phosphatase (RPTP) β/ζ inactivates RPTPβ/ζ.

Previous studies demonstrated that the PTN signaling mechanism is through its high affinity interaction with its receptor, the receptor protein tyrosine phosphatase (RPTP) β/ζ [21]. Most RPTPs exhibit an extracellular domain, a single transmembrane domain and one or two catalytic PTP domains. In the case of RPTPβ/ζ (being the gene, Ptprz), the membrane proximal domain (D1) has the PTP activity whereas the distal

domain (D2) has little or no catalytic activity [22]. Four 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, the secretory variant of the full length form Ptprz-S (also known as 6B4 proteoglycan/phospacan) [23] and the PSI isoform, expressed only in neurons [24]. Interestingly, it has been recently demonstrated that the extracellular region of these receptor isoforms is cleaved by metalloproteinases and by presenilin/gamma-secretase, causing the release of the intracellular region of RPTPβ/ζ into the cytoplasm [25].

The interaction of RPTPβ/ζ with PTN inactivates the intrinsic tyrosine phosphatase activity of RPTPβ/ζ; the inactivation of RPTPβ/ζ is presumed to result from a PTN-enforced conformational change in RPTPβ/ζ that denies substrates access to the active site in the D1 domain of RPTPβ/ζ, a mechanism suggested by the crystallographic analysis of the highly homologous D1 (active site) domain of RPTPα [26-29], and a mechanism supported by the demonstration that PTN directly abrogates the protein tyrosine phosphatase activity of RPTPβ/ζ [21]. The hypothesis of the PTN mechanism of action was confirmed by Fukada and colleagues [30], who succeeded in inducing the oligomerization of RPTPβ/ζ using an artificial dimerizer, polyclonal antibodies against the extracellular region of RPTPβ/ζ and by PTN. However, to the best of our knowledge, it has only been demonstrated the binding of PTN to 6B4 proteoglycan/phosphacan, that corresponds to the extracellular region of RPTPβ/ζ, with low (Kd = 3 nM) and high (Kd = 0.25 nM) affinity binding sites [31].

The inactivation of RPTPβ/ζ leaves unchecked the constitutive activity of different protein tyrosine kinases which target the same sites in the substrates of RPTPβ/ζ that are normally dephosphorylated by RPTPβ/ζ. The activity of the different tyrosine kinases thus increases the steady state levels of tyrosine phosphorylation of the

RPTPβ/ζ substrates, whose levels of tyrosine phosphorylation are otherwise maintained in balance by RPTPβ/ζ in cells not stimulated by PTN. The different targets of the PTN/RPTPβ/ζ signaling pathway thus far identified raise the possibility that through its capacity to inactivate RPTPβ/ζ, PTN coordinately regulates the steady state levels of tyrosine phosphorylation of many key proteins in different functional systems in the neuron. The downstream targets of the PTN/RPTPβ/ζ signaling pathway thus far identified include β-catenin [21], G protein-coupled receptor kinase interactor 1 (Git1) [32], p190 RhoGAP and membrane-associated guanylate kinase, WW, and PDZ domain containing 1 (Magi 1) [33]; Fyn [34] and β-adducin [35, 36]. Interestingly, anaplastic lymphoma kinase (ALK), another proposed receptor for PTN [37], has recently been described as a substrate of RPTPβ/ζ [38]. In this work, it was shown that ALK activation is entirely independent of a direct interaction between PTN and ALK itself. In addition, it has to be noted that N-Syndecan is also a receptor for PTN [39] and is responsible for some of the PTN-induced neurite outgrowth effects [34]. However, its possible role in the PTN neuroprotective effects in Parkinson´s disease remains to be studied. As we discuss below, some of the substrates of RPTPβ/ζ have turned out to be critical in the survival and differentiation of dopaminergic neurons. The PTN/RPTPβ/ζ signaling pathway is summarized in Figure (**1**).

Recently, in an effort to identify new signaling pathways regulated by PTN and its highly homologous MK, a wide transcriptional profiling study was performed in various organs of PTN and MK genetically deficient mice (PTN -/- and MK -/-). It was found that PTN and MK regulate the renin-angiotensin II pathway in vivo [40, 41], which was then linked to the capacity of PTN to generate new functional vasculature in vivo [42], an event that, when occurring within the brain, may be key for PTN neuroprotective functions [43]. In addition, it was also found that PTN and MK regulate

the catecholamine biosynthesis in those transcriptional studies [44, 45]. It was found that the catecholamine biosynthetic enzymes are upregulated in the aortae of PTN-/- and MK-/- mice. In contrast, PTN -/- and MK -/- mice exhibit lower levels of tyrosine hydroxylase, the rate-limiting enzyme of the catecholamine biosynthesis, in different brain areas [46], suggesting PTN and MK regulate the synthesis of the main neurotransmitter whose levels are significantly downregulated in Parkinson´s disease, dopamine. These apparent contradictory results may be explained by the fact that other signaling pathway capable to regulate the levels of expression of the catecholamine biosynthetic enzymes, the angiotensin II signaling pathway [47], is also regulated in the aortae of PTN-/- and MK-/- mice [40, 41].

Does PTN have a role in Parkinson´s disease?

In previous studies, a PTN dose-dependently increase in the number of tyrosine hydroxylase positive neurons in primary cultures of mesencephalic neurons was found [48]. In addition, Jung et al. [12] demonstrated that PTN promotes production of dopaminergic neurons and increased levels of tyrosine hydroxylase mRNA in embryonic stem cell derived, nestin-positive cells. Interestingly, we recently found that PTN is a survival factor for the catecholaminergic PC12 cell line [49]. Accordingly, the ability of PTN to promote the survival and differentiation of dopaminergic neurons in vitro [12, 48, 50, 51] and to regulate the expression levels of tyrosine hydroxylase in vivo [46] strongly suggest PTN as a potent regulator of dopamine synthesis in the central nervous system.

PTN has also been shown to exert key trophic effects on donor cells in neural transplantation in vivo to achieve functional recovery of nigrostriatal pathways [52]. In addition, fetal striatum- and ventral mesencephalon-derived neurospheres grafted into

the mouse midbrain have served to identify PTN as one of the critical factors that mediates the rescue of nigral dopaminergic neurons from degeneration [53]. More importantly, PTN has been shown to significantly increase the functional recovery of Parkinsonian rats just by being added to donor cells from ventral mesencephalon before these cells are grafted into striatum of these rats [52]. All these results turned out to be very promising when PTN was recently found to be highly upregulated in the substantia nigra of patients with Parkinson´s disease [50].

L-DOPA is still the drug of election, alone or in combination with other drugs, in patients with Parkinson´s disease. In this pathological condition, L-DOPA acts as an exogenous precursor to increase dopamine synthesis in the remaining dopaminergic neurons of patients with Parkinson´s disease. However, it is also believed that L-DOPA greatly contributes to the support of a trophic environment for dopaminergic terminals in the striatum [54, 55]. In an attempt to uncover the mechanisms involved in these L-DOPA effects, Ferrario and colleagues [56] performed an analysis of differential gene expression in the striatum of L-DOPA-treated rats with partial lesions of the nigrostriatal system, identifying PTN as one factor highly upregulated in this model. Importantly, the levels of RPTPβ/ζ have recently been found to be increased in the dopaminergic neurons of the substantia nigra and their targets, the striatal medium spiny neurons, of L-DOPA-treated Parkinsonian rats [43] that could potentially lead to changes in the phosphoproteome in brain areas of these L-DOPA-treated Parkinsonian rats. This hypothesis may be important since L-DOPA effects on the recovery of dopaminergic nerve terminals have been paralleled with altered protein phosphorylation [57]. The data strongly suggest the possibility that the PTN/RPTPβ/ζ signaling pathway may be involved in the plastic changes triggered by L-DOPA in patients with Parkinson's disease.

Could the effectors of the PTN/RPTPβ/ζ signaling pathway be responsible for PTN effects on the survival and differentiation of dopaminergic neurons?

a) Beta-catenin is a downstream target of the PTN/RPTPβ/ζ signaling pathway.

Beta-catenin was the first substrate to be described for RPTPβ/ζ [21]. Beta-catenin is a ~92 kDa protein that interacts with the cytosolic tail of cadherins and connects them to actin filaments through α-catenin. The interaction between β-catenin and cadherins is vulnerable to dissociation by tyrosine phosphorylation of β-catenin. Increases in steady state levels of tyrosine phosphorylation of β-catenin decrease the binding affinity of β-catenin to cadherins, therefore disrupting cell-cell adhesion [58], all events needed in neuronal differentiation processes (Fig. (**1**)).

Interestingly, high β-catenin levels have been found in Nurr1+ precursor cells in the mouse ventral midbrain region [59]. β-catenin binds Nurr 1 and acts as a transcriptional cofactor regulating the development of Nurr 1+ precursor cells in vivo [60], a preliminary step in the expansion and differentiation of dopaminergic neurons. Thus, increases of β-catenin function in ventral mesencephalic precursors result in increased dopamine neuron differentiation [61]. 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 [62].

b) Beta-adducin is a downstream target of the PTN/RPTPβ/ζ signaling pathway.

Beta-adducin belongs to a family of proteins that binds to actin-spectrin junctions and stabilizes the growing actin filaments and actin-spectrin networks [39, 63, 64]. Pleiotrophin activates protein kinase C (PKC) and stimulates the PKC-catalyzed phosphorylation of serines 713, 726 in the myristoylated alanine-rich protein kinase C substrate (MARCKS) domain of β-adducin and it also stimulates translocation of β-adducin phosphorylated in serines 713, 726 to either nuclei where it is associated with nuclear chromatin and with the centrioles of dividing cells or to a membrane associated site, depending on the cell growth phase [35]. Since phosphorylation of serines 713, 726 in β-adducin markedly reduces the affinity of β-adducin for spectrin and actin and uncouples actin/spectrin/β-adducin multimeric complexes needed to stabilize the cytoskeleton, the PTN stimulated phosphorylation of serines 713, 726 in β-adducin contributes to the disruption of cytoskeletal complexes and is thus an important component of the previously demonstrated loss of cytoskeletal integrity and homophilic cell-cell adhesion in PTN-stimulated cells [35]. These studies also suggested the hypothesis that β-adducin has new and important roles in the regulation of the chromatin structure or mitosis and that PTN, through the PTN/RPTPβ/ζ signaling pathway, phosphorylates both β-catenin and β-adducin, and through them, initiates cytoskeletal disruption, events that, again, are necessary for neuronal differentiation processes (Fig. (**1**)).

c) Fyn is a downstream target of the PTN/RPTPβ/ζ signaling pathway.

We previously demonstrated that Fyn binds to the active site (D1) domain of RPTPβ/ζ, that Fyn is a substrate of RPTPβ/ζ, and that tyrosine phosphorylation of Fyn is sharply increased in PTN-stimulated cells [34]. The importance of Fyn in PTN signaling may be high. Fyn is a Src-like kinase, a likely candidate to phosphorylate

tyrosines that are a substrate of RPTPβ/ζ when RPTPβ/ζ is inactivated in PTN-stimulated cells.

It has recently been shown that Fyn is required for both neural cell adhesion molecule (NCAM)-induced neurite outgrowth and neuronal survival [65], suggesting the involvement of Fyn in the survival effects of PTN on dopaminergic neurons and catecholaminergic PC12 cells [49].

Blocking RPTPβ/ζ signaling pathway: A novel approach to treating Parkinson´s disease.

The pathogenic mechanisms of Parkinson's disease and the neuronal repair processes initiated by PTN, strongly suggest a novel therapeutic target for Parkinson´s disease: the PTN/RPTPβ/ζ signaling pathway. This is a relatively novel pathway [21] and to the best of our knowledge, no current therapies targeting RPTPβ/ζ for this or any other indication are available in humans. As mentioned above, the evidences compiled here strongly recommend the initiation of drug discovery and evaluation studies. To the best of our knowledge, only one inhibitor of RPTPβ/ζ has been synthesized (see below). However, based on drug discovery studies on other PTPs, various strategies may be proposed as initial steps.

a) PTN.

It seems reasonable to start drug discovery studies focusing on the known endogenous blocker of RPTPβ/ζ, PTN. PTN exerts a high binding affinity for RPTPβ/ζ to efficiently block its phosphatase activity [21, 30]. PTN has already been shown to promote the survival and differentiation of dopaminergic neurons in vitro and in vivo

[12, 48, 50-53]. Thus, the body of evidence compiled in this review suggests administration of PTN as a reasonable way to initiate critical studies to block the instrinsic phosphatase activity of RPTPβ/ζ.

Research focusing on cytokines and their therapeutic targets has greatly advanced during the last two decades, the administration of purified recombinant cytokines being widely used in humans in some pathologies (for a review of the topic, see [66]). In this context, local administration of PTN will follow the path opened by other neurotrophic factors and cytokines. There is wide experience in the use of intracerebral administration in humans in similar conditions to those cited here. For example, implanted intracerebroventricular administration of glial cell line-derived neurotrophic factor (GDNF) has been tested in clinical trials in patients with Parkinson´s disease [67] and has been shown to improve the bilateral motor functions after unilateral intraputamenal infusion [68] and to promote neuronal sprouting in human brain [69]. However, it is to be noted that recent double-blind clinical trials showed minimal effects of intraputamenal GDNF infusion in patients with Parkinson´s disease [70]. We should not be discouraged by the controversial effects of GDNF in humans since it is known that molecules highly expressed during developement, such as PTN, usually peak later in life in response to injury and disease, just as PTN does in the substantia nigra of patients with Parkinson´s disease [50], to initiate repair processes, and thus, deserves further evaluation for therapeutic purposes. Obviously, given the complexity of this route of administration, a profound evaluation of the balance benefits/risks for this therapy is required. Nevertheless, the devastating effects of Parkinson´s disease recommend intense consideration of this option. Technological studies to achieve PTN sustained-release systems to minimize the number of

administrations or, even better, systemic administration of PTN, would be potentially of great benefit.

Considering potential side effects of PTN administration, it has to be noted that PTN exhibits angiogenic potential when it is expressed in tumors [71] and may alter the vascular tone of aorta since it may contribute to the regulation of catecholamine synthesis in this organ [44]. However, systemic administration of PTN may not increase the possibility of suffering side effects in other tissues since intracellular phosphorylation balance in non-injured cells would prevail, the effects of PTN being still of critical importance in the injured brain cell. This is strongly supported by studies in RPTPβ/ζ genetically deficient mice. In normal conditions, these mice do not exhibit gross abnormalities, suggesting other PTPs are compensating for the absence of the phosphatase activity of this receptor [72]. However, it has to be noted that RPTPβ/ζ knockout mice show learning and memory deficits [73, 74], and impaired recovery from demyelinating disease [75]. In any case, further studies are needed to evaluate these as possible adverse effects to occur after PTN administration.

b) RPTPβ/ζ.

The cellular phosphatase activity of PTPs is precisely balanced by the kinase activity of other familiy of enzymes, the protein tyrosine kinases (PTKs). Disruption of this balance underlies different diseases [76-78]. For this reason, PTPs (including the receptor-like class) are currently being considered as prime targets for drug design [79], following the path opened by selective PTK inhibitors that were previously developed and reached clinical use [80]. The major problem in the design of novel PTPs inhibitors is that this type of compounds usually needs a highly charged active site which electrostatic properties optimize for binding the phosphate moiety [81], which finally

compromises the membrane permeability of the inhibitor and its oral availability [82]. In an attempt to improve the cellular permeability of PTPs inhibitors, phospho-tyrosine (pTyr) residue isostere mimetics have been used 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 [83]. Both pTyr and phosphate isostere mimetics that have been recently reviewed [84] include the replacement of the bridging oxygen atom with methylene moiety to achieve a hydrolytically stable phosphonate group and phosphinate isosteres with reduced charge and greater membrane permeability. In addition, to try to mimic a bound water molecule at the active site, α,α-difluoro-β-ketophosphonic acids have been used, whereas carboxylate-based isosteres, including combinations of a carboxylate group and a polar group, have been tested to try to capture phosphate-like electrostatic interactions in a functional group composite more cell-permeable than phosphate [81].

The structure-based drug design has been a useful tool for understanding the enzymatic mechanism of PTPs, a necessary preliminary step in the development of new PTPs inhibitors. Accordingly, the comprehensive study of the interaction of PTP-1B with the dephosphorylated activation loop of the insulin receptor [85] was critical to elucidate the molecular mechanism for the dephosphorylation of the insulin receptor by PTP-1B. These efforts joined to X-ray crystallography have significantly helped researchers to understand and optimize the potency and selectivity of PTP-1B inhibitors [81, 86-88] that have reached clinical use [84]. Clearly, these types of studies seem a reasonable strategy in generating additional structural information to improve our knowledge of the PTP family of enzymes.

Interestingly, reports of RPTPs inhibitors usually come from PTP-1B program screening panels. For example, RPTPβ/ζ is often found in selection panels in PTP

inhibitor screens [89]. Following this path, Huang and colleagues employed a non-charged phosphate mimic and non-peptidyl structural components to successfully design a trifluoromethyl sulfone (4-Trifluoromethylsulfonylbenzyl 4-trifluoromethylsulfonylphenyl ether) inhibitor of RPTPβ/ζ (Fig. (**2**)) with an IC50 of 3.5 μM that is 2-fold selective vs. RPTPε and ~10-fold selective vs. RPTPδ [90]. To the best of our knowledge, this is the only RPTPβ/ζ inhibitor synthesized with relative selectivity (Fig. (**2**)). However, comparative pharmacological studies with the endogenous inhibitor of RPTPβ/ζ, PTN, are lacking. This is a gap in knowledge that needs to be filled in order to postulate or to discard this molecule as a possible therapeutic option in the treatment of Parkinson's disease.

Since the final goal in the development of RPTPβ/ζ inhibitors is to find molecules capable to mimic the PTN effects on preclinical models of Parkinson´s disease, attention should be paid to small molecules inhibiting the catalytic intracellular domain of PTPs [79], such as antisense oligonucleotides. RPTPβ/ζ antisense oligonucleotides could be designed based in the example of ISIS-113715, a 20-mer antisense oligonucleotide against PTP-1B, developed by Isis Pharmaceuticals currently in phase II clinical trials for the treatment of type 2 diabetes. In addition, Xie and colleagues [91] have developed a new strategy to inhibit PTP function based on 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 substrate entrance to the catalytic domain [26, 28], again mimicking the molecular mechanism of action of PTN. As a result, the specific inhibition of the phosphatase activity after administration of cell-permeable wedge-domain peptides was then demonstrated [91], providing an innovative strategy to inhibit PTPs.

As mentioned before, the study of ligands capable of binding any of the RPTPs and, more importantly, of inducing an effect on the catalytic activity of these receptors has only been successfully achieved in the case of PTN and RPTPβ/ζ [21]. Engineering the extracellular and catalytic domains of RPTPβ/ζ based on its structure will allow researchers on the field to crystallize inhibitor complexes and, thus, to identify small molecule inhibitors of this receptor. Nevertheless, although inhibitors of the catalytic domain of PTPs have been successfully designed [84], it is important to note that the high diversity of extracellular domains of RPTPs contribute to a diversification of epitopes available for ligand binding that may greatly contribute to specific ligand-induced effects. Thus, current efforts are consistently directed towards the identification of additional RPTP functional ligands (see for example [92]). Furthermore, very significant advances on the structures of RPTPμ and RPTPκ have been recently achieved uncovering previously unknown ectodomain-dependent mechanisms that regulate these receptors [93], thus helping in 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 prime target in the development of new drugs to efficiently treat Parkinson's disease. The novelty of the PTN/RPTPβ/ζ signaling pathway and the existence of only one RPTPβ/ζ inhibitor prototype make the drug design to target this pathway a rational and very promising but imposing task.

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LIST OF 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.

GDNF: Glial Derived Growth Factor.

NGF: Nerve 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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FIGURES:

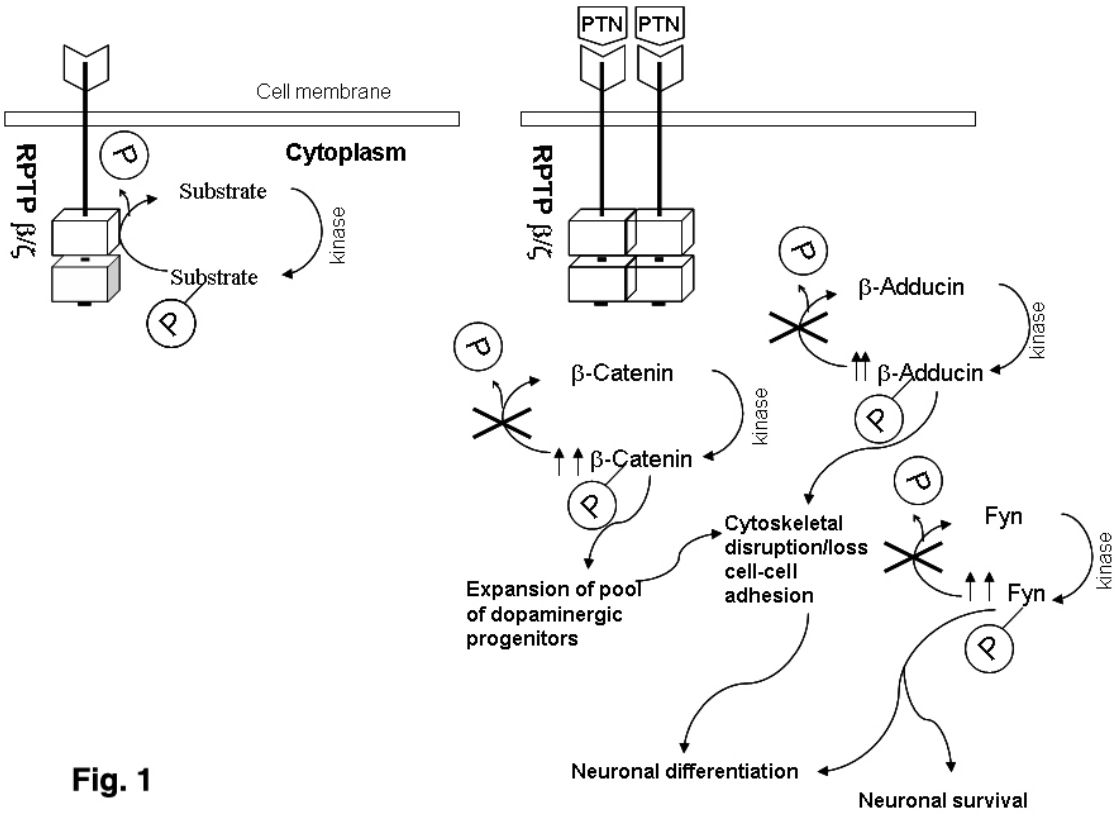

Fig. 1

Fig (1): The PTN/RPTPβ/ζ signaling pathway contributes to the proliferation of dopaminergic progenitors and survival and differentiation of dopaminergic neurons. Left side: RPTPβ/ζ is found in monomeric form in the cell membrane in the absence of PTN. In this form, RPTPβ/ζ exerts its phosphatase activity dephosphorylating its substrates 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. As a result, increases in the phosphorylation levels of the different substrates such as β-catenin, β-adducin and Fyn are observed. These substrates are known to exert critical functions on dopaminergic neurons.

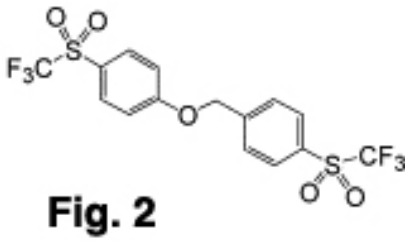

Fig. 2

Fig. (2). A trifluoromethyl sulfone (4-Trifluoromethylsulfonylbenzyl 4-trifluoromethylsulfonylphenyl ether) is the only synthesized inhibitor of RPTPβ/ζ with relative success.