Review

Protein tyrosine phosphatase 1B (PTP1B) as a potential therapeutic target for neurological disorders

Jordi Olloquequi [a,b], Amanda Cano [c,d,e,f], Elena Sanchez-López [c,d,f,g], Marina Carrasco [c,h,i,j], Ester Verdaguer [c,i,k], Ana Fortuna [l,m], Jaume Folch [c,j], Mònica Bulló [j,n,o], Carme Auladell [c,i,k], Antoni Camins [c,h,i,*,1], Miren Ettcheto [c,h,i,*,1]

[a] Department of Biochemistry and Physiology, Faculty of Pharmacy and Food Sciences, Universitat de Barcelona, Spain
[b] Institute of Biomedical Sciences, Faculty of Health Sciences, Universidad Autónoma de Chile, Talca, Chile
[c] Biomedical Research Networking Centre in Neurodegenerative Diseases (CIBERNED), Madrid, Spain
[d] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, Universitat de Barcelona, Spain
[e] Ace Alzheimer Center Barcelona – International University of Catalunya (UIC), Barcelona, Spain
[f] Institute of Nanoscience and Nanotechnology (IN2UB), Universitat de Barcelona, Barcelona, Spain
[g] Unit of Synthesis and Biomedical Applications of Peptides, IQAC-CSIC, 08034 Barcelona, Spain
[h] Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, Universitat de Barcelona, Spain
[i] Institut de Neurociències (UBNeuro), Universitat de Barcelona, Spain
[j] Department of Biochemistry and Biotechnology, Rovira i Virgili University, Spain Unit of Biochemistry and Pharmacology, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, Reus, 43201 Reus, Tarragona, Spain
[k] Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, Universitat de Barcelona, Spain
[l] Laboratory of Pharmacology, Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal
[m] CIBIT/ICNAS – Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, Coimbra, Portugal
[n] Institute of Health Pere Virgili—IISPV, Nutrition and Metabolic Disorders Research Group, 43204 Reus, Spain
[o] CIBER Physiology of Obesity and Nutrition (CIBEROBN), Carlos III Health Institute, 28029 Madrid, Spain

ARTICLE INFO

ABSTRACT

Protein tyrosine phosphatase 1B (PTP1B) is a typical member of the PTP family, considered a direct negative regulator of several receptor and receptor-associated tyrosine kinases. This widely localized enzyme has been involved in the pathophysiology of several diseases. More recently, PTP1B has attracted attention in the field of neuroscience, since its activation in brain cells can lead to schizophrenia-like behaviour deficits, anxiety-like effects, neurodegeneration, neuroinflammation and depression. Conversely, PTP1B inhibition has been shown to prevent microglial activation, thus exerting a potent anti-inflammatory effect and has also shown potential to increase the cognitive process through the stimulation of hippocampal insulin, leptin and BDNF/TrkB receptors. Notwithstanding, most research on the clinical efficacy of targeting PTP1B has been developed in the field of obesity and type 2 diabetes mellitus (TD2M). However, despite the link existing between these metabolic alterations and neurodegeneration, no clinical trials assessing the neurological advantages of PTP1B inhibition have been performed yet. Preclinical studies, though, have provided strong evidence that targeting PTP1B could allow to reach different pathophysiological mechanisms at once. herefore, specific interventions or trials should be designed to modulate PTP1B activity in brain, since it is a promising strategy to decelerate or prevent neurodegeneration in aged individuals, among other neurological diseases. The present paper fails to include all neurological conditions in which PTP1B could have a role; instead, it focuses on those which have been related to metabolic alterations and neurodegenerative processes. Moreover, only preclinical data is discussed, since clinical studies on the potential of PTP1B inhibition for treating neurological diseases are still required.

* Corresponding authors at: Biomedical Research Networking Centre in Neurodegenerative Diseases (CIBERNED), Madrid, Spain.
E-mail addresses: acano@fundacioace.org (A. Cano), camins@ub.edu (A. Camins), camins@ub.edu, mirenettcheto@ub.edu (M. Ettcheto).
[1] Both authors have contributed equally.

1. Introduction

Among the different mechanisms that cells use to control regulatory processes, protein phosphorylation and dephosphorylation stands as one of the most importants. This reversible mechanism consists of the addition or extraction of a phosphate group to various amino acids by a protein kinase (PK) or phosphatase (PP), respectively, triggering a conformational change that modulates the activity of the target protein [1].

Phosphorylation and dephosphorylation of tyrosine residues (Tyr) in proteins have been shown to play a paramount role in several cell processes such as growth, differentiation, transcription, communication, migration or survival, thus influencing physiological outcomes such as immune responses or metabolism, among others [2,3]. For that reason, disturbances in protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) activity have been linked to several pathologies, including hypertension, rheumatoid arthritis, cancer and diabetes [4,5].

In the context of signalling, the role of PTPs becomes more crucial, as their protein-protein interaction abilities come into play along with phosphatase activity [6]. PTPs belong to a large family of protein phosphatase enzymes that have been classified into four categories [1]. This classification is based on the differences in the amino acid sequence in their catalytic domains and the nucleophilic amino acid used in the catalytic reaction. Hence, classes I, II, and III are formed by cysteine based PTPs and class IV are formed by aspartate based PTPs [5–7]. Moreover, classes I-III are characterized by the presence of a catalytic domain which contains the phosphate-binding pocket, also known as "P-loop", with the signature motif cysteine-X5-arginine (where X can be any amino acid) [7,8].

The class I Cys-based PTPs is the most important family, and it can be classified into two subfamilies: classical or tyrosine-specific PTPs, which include receptor-like PTPs (PTPRs) and non-receptor-like PTPs (NRPTPs); and dual-specificity phosphatases (DUSPs), which are the most diverse group. In terms of substrate specificity, in addition to pTyr, they can dephosphorylate phosphoserine (pSer), phosphothreonine (pThr), and/or phosphoinositide (PIP), in addition to pTyr [7,8]. RPTPs contain an extracellular sequence, a transmembrane sequence and a cytoplasmic sequence that includes two tandem domains: D1 (membrane-proximal and catalytic) and D2 (membrane-distal and regulatory) [9]. By contrast, NRPTPs consist of a conservative domain responsible for dephosphorylation and another domain that modulates the activity and intracellular transport of the enzyme [9,10].

Class II Cys-based Tyr phosphatases contain a single member, the low molecular weight phosphatase (LMW-PTP), which is encoded by the ACP1 gene. LMW-PTP is involved in the modulation of various pathways, including the dephosphorylation and inactivation of various growth factor receptors (such as platelet-derived growth factor receptor and ephrin type-A receptor 2) and proteins related to cell signalling and cell migration (such as JAK, FAK, and Rho-GAP) [7–13]. Likewise, this phosphatase has been related to the control of cell growth and invasion in oncogenic processes.

Class III cysteine-based phosphatases, which are comprised of three enzymes (CDC25A, CDC25B and CDC25C) are involved in regulating cell cycle progression, as well as checkpoint pathways related to the response to DNA damage [5–9]. This process is orchestrated by the activation of cyclin-dependent kinases through the dephosphorylation of Thr14 and Tyr15 in the ATP binding loop of these kinases.

Finally, class IV PTPs include the Eya (Absent Eyes) proteins that are related to Haloacid Dehalogenases (HAD) and, as we have already mentioned, have an aspartate in the active site of the enzyme, instead of a cysteine [1–5]. A well characterized target for the Tyr phosphatase activity of EYAs is the histone H2AX [7].

In the next sections, we will focus on PTP1B, a class I phosphatase which is a widely expressed nonreceptor PTP capable of inhibiting several membrane receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR), the macrophage colony stimulating factor receptor (MCSFR), the platelet-derived growth factor receptor, the insulin receptor (IR) and the insulin-like growth factor receptor-1 [5–10]. It also inhibits the cascade of the brain-derived neurotrophic factor (BDNF)/ tropomyosin receptor kinase B (TrkB) receptor pathway, and it is involved in the regulation of the apoptotic process via activation of ERK and decrease of Smad2/ Smad3 phosphorylation [6]. The involvement of PTP1B in such a myriad of signalling pathways explains its participation in several activities in different cells, including activation of T cells, embryonic development, spermatogenesis, erythrocyte development and growth and differentiation of neuronal cells [7–11]. For the same reason, PTP1B is involved in the pathogenesis of several human diseases, including cancer, metabolic and autoimmune diseases, cardiovascular and neurological disorders [3–6]. In this regard, dysregulation of PTP1B function may be due to the loss of protein expression or its overexpression, among other factors. For instance, in most preclinical studies, increased PTP1B expression in obesity models correlates with increased PTP1B activity, thus suggesting that the regulation of PTP1B expression is a major mechanism mediating increased activity of the enzyme [10–12].

The aim of the current review is to discuss the most notable recent associations of neurological diseases with PTP1B, in addition to their potential treatment with PTP1B inhibitors. We will focus on the role of PTP1B as a link between metabolic and neurological disorders. Since there is a lack of clinical studies, we will especially focus on preclinical evidence.

2. PTP1B biology

PTP1B is a NRPTP of 435 amino acids, which is located on the cytoplasmic side of the endoplasmic reticulum of several tissues such as liver, adipose tissue, skeletal muscle and brain [11].

PTP1B shares a general similarity of 72% with the T-cell protein tyrosine phosphatase (TC-PTP), also known as protein-tyrosine phosphatase non-receptor 2 (PTPN2), with catalytic sites of both enzymes sharing 94% identity [14]. For this reason, some compounds developed to target the catalytic domain of PTP1B also resulted in the inhibition of TC-PTP, leading to significant undesirable side effects. For instance, although mice deficient in PTP1B showed better insulin sensitivity and resistance to obesity induced by a diet enriched in fatty acids (high-fat diet, HFD), deficiencies in TC-PTP function caused them to die prematurely due to increased general inflammation and severe anaemia [15–17]. Indeed, TC-PTP is mainly involved in the regulation of immune responses and bone metabolism [16,17]. However, whereas PTP1B is encoded by the PTPN1 gene, TC-PTP is encoded by the PTPN2 gene.

The regulation of PTP1B function by several chemical modifications opens interesting possibilities in biomedical research. For instance, the oxidation of PTP1B Cys215 causes significant conformational changes in the architecture of the active site that inhibit substrate binding [21]. Likewise, reactive nitrogen species (RNS) also suppress the activity of PTP1B [20]. Besides oxidation and nitrosylation, other modifications such as sumoylation, phosphorylation and proteolytic cleavage can also modulate PTP1B activity [18–22].

These biological characteristics make PTP1B an interesting therapeutic target for modulating mechanisms involved in both physiological and pathophysiological pathways.

3. Role of PTP1B in glucose metabolism and control of body weight

In physiological conditions, the binding of insulin to the insulin receptor (IR) induces conformational changes that activate the tyrosine kinase domain of the receptor in its cytoplasmic region. This leads to autophosphorylation and interaction with IR substrate (IRS) proteins 1–4 and other adaptor molecules (e.g. Grb2 and Shc) that, in turn, activate the phosphatidylinositol 3-kinase (PI3K)–AKT/protein kinase B (PKB) pathway [23,24]. Regarding glucose regulation, specifically, PI3K

activation triggered by insulin favours the process of cellular glucose uptake through an increase of cell glucose transporters 3 and 4 (GLUT3 and GLUT4) in the plasma membrane.

PTP1B activation attenuates insulin signalling through the dephosphorylation of IRS-1 and the Tyr residues 972, 1162, and 1163 of the IR, leading to the inactivation and termination of IR signalling [23]. In this manner, the activation of PTP1B negatively regulates the insulin signalling pathway and contributes to the entire process of insulin resistance. The importance of PTP1B in insulin metabolism was confirmed in studies with PTP1B knockout (KO) mice, which showed lower blood glucose and insulin levels than their wild-type (WT) littermates [25]. Likewise, PTP1B KO mice were resistant to weight gain and remained insulin-sensitive after being subjected to a chronic hypercaloric diet. After insulin injection, PTP1B KO mice showed increased IR phosphorylation in the liver, demonstrating that PTP1B is a key regulator of insulin signalling [25,26].

In addition to the direct effect of PTP1B on insulin signalling, this phosphatase is also involved in the regulation of body weight by regulating leptin signalling. Leptin is a 16 kDa peptide hormone produced by the ob gene [27]. It has a key role in the process of regulating food intake through specific receptors in the hypothalamus involved in appetite decrease [28,29]. Indeed, leptin levels increase after food intake, acting as a signal of satiety, whereas food restriction or fasting results in a decrease in leptin [30]. In addition, leptin also increases energy expenditure, by acting on the cardiovascular system and enhancing thermogenesis in brown adipose tissue [31]. It also has a key role in controlling the content of body fat, since it is mainly found in white adipose tissue [27–29]. Studies in PTP1B KO mice demonstrated that PTP1B attenuates leptin signalling. In this animal model, PTP1B is capable of dephosphorylating janus kinase 2 (JAK2), a known downstream effector of the leptin receptor, resulting in an inhibition of the synthesis of neuropeptide Y, an appetite-stimulating hormone [32]. In this line, Kaszubska et al. showed that overexpression of PTP1B dampened leptin receptor signalling in a hypothalamic cell line [33]. Moreover, global deletion of PTP1B in mice results in thinness, leptin hypersensitivity and obesity resistance [34].

All these results point to the fact that the pharmacological inhibition of PTP1B could have a fundamental role in the regulation of metabolism, the food intake and obesity.

4. Relevance of PTP1B in the brain

Another important pathway in which PTP1B has been involved is the BDNF / TrkB pathway [35]. BDNF is the most abundant neurotrophin in the CNS, and preclinical studies suggest that increasing its levels is a suitable strategy to enhance the cognitive process [36]. After binding to its receptor, BDNF carries out key functions related to neuronal survival, axonal synaptic structure and plasticity, neurotransmission, induction, and maintenance of long-term potentiation (LTP) and the regulation of dendritic spine numbers and morphology [37]. In this regard, some experimental studies aimed to increase the cognitive process by increasing the levels of BDNF [38]. This could be achieved by transplanting stem cells in mice models of AD, for instance, or through the administration of a gene therapy construct that can maintain the BDNF / TrkB signalling pathway [39].

Interestingly, it has been reported that PTP1B overexpression reduces TrkB phosphorylation and, as a result, it also reduces the activation of downstream signalling pathways, such as those of the central BDNF. By contrast, PTP1B inhibition enhances TrkB signalling and improves memory in mice, which supports a role of PTP1B in neuronal survival, morphogenesis and plasticity [40]. Deepening at the molecular level, the pathways activated by BDNF / TrkB in the LTP process include the Rho GTPase Rac1 proteins, as well as RhoA and Cdc42, which are involved in the regulation of the actin cytoskeleton of dendritic spines and, therefore, in their structural and functional plasticity [41]. Hence, we could hypothesize that TrkB receptor modulation by PTP1B

facilitates the physiological actions of BDNF in the hippocampus through Rac1 activation. Indeed, Rac1 acts through a cascade of serine / threonine-protein kinase PAK1-LIM kinase of domain 1 (LIMK1) to phosphorylate and inhibit cofilin, and to block its separation from actin, hence facilitating the cognitive process [42]. Accordingly, although several compounds acting as agonists of the BDNF / TrkB receptor have been developed, activating the receptor by pharmacological inhibition of PTP1B may also be a good strategy to increase or modulate the cognitive process in neurological disorders [43,44].

Taken together, these results suggest that brain PTP1B inhibition could enhance BDNF functions, leading to a cognitive improvement.

5. Neurodegeneration and insulin resistance

As already mentioned, insulin and leptin are peptide hormones classically associated with metabolic control and energy balance of the human body through hypothalamic regulation. However, they are also significantly involved in the process of cognition, mainly at the hippocampus [45–47]. For this reason, the potential connection between diabetes, obesity and cognitive decline have been intensively studied since the end of the last century. Hence, some studies have demonstrated a key role of hippocampal insulin and leptin receptors alterations in cognitive decline [48,49]. Moreover, previous studies by Ott et al. indicated that type 2 diabetes mellitus (T2DM) patients are more susceptible to cognitive impairment, possibly due to alterations in the structure and functions of brain [50]. In turn, a magnetic resonance imaging (MRI) study performed by Moran and colleagues demonstrated an association between T2DM and a regional cerebral atrophy with deterioration in cognitive function [51].

5.1. The link between cognitive loss in Alzheimer's disease and diabesity

AD is responsible for approximately 60–80% of dementia cases. It is characterized by a progressive neurodegeneration caused by the death of neurons in some brain areas, such as the hippocampus and surrounding para-hippocampal regions. Moreover, in the affected areas, there are production and extracellular deposition of the β-amyloid peptide (Aβ), together with an accumulation of the micro tubule-associated protein tau, which becomes abnormally phosphorylated and forms intracellular inclusions throughout the brain [52]. According to its aetiology and progression, there are two different forms of AD: the early-onset AD (EOAD) and the idiopathic late-onset AD (LOAD). EOAD is the least common (5% of cases) and it is also known as familial AD (FAD); it may be inherited and is associated with mutations in the amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN and 2) genes. Conversely, LOAD constitutes over 95% of all AD cases and has a complex aetiology, having been associated to many different risk factors. Among them, the apolipoprotein E (APOE) ε4 allele constitutes the main gene associated with LOAD, as multiple genetic studies have consistently reported [53]. Due to its high prevalence and the fact that currently there is no effective treatment to stop or delay its course, in this review we will focus more specifically on LOAD.

The onset of LOAD has been associated with several risk factors, including the aging process, midlife hypertension, neuroinflammation, insomnia (which would be associated with a decrease in the elimination of amyloid) and metabolic factors such as obesity and T2DM, which, collectively, have been called "diabesity" [54–56]. Regarding the last one, the idea that AD should be considered a "whole-organism disease" instead of being restricted to the brain is gaining attention. Accordingly, AD could be originated in other peripheral tissues that can generate an inflammatory response, such as the gastrointestinal tract [56–58]. In this sense, although the exact molecular mechanisms by which the obesity-associated insulin resistance process occurs are not fully understood, several hypotheses have been proposed. Among them, an increase in plasma levels of circulating pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, alterations in adipokines (such as

leptin, resistin, adiponectin), glucotoxicity mediated by reactive oxygen species and lipotoxicity resulting from increased circulating levels of non-esterified fatty acids, could lead to impaired insulin signalling and hence to insulin resistance [55–59].

Importantly, it has been widely demonstrated that the physiological actions of insulin are not limited to the peripheral tissue but are also fundamental in the brain [60]. Indeed, it has been shown that the activation of the hippocampal insulin receptor is necessary for the processes of neuronal synaptic plasticity, learning and memory [63–68]. Hence, several authors have demonstrated the synaptic localization of the insulin receptor in the hippocampus, which could explain the role of insulin in promoting the formation of synapses, dendritic spines, LTP and the involvement of this receptor in neuroprotection processes [60, 66–69]. Likewise, the inhibition of the brain insulin receptor favours the increase in Aβ levels and the phosphorylation of tau [68]. In this sense, Grillo et al. reported that the intrahippocampal administration of a lentiviral vector that expresses an IR antisense sequence (LV-IRAS) induces a deficit of synaptic transmission, associated with alterations in LTP and in the expression and phosphorylation of the glutamate receptor, which could impair the hippocampal learning process [67]. At a molecular level, insulin activates the PI3K / Akt / mTOR signalling pathway, which, in turn, promotes dendritic spine formation through the regulation of Ras-related C3 botulinum toxin substrate 1 (Rac1) [66]. These suggest that insulin resistance in the brain could be associated to and be partially responsible for cognitive alterations in AD [60–64,66–71]. Regarding glucose regulation, specifically, PI3K activation triggered by insulin favours the process of cellular glucose uptake through an increase of cell glucose transporters 3 and 4 (GLUT3 and GLUT4) in the plasma membrane. These transporters are essential to increase glucose availability in neurons during the cognitive process [72]. Likewise, leptin, has also an important role in neuronal development and the cognitive process. In this regard, Li and colleagues demonstrated that leptin receptors deficient rodents (Zucker fatty rats and db / db mice) exhibited alterations in the process of LTP and long-term depression (LTD) in the hippocampal CA1 region, which affected memory and learning [73]. These results were the first to suggest a key role for leptin receptors in the cognitive process, especially those in the hippocampus and the cerebral cortex. Furthermore, studies by Morrison and colleagues demonstrated that leptin participates in neurogenesis, synaptogenesis and in regulating dendritic morphology [74]. In addition, Greco and colleagues reported that leptin plays an important neuroprotective role against Aβ and tau hyperphosphorylation, in addition to modulate BACE1 activity [75]. In this line, Bonda et al. reported an alteration in leptin signalling in the hippocampus of AD patients [76]. Considering all these results, an increase in leptin signalling may be a suitable strategy to restore or improve the cognitive process in AD.

Collectively, the above-mentioned data has contributed to accept the existence of a clear link between metabolic alterations and neurodegeneration. Hence, molecular targets involved in both processes should be studied in deep in order to find effective treatments.

5.2. Potential of PTP1B in the treatment of diabesity-associated cognitive loss

Given the existent connection between LOAD and diabesity, drugs used in the treatment of T2DM may have a beneficial effect on LOAD. As above-explained, PTP1B has a key role in the phosphorylation of the IR, IRS and JAK2, hence modulating insulin and leptin pathways. Consequently, the initial interest in PTP1B was explained by its key role in the regulation of receptors that play important functions related to metabolic processes, diabetes, and obesity. Indeed, preclinical studies showed that mice with a genetic deletion of PTP1B were resistant to weight gain and remained sensitive to insulin after treatment with a HFD [77,78]. It is important to note that rodents under a HFD have been widely used as a model of obesity-induced peripheral and central insulin resistance. Likewise, the role of a HFD as a risk factor in AD has been much investigated, and this preclinical model are very useful to study the molecular pathways involved in the alterations of the cognitive process [55–58].

The pro-inflammatory effect of a HFD in brain is well known, and there is an increasing interest in unveiling the molecular pathways involved in the hippocampal neuroinflammatory process associated with an excessive consumption of saturated fatty acids [79–81]. In this sense, Nakandakari et al. reported that the consumption of HFD caused a neuroinflammatory process in mice hippocampus with a significant increase in TNFα, IL1β, pIKK and PTP1B, which would be responsible for the induction of the classic markers of AD pathogenesis (Aβ and p-tau) [82]. Besides, HFD also generates endoplasmic reticulum stress associated with the unfolded protein response (peIF2α and CHOP) and apoptosis, evidencing the adverse effects of HFD consumption on the hippocampus [82]. In addition, it has been suggested that the HFD-associated increase in PTP1B could inhibit the phosphorylation of STAT3 and favour the activation of the microglia. Moreover, in mice with PTP1B deficiency, the hypothalamic inflammatory response provoked by a HFD becomes attenuated through the activation of the JAK2-STAT3 signalling pathway in microglial cells [83]. Inhibition of PTP1B also proved to be effective to prevent memory loss in rats treated with a high-glucose-fat diet plus STZ injection to generate a T2DM [84]. In this respect, Wang and colleagues studied the neuroprotective effects of ferulic acid on cognitive deficits in this preclinical diabetic model and suggested that this compound could prevent the appearance of AD [85]. They showed that the administration of ferulic acid in diabetic rats could exert a neuroprotective effect through the reduction in the expression on PTP1B, thus causing an activation of the insulin signalling pathway in the brain. In addition, they observed a decrease in the levels of accumulation of Aβ and p-tau in the brain, leading to an improvement in learning and memory functions. They also found a decrease in the levels of cytokines associated with the neuroinflammatory process. Finally, Wu and colleagues have shown that ferulic acid was able to significantly inhibit the activity of the PTP1B enzyme in the liver [86].

On another front, previous studies have shown that BDNF plays a key role in the regulation of synaptic plasticity [87]. By binding to its TrkB receptor, BDNF modulates synaptic structure to generate LTP, hence participating in memory and learning processes [88]. In fact, it has been shown that BDNF levels are reduced in AD brains and preclinical disease stages [89–91]. Therefore, stimulation of BDNF signalling can be a suitable therapeutic strategy for AD. In this sense, a treatment with the synthetic derivative of the oleanolic acid, bardoxolone methyl (BM), improved the cognitive process in mice under a HFD through an increase in BDNF levels and the TrkB signalling [74]. Likewise, the authors detected an increase in p-AMPK and a decrease in PTP1B expression in the prefrontal cortex and in the hippocampus after the BM treatment, as well as an improvement in the activation of NMDA receptors and the neuroinflammatory process. Accordingly, the authors concluded that a decrease in PTP1B protein expression associated with an increase in BDNF protein levels and TrkB activation may be key in improving synaptic plasticity of neurons in the hippocampus and prefrontal cortex [92].

It is well known that hypothalamic inflammation plays a fundamental role in the pathology of obesity, inducing resistance to leptin at the CNS by activating the negative regulators of leptin signalling, SOCS and PTP1B [93–97]. Indeed, Mendes and colleagues reported that knocking down PTP1B with antisense oligonucleotides in the central nucleus of the amygdala alter food intake in rats [97].

In this sense, it has been shown that the therapeutic effect of ginsenoside Rb1 improved the inflammatory response associated with obesity, the target being the inhibition of PTP1B and, possibly, also SOCS3 in the hypothalamus of obese mice [98]. In addition, related to the neuroinflammatory process, Song et al. have shown that the expression of PTP1B is regulated by inflammatory stimuli such as the intracerebral administration of lipopolysaccharide (LPS), which

promotes a substantial increase in brain cytokines that impair synaptic plasticity, including TNFα [99,100]. Likewise, PTP1B overexpression causes microglial activation associated with increased gene expression of the pro-inflammatory markers TNF-α, iNOS, and IL-6. Consequently, the study suggests that a PTP1B inhibitor could regulate the neuro-inflammatory process and constitute a new strategy in the treatment of neuroinflammatory processes and neurodegenerative diseases [93–95].

PTP1B presents a localization associated with the endoplasmic reticulum (ER) and other intracellular membranes via a hydrophobic interaction of its C-terminal 35 amino acids [101–103]. The ER plays a fundamental role in protein biosynthesis and folding, lipid biosynthesis and cellular calcium storage. Interestingly, it has been shown that PTP1B is involved in ER homeostasis by regulating the unfolded protein response (UPR) [102]. Under physiological conditions, the ER is involved in the synthesis of proteins with an appropriate tertiary conformation [104–107]. However, under pathological conditions, there may be alterations in the folding capacity of ER proteins, which become misfolded, cannot access the Golgi apparatus, and accumulate within the ER lumen generating ER stress [104–106]. UPR depends on three stress sensors, inositol-requiring protein 1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK) and activating transcription factor 6 (ATF6) [105,106]. These sensors transduce information about the folding status of the ER to the cytosol and nucleus to restore protein-folding capacity [104–109]. Importantly, several research studies have reported that alterations in the UPR play a prominent role in the pathogenesis of neurodegenerative disorders [105–107]. Indeed, the activation of IRE1α triggers the translocation of the binding protein 1 (XBP1) from the dendrites to the nucleus [107]. After that, XBP1s enhances the transcription of genes encoding for BDNF, which can then be localized extracellularly and activate the TrkB receptor. Therefore, the expression of target genes involved in synaptic plasticity and memory is promoted. In turn, PERK phosphorylates the α subunit of eukaryotic translation initiation factor 2 (eIF2α), which plays a prominent role in the learning and memory process [108]. In this case, phosphorylation of eIF2α leads to global attenuation of translation and selective expression of ATF4, which represses the element-binding protein that responds to cAMP (CREB) and inhibits the expression of genes involved in synaptic plasticity and memory [105]. ATF4 also regulates apoptosis through a complex process of expression of proteins of the BCL-2 or BH3-only family, including NOXA, BIM, PUMA and others [105–108]. Hence, although UPR is activated to prevent the accumulation of misfolded proteins in the ER lumen, a persistent or severe ER stress induces apoptosis and neuronal death [109]. Finally, when ATF6 is activated in the cytosol, it translocates to the nucleus and activates the transcription of UPR target genes encoding factors involved in amino acid biosynthesis, the antioxidative response, autophagy and apoptosis [110].

Previous studies have shown a key role of the involvement of PTP1B in the regulation of ER stress signalling [102–104]. In the liver, PTP1B deficiency prevents the ER stress induced by HFD [111]. In turn, Jeon and colleagues demonstrated that PTP1B inhibition attenuates ER neuronal stress toxicity in SH-SY5Y neuroblastoma cells [112]. Furthermore, the authors demonstrated that PTP1B inhibition in SH SY5Y cells also protects against rotenone and MG132-induced cell death and prevents eIF2 phosphorylation [112]. Tunicamycin induces ER stress as it inhibits the glycosylation of newly synthesized proteins within the ER, which causes the interruption of the proper folding of proteins in endothelial and neuronal cells [113,114]. Interestingly, the effects of tunicamycin on insulin resistance mediated by ER stress were attenuated when silencing PTP1B [114].

Another very interesting point is that, after anaesthesia with sevo-flurane, memory alterations can occur due to multiple processes, including neuroinflammation and alteration of synaptic plasticity. These could be mediated by the UPR associated with the activation of PTP1B [115]. Hence, in a murine study by Liu et al., the results showed that the inhibition of PTP1B reduces the activation of the UPR and

neuroinflammation caused by sevoflurane, hence protecting against cognitive deterioration [115]. Consequently, the authors suggested that the inhibition of PTP1B could be a therapeutic strategy against cognitive dysfunction caused by general anaesthetics.

Besides its involvement in ER function, PTP1B also seems to play a role in mitochondria. Indeed, PTP1B regulates SRC and plays an important role in modulating the enzymatic activity of OxPhos complexes in brains of rodents [116,117]. In this sense, Lyu et al. showed that, after LPS-induced sepsis, both PTP1B and Src are involved in the decrease of mitochondrial protein tyrosine phosphorylation. Authors concluded that Src/PTP1B pathway induced changes in brain energy metabolism resulting from mitochondrial dysfunction in rats [118].

Bearing in mind all the above-explained, we can highlight at least five pathways modulated by PTP1B in the brain that can affect the cognitive process (Fig. 1): i) activation of the glia, especially the microglia, ii) increase in endoplasmic reticulum stress and mitochondrial dysfunction, iii) alteration of the BDNF / TrkB pathway, iv) alteration of the hippocampal insulin receptor and v) alteration of the leptin receptor.

6. PTP1B inhibitors

Fuelled by the worldwide increase in the prevalence of obesity and diabetes, the establishment of PTP1B as a therapeutic target for these metabolic syndromes prompted studies of small inhibitors of PTP1B by pharmaceutical companies and academic laboratories. However, as we have mentioned, inhibiting PTP1B may also have a beneficial effect in AD and related neurological disorders associated with cognitive loss. In recent years, many studies on the synthesis and development of new PTP1B inhibitors have been published. However, very few PTP1B inhibitors have been tested in clinical studies so far. In the present section, we aim to provide information on the inhibitors that are in clinical trials. Hence, not all synthesized PTP1B inhibitors are discussed.

The first point to note is the urge for developing highly selective PTP1B inhibitors that allow to avoid possible undesirable effects. Accordingly, the first PTP1B inhibitor with a potential application for the treatment of AD was trodusquemine (MSI-1436), a compound present in the liver of *Squalus acanthia*, a dogfish shark [119–121]. This compound targets the C-terminal region of PTP1B with a very high selectivity, and it does so in a reversible and non-competitive manner. Thus, Krishnan and colleagues reported that trodusquemine was effective in inhibiting the activity of PTP1B by binding to the intrinsically disordered C-terminal end of PTP1B, demonstrating that it acts allosterically and does not lead to aggregation of PTP1B nor causes undesired side effects [122–124]. At the preclinical level, trodusquemine showed high efficiency in mice with HFD-induced obesity, which showed a significant reduction in fat and insulin levels [125,126]. Besides, this drug was able to cross the blood–brain barrier (BBB) and significantly increased the insulin-stimulated Tyr phosphorylation of IR and STAT3 in the murine hypothalamic tissues.

In addition to PTP1B inhibition, trodusquemine has been reported to prevent the toxicity of isolated or stabilized oligomers composed of 40 residues of Aβ40 and Aβ42 [127–130]. The proposed mechanism is based on the displacement of the oligomer from the cell membrane, in addition to its ability to modulate the kinetics of its assembly [127,128, 130]. Both the inhibition of Aβ42 aggregation and the acceleration of Aβ42 fibril formation can reduce the toxicity of the oligomer by decreasing the number of toxic species produced over time. Therefore, trodusquemine appears to be effective in lowering the concentration of both cytotoxic protein aggregates and membrane displacement seems an effective strategy to combat multiple protein misfolding diseases [127].

Due to the promising results of trodusquemine, other derivatives such as claramine were developed, which has similar pharmacological effects with the additional advantage of being easier to synthesize [131]. Likewise, the trodusquemine analogue DPM-1001 is also a potent selective inhibitor of PTP1B with the advantage of high oral
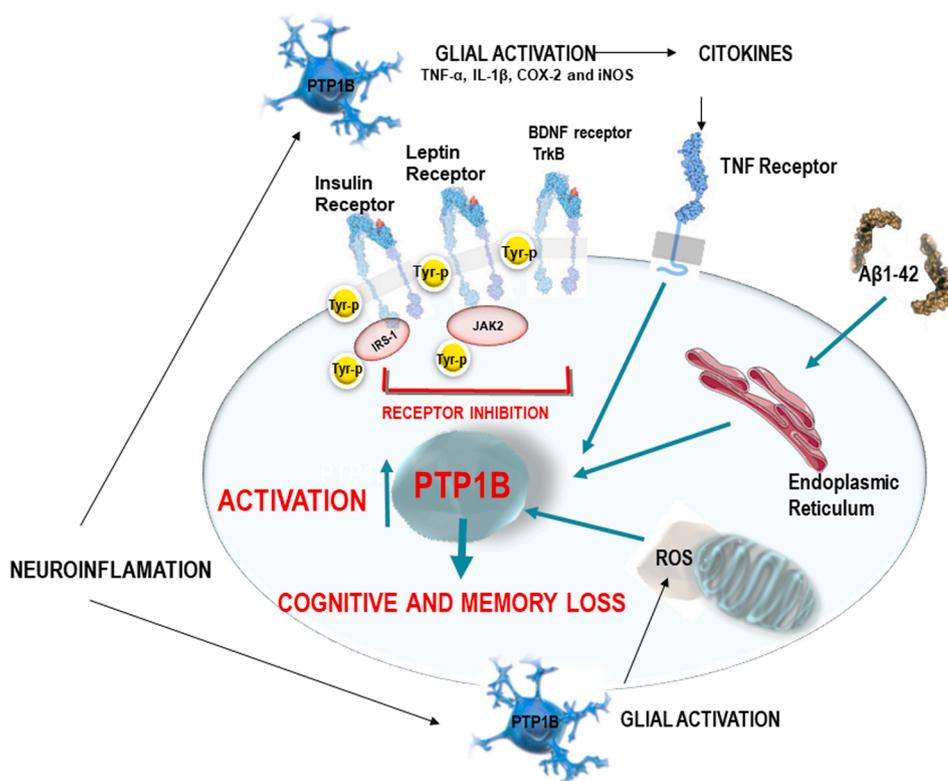
Fig. 1. Pathophysiological mechanisms associated with PTP1B activation. PTP1B regulates multiple mechanisms implicated in the pathogenesis of neurological diseases. In microglia, PTP1B is a positive regulator of neuroinflammation, and it is involved in the release and modulation of proinflammatory mediators, such as TNF-α, IL-1β, COX-2 and inducible nitric oxide synthase (iNOS). In neurons, PTP1B is upregulated by endoplasmic reticulum (ER) stress, a cellular response activated by amyloid-β oligomers in AD. Increased PTP1B levels inhibit pathways related to memory and cognitive processes. PTP1B acts on different enzymes that have been implicated in neurological diseases, including the insulin receptor and its substrate IRS-1, the leptin receptor, and its immediate downstream effector Janus kinase 2 (JAK2), and the BDNF receptor TrkB.

bioavailability, hence overcoming the low absorption through the oral route of trodusquemine [132,133]. Despite the development of all these compounds, very few are currently in the clinical phase [134]. Notwithstanding, trodusquemine has been investigated in recent years in completed Phase I clinical trials for the treatment of obesity and diabetes (https://clinicaltrials.gov/ ID NCT00509132, NCT00606112, NCT00806338, Genaera Corporation) and in the treatment of breast cancer (NCT02524951) [132–134].

In addition to trodusquemine, other inhibitors of natural origin have been identified. For example, ursolic acid (UA), which is a member of the ursan family of pentacyclic triterpenoids, is a non-selective competitive inhibitor of PTP1B, since it also inhibits other phosphatases such as TCPTP and SHP2 [135]. Taking advantage of the beneficial effects of UA, more powerful, specific, and effective antidiabetic derivatives have been developed. For instance, UA0713 is a high potent novel derivative which have shown to improve glucose transport in different cellular models, hence suggesting a potential application in insulin resistance and associated neurological disorders [135]. Norethyrriol is another natural product isolated from plants such as *Hypericum elegans* and *Tripterospermum lanceolatum*. Although this compound inhibits PTP1B with low affinity, an attempt was made to develop more potent derivative compounds, which allowed the development of XWJ24, a much more potent PTP1B inhibitor than norethyrriol. Thus, XWJ24 is a competitive and selective inhibitor of PTP1B as it is 4.5 times more selective for PTP1B than for TC-PTP [136].

Hussain et al. recently reviewed the PTP1B inhibitors synthesized the last years [119]. Among them, ertiprotafib constitutes an example of the difficulty to identify selective, safe, and effective PTP1B inhibitors. Unlike trodusquemine, ertiprotafib was shown to induce oligomerization / aggregation of PTP1B and exhibited a poor specificity, since it also binds and activates PPAR α and γ receptors. Although this could explain its antidiabetic properties, ertiprotafib was withdrawn from phase II clinical trials for dose-limiting adverse effects observed in some patients [137,138]. In turn, Swarbrick et al. proposed another strategy of PTP1B inhibition through genetic selection of PTP1B. Therefore, they used

antisense oligonucleotides (ISIS 113715) in monkeys. Interestingly, ISIS 113715 significantly improved insulin sensitivity and caused an increase in adiponectin levels [139]. This compound has completed phase II clinical trials (NCT00330330) for potential application in the treatment of diabetes.

Despite these efforts, none of the available inhibitors has made their way through to the clinical trials yet. In this sense, several identified synthetic small molecules can pave the way towards developing more efficient and improved inhibitors. Such molecules include the PTP1B inhibitor difluoromethylene phosphonates, a heterocyclic carboxylic acid and vanadate-based phosphotyrosine mimetics [121].

7. PTP1B as a therapeutic target in neurological diseases

7.1. Role of PTP1B in Alzheimer's disease

The fight against the LOAD process has basically focused on trying to eliminate beta amyloid and reducing tau levels in the brain. In this regard, the first treatment to attack the process that causes AD has been recently introduced. Hence, a monthly intravenous infusion of aducanumab, a monoclonal antibody directed against the amyloid beta protein, reduces amyloid beta plaque, which could slow cognitive decline in AD patients [140]. However, more studies on this drug are being evaluated, as there is still much controversy about its efficacy in treating dementia.

On another front, sodium oligomannate, which has been conditionally approved in China for the treatment of LOAD, seems to act mainly by regulating amino acid metabolism at the level of the intestinal microbiota, mainly affecting the decrease in phenylalanine levels and isoleucine [141]. The final effect of this drug would be a decrease in the activation process of the cerebral microglia and, therefore, decreasing the neuroinflammatory response in LOAD [142].

In addition to amyloid and neuroinflammation, it must be noted that the accumulation of tau protein in the brain at the molecular level has a role in neural degeneration and cognitive impairment in AD [140].

However, effective, or disease-modifying drugs for AD are still lacking today. Clinical trials targeting these events are under evaluation [140]. Despite these advances, AD still requires efficient treatments that will be able to delay the disease.

The first approach to a potential involvement or relevance of PTP1B in AD was indirectly reported by Leuba et al. in 2004. Through immunocytochemistry, they found a decreased expression of LMO4, an endogenous inhibitor of PTP1B, in the entorhinal cortex and in the hippocampal region CA1 of AD patients, whereas the control group exhibited high LMO4 levels [143]. Moreover, the authors showed a correlation between the decrease in LMO4 and the number of neurofibrillary tangles (NFT) in the degenerate neurons, as well as in the deposition of senile plaques. Despite this study did not assess the expression of PTP1B, its results are relevant because a decreased expression of a PTP1B inhibitor in brains of AD patients suggests a potential dysregulation of the PTP1B signal pathway.

As we have explained, PTP1B is also involved in the process of cell plasticity. In this sense, Zhang et al. showed that aberrant activation of PTP1B correlated with dephosphorylation and inactivation at the pre-synaptic level of NMDA receptors in neurons from hAPP-J20 mice [144]. This led to an alteration in the modulation of synaptic plasticity. Given that spatial learning and memory depend on NMDA receptors in the hippocampus at CA3 CA1 synapses, PTP1B could orchestrate alterations in these outcomes. Moreover, when PTP1B was inhibited with trodusquemine, these cognitive alterations were restored in mice, evidencing the key role of this phosphatase in the regulation of cognitive processes in AD. Regarding to this synaptic effects, Fuentes and colleagues reported that PTP1B is linked to the hippocampal synapses, specifically in dendritic spines, where it co-localizes with synapsin-1, a protein implicated in synaptogenesis and the modulation of

Table 1
PTP1B inhibitors with experimental evidence.

Row	Reference	Disease model	Drug	Drug dose	Duration of therapy	Main findings
1	[151]	APPswe/ PS1dE9	Bis(ethylmaltolato) oxidovanadium (IV)	0.2 and 1.0 mmol/L	3 months	Reduced Aβ production and inhibit BACE1 expression. Inhibiting PTP1B decrease tau hyperphosphorylation possibly by expression and regulating the IR/IRS-1/PI3K/Akt/GSK3β pathway.
2	[150]	3 ×Tg-AD	Bis(ethylmaltolato) oxidovanadium (IV)	0.2 and 1.0 mmol/L	3 month	Significantly improved contextual memory and spatial learning, increased brain glucose metabolism, reduced Aβ plaques and neuronal impairment, and decreased tau hyperphosphorylation in AD mice.
3	[153]	hAPP-J20	Trodusquemine	5 mg/kg (every 5d)	1 month	Inhibition of PTP1B or PTP1B ablation in neurons ameliorate spatial learning and memory and prevent hippocampal neuron loss.
4	[85]	High Fat diet male Sprague-Dawley (SD) rats	Ferulic acid	15 or 30 mg/kg	4 weeks	Ferulic acid could improve High fat diet-induced cognition impairment through the inhibition of PTP1B. Attenuated brain inflammation and prevented the AD neuropathology in brain diabetic rats
5	[154]	5xFAD	8-[2-(2-Pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA)	1 mg/kg	7 days	DCP-LA suppresses Aβ-induced GSK-3β activation and Tau phosphorylation due to PKCε activation and to PTP1B inhibition.
6	[84]	ICV streprozotocin treated male Wistar rats	Alendronate	3 mg/kg/day, p.o	28 days	Alendronate improved behavioural deficits, through the PTP1B inhibition and improved brain of insulin signalling pathway.
7	[157]	Intraperitoneal ketamine treatment 10, 50 or 100 mg/kg, male mice	Trodusquemine	5 mg/kg	10 days	Trodusquemine prevent ketamine-induced deficits in working memory, sensorimotor gating and hyperlocomotion. The study suggested that PTP1B inhibitors could be novel antpsychotic agents.
8	[168]	Rat cerebral ischemia/ reperfusion	sc-222227	(5 and 10 μM) was injected ICV	1 days	sc-222227, reduced cerebral IR injury, prevented microglial activation and subsequent neuroinflammation by modulating the ER stress-autophagy axis via PERK signaling in microglia.
9	[166]	Transient middle cerebral artery occlusion	KY-226	10 mg/kg	2 h after transient middle cerebral artery occlusion	KY-226 increases the phosphorylation of Akt in ischemic conditions. Phosphorylation of FoxO1, dependent on Akt activation (pAkt), prevents FoxO1 localization in the nucleus, leading to the transcription of ZO-1
11	[112]	Rotenone and tunicamycin in cell cultures	PTP1B (CAS-765317–72–4) inhibitor	concentrations ranging from 5 to 20 μM		PTP1B inhibition attenuates ER stress via mitochondria-independent mechanisms in neuronal cells.
12	[118]	LPS- i.p. at a dose of 5 mg/ kg induced neuroinflammation	PTP1Bi	was administered intracerebroventricularly (i. c.v.)		Inhibition of PTP1B activity provides a therapeutic strategy for neuroinflammatory and neurodegenerative diseases.
13	[174]	*Mecp2*-mutant mice (Rett syndrome)	CPT157633 and UA0713	(5 mg/kg)		Increased tyrosine phosphorylation of TRKB in the brain, which would augment BDNF signaling. This study presents PTP1B as a mechanism-based therapeutic target for RTT
14	[161]	LMO4 deficient mice	Trodusquemine	5 mg/kg, i.p.		Trodusquemine could restore TrkB signaling and ameliorate the schizophrenia-related deficits in LMO4-deficient mice

neurotransmitter release [145]. They also reported that PTP1B is involved in spine maturation and synapse formation through the regulation of N-cadherin. Thus, the hippocampal disruption of PTP1B leads to an elongation of dendrites and to an improvement in learning and memory processes [145]. Finally, mice with a genetic PTP1B deficiency show alterations that affect the morphology of the spines, resulting in an impairment of the synaptic structures. All these results underpin the need for more research on the role of PTP1B in neural plasticity.

Regarding the link between AD and metabolism, it is noteworthy that APPSwe/PS1dE9 mice are susceptible to an increase in body weight induced by a HFD associated with insulin resistance [146]. These metabolic effects are also associated with a significant increase in brain levels of PTP1B, a decrease in Akt activity and activation of GSK3 that favours alterations in the brain insulin pathway [146]. These preclinical results suggest that a diet rich in fat may worsen the development of AD, the increase in body weight being a risk factor. In this sense, King and colleagues reported a significant increase in the mRNA expression of PTP1B that altered the leptin receptor pathway in the hippocampus of APPSwe/PS1dE9 and control mice, especially in aged animals [147]. It is conceivable that the increase in the expression of PTP1B is involved in a resistance to leptin that could be associated with a significant increase in the production of Aβ related to the aging process. Thus, this study suggests a relation among PTP1B pathway, brain leptin resistance and cognitive impairment. In the same line, Kuga et al. reported a significant age-related increase in the hippocampal PTP1B protein levels in rats [148]. PTP1B overexpression was associated with a cognitive loss, probably due to a reduction in the insulin/BDNF signalling in the hippocampus [148].

Other authors assessed the preclinical effects of vanadium compounds, which were described as the first competitive inhibitors of PTP1B, although they are not specific. In particular, Bis(ethylmaltolato) oxidovanadium (IV) (BEOV), which has been reported to have hypoglycemic properties, was given to APPSwe/PS1dE9 mice (Table 1). He and colleagues reported that a treatment with BEOV for 3 months significantly decreased Aβ levels PPARγ and IDE activation, as well as by inhibition of BACE1 activity in 6-month-old APPSwe/PS1dE9 [149–151]. BEOV also decreased the expression of PTP1B, which induced the activation of the insulin pathway IRS-1/PI3K/Akt, hence inhibiting GSK3β and leading to a reduction in tau hyperphosphorylation [149–151]. In addition, authors reported that BEOV was involved in the modulation of the autophagic process that increased the clearance of Aβ aggregates [149]. The same group also provided evidence about the efficacy of an antidiabetic compound such as BEOV in the 3Tg-AD preclinical model. Therefore, BEOV constitutes an example of a multitarget drug that could act on the neuropathology of AD, by increasing cerebral glucose uptake and by improving synaptic connections and cognition in mice.

On another front, Kumar et al. reported that sodium orthovanadate was effective in improving the cognitive deterioration caused by hyperhomocysteinemia-associated vascular dementia in rodents, probably through the PTP1B inhibition [152] (Table 1). This compound could also improve oxidative stress parameters and cholinergic function, which play a key role in the process of learning and memory. In turn, Ricke and colleagues reported a neuroprotective effect of trodusquemine in a transgenic AD mice model with Aβ pathology (hAPP-J20 mice) [153]. In this preclinical study, the authors demonstrated that neuronal PTP1B is a key player in the appearance of spatial memory deficits and neurodegeneration in the hAPP-J20 mice. Furthermore, the authors also demonstrated that the selective pharmacological inhibition and the ablation of neuronal PTP1B was sufficient to improve the memory deficits and to prevent the loss of hippocampal neurons. This neuroprotective effect was associated with the modulation and inhibition of brain GSK3β, which is regulated by the brain insulin receptor. Moreover, while trodusquemine was able to reverse the neuroinflammatory process in hAPP-J20 mice, neuronal inhibition of PTP1B was not effective in this process. Notwithstanding, neuronal ablation of PTP1B decreased

the size of the hippocampal Aβ plaques without affecting brain Aβ protein levels [153].

In turn, Kanno and colleagues reported that DCP-LA has neuroprotective effects through both inhibition of PTP1B and activation of PKC isozyme PKCε [154] (Table 1). This compound improved spatial learning and memory impairment in 5xFAD mice through GSK-3β inhibition, tau phosphorylation and activation of insulin receptor / Akt pathway mediated by PTP1B. Authors proposed that the dual inhibition of both targets is a suitable therapeutic strategy for AD.

Finally, Bansal and colleagues reported that alendronate, an inhibitor of alkaline phosphatase in bone used in the treatment of osteoporosis, is also a PTP1B inhibitor with a promising neuroprotective effect in the streptozotocin model of AD [84]. In this preclinical model, the intracerebroventricular (ICV) administration of streptozotocin in rats caused an increase in the activity of brain PTP1B, induced cognitive deficits associated with alterations in insulin signalling, decreased PI3-k/Akt and BDNF/TrkB signalling, increased neuroinflammatory markers and the activity of acetylcholinesterase. Interestingly, the inhibition of PTP1B by alendronate improved the cognitive process and normalized the brain insulin-signalling pathway at the molecular level, confirming the efficacy of inhibitors of this enzyme as potential strategy in AD.

Collectively, all these data reinforce the notion that PTP1B inhibition could have a therapeutic impact in different mechanisms associated with neuronal loss.

7.2. Role of PTP1B in schizophrenia

Schizophrenia is a highly complex mental illness characterized by multiple cognitive, behavioural, and emotional dysfunctions. As with AD, although different hypotheses have been proposed to explain schizophrenia's origin (including environmental, genetic, mental, neurodevelopmental, and neurochemical effects), the pathophysiological mechanism of the onset and its progression have not yet been identified. From the clinical point of view, the most striking clinical characteristic of schizophrenia related to psychosis are hallucinations, personality alterations, delusions, and behavioural disorganization. Cognitive alterations also constitute a central symptom of dysfunction in the disease [155,156].

Qin et al. were the first to introduce a potential role of PTP1B in schizophrenia by using mice deficient in LMO4 (LKO mice), an endogenous inhibitor of PTP1B [157] (Table 1). These mice showed an endogenous activation of PTP1B. Moreover, since the use of cannabis increases the risk of schizophrenia, the authors also assessed the effect of the interaction between TrkB receptor and endocannabinoids in LKO mice. Cannabis alters the endogenous cannabinoid system (endocannabinoids) that include 2-arachidonoylglycerol (2AG) and anandamide [157–159]. These endocannabinoids play a key role in lipid signals and regulation of both excitatory and inhibitory synaptic neurotransmission by binding to the presynaptic receptor CB1 [160]. The authors demonstrated that mice lacking LMO4 in pyramidal neurons of the glutamatergic projection in prefrontal cortex were deficient in neuronal TrkB-dependent eCB signalling, which lead to schizophrenia-like deficits. By contrast, pharmacological inhibition of PTP1B by trodusquemine restored TrkB and eCB signalling, hence ameliorating schizophrenia-related illness.

In another preclinical study, the same authors evaluated the effect of subanaesthetic doses of the anaesthetic ketamine, a NMDAR receptor antagonist that causes symptoms and cognitive deficits that resemble schizophrenia [161]. The interest of the study relays on the fact that schizophrenia patients treated with ketamine show an exacerbation of the symptoms [161,162]. At the molecular level, it has been suggested that the proposed mechanism of action is the phosphorylation of the NMDA receptor by the Src tyrosine kinase, which would cause an increase in the activation of the NMDA receptor without affecting the conductance of the channel [163]. Furthermore, Src inhibitors have

been shown to protect from neuronal damage caused by MK801 (a high affinity receptor antagonist). Given that PTP1B activates Src, genetic ablation or pharmacological inhibition of PTP1B could explain the prevention of potential effects on schizophrenia by ketamine. Interestingly, it has been proposed that other atypical antipsychotic drug such as aripiprazole, could have a similar mechanism of action, in part through the inhibition of Src [164].

These data suggest that PTP1B inhibition could constitute a potential pharmacological target for the development of a novel class of antipsychotic agents.
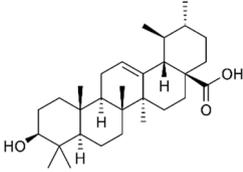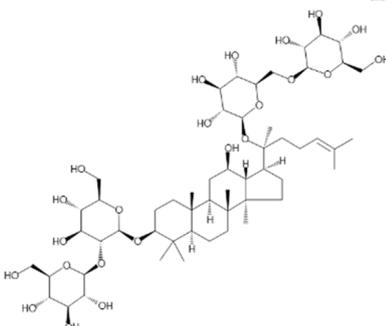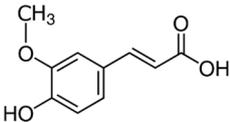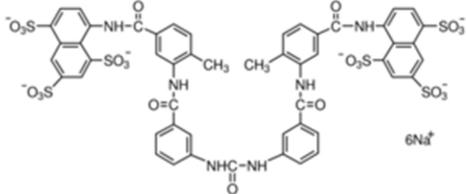
7.3. Role of PTP1B in brain ischemia

A stroke is defined as an alteration or a decrease in the blood supply to the brain. Currently, strokes are the second leading cause of death worldwide [165]. Cerebrovascular accidents are classified in two groups: i) ischemic strokes, representing approximately 85% of all clinical cases and caused by an occlusion of the blood vessels (e.g., by a clot) and ii) haemorrhagic strokes, caused by a rupture of the blood vessels and accounting for 15% of all cases. It is well known that once a cerebrovascular accident occurs, the central region suffers a sudden death by necrosis, while the surrounding injured regions, called penumbra, can present neuronal death due to apoptosis, although they can recover part of their functions.

Sun et al. reported a potential role for PTP1B in ischemic damage. They found that the allosteric PTP1B inhibitor KY-226, which was developed for the treatment of diabetes and obesity, showed neuroprotective effects in ischemic injury (ischemia/reperfusion) in a murine model of middle cerebral artery occlusion [166,167] (Table 1 and Table 2). Thus, KY-226, significantly decreased the volume of the

Table 2

Chemical structure of some PTP1B included in the manuscript.

KY-226	Is a benzoylsulfonamide derivative non-competitive allosteric PTP1B inhibitor	
SC-222227	A selective PTP1B inhibitor.	
Ursolic acid	Has biological properties such as anticancer, anti-inflammatory, antimicrobial, antidiabetic and cardiovascular effects	
Ginsenoside Rb1	Is a main bioactive ingredient in ginseng. It is used as a cognitive and antidiabetic agent.	
Ferulic acid	Has several functions such as anti-inflammatory, antioxidant, antidiabetic and anticancer. Additionally, it has been verified effective against Aβ-induced memory impairment.	
Suramin (sodium salt) (sodium salt)	Suramin, through the inhibition of PTP1B, could improve neuronal damage in PD models.	
Trodusquemine	Is an allosteric inhibitor of protein-tyrosine phosphatase 1B. Shown neuroprotective effects in preclinical models of AD.	
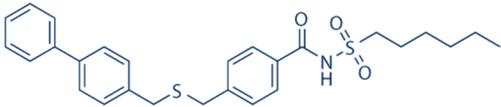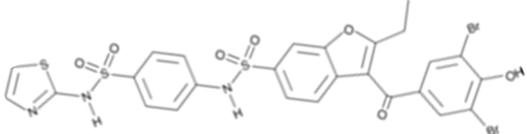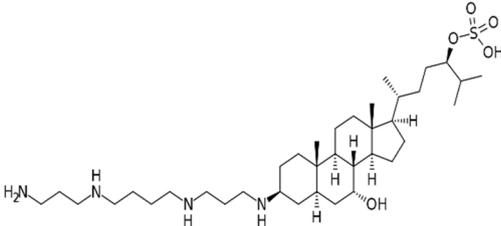
cerebral infarct, and improved neurological deficits in ischemic mice. Moreover, the authors demonstrated that these neuroprotective effects were due to an inhibition of PTP1B, which in turn activated neuroprotective pathways such as Akt / eNOS and the ERK signalling pathway. In a similar study carried out by the same authors, it was found that the inhibition of PTP1B by KY-226 attenuated the disruption of BBB induced by ischemia and reperfusion through the regulation of the expression of proteins of tight junctions. In the ischemic cerebrovascular process, the inactivation of Akt inhibits the phosphorylation of FoxO1 and its translocation to the cytoplasm. This causes the accumulation of FoxO1 in the nucleus, enhancing its interaction with the DNA-binding domain in the ZO-1 promoter and repressing its transcription. This causes the loss of ZO-1 protein in tight junctions, altering the endothelial barrier function and increasing the permeability of the BBB. The authors found that KY-226 restored tight junctions proteins, mainly ZO-1, partially through the activation of the Akt / FoxO1 pathway. According to this, inhibiting PTP1B prevents BBB disruption in ischaemia/reperfusion.

In turn, Zhu et al. reported that a treatment with the PTP1B inhibitor sc-222227 prevented ischemic stroke-induced microglial ER stress, as well as downstream autophagy, and ultimately mitigated deleterious activation of microglia [168]. The molecular mechanism suggested was PTP1B inhibition /microglial ER stress inhibition, probably through the inhibition of PERK signalling.

Finally, Cruz and colleagues have reported that neuronal inhibition of PTP1B produces a beneficial effect in the recovery of stroke, improving sensory and motor functional recovery, as well as preventing mood disorders such as anxiety and depression that are associated with a stroke injury [169].

Considering all these results, PTP1B may be a promising target to improve stroke recovery.

7.4. Role of PTP1B in Parkinson's disease

Parkinson's disease (PD) is characterized by tremor, rigidity, bradykinesia, as well as by postural instability in some patients. It is the second most common neurodegenerative disorder after AD, and its pathophysiology mainly includes loss of nigrostriatal dopaminergic innervation, although other neurons can also be affected [170].

The number of preclinical studies assessing the efficacy of PTP1B inhibition in PD treatment is scarce. Feng and colleagues assessed the effects of the PTP1B inhibitor suramin in in vitro and in vivo models of PD, reporting a neuroprotective action in both cases (Table 2) [170]. The authors suggested that the inhibition of PTP1B by suramin prompted an anti-inflammatory response and reduced ER stress, which lead to neuroprotection. Suramin also increased BDNF levels in cells. In another study, PTP1B inhibition exerted a neuroprotective effect in SH-SY5Y cells and in mouse primary cortical neurons treated with rotenone, an insecticide widely used to induce PD in experimental models [171]. In this case, the authors also proposed that the inhibition of UPR may be the molecular mechanism involved in neuroprotection. Despite these promising results, more research studies are necessary to establish the potential application of PTP1B inhibitors in the treatment of PD.

Interestingly, beyond PTP1B, the use of natural products as promising therapies is gaining momentum, since they contain natural antioxidant compounds (such as phenols and flavonoids) that exhibit a wide range of neuroprotective effects [172,173]. Among them, *Mucuna pruriens* stands out. It has been used in the treatment of parkinsonism in the ancient Ayurveda of India, since it has been shown that the ethanolic extract of the seeds of Mucuna pruriens contains a high content of levodopa (L-DOPA) found naturally [172,173]. Although Levodopa (L-DOPA) is currently effective for the symptomatic treatment of PD, it does not modify the disease evolution [172]. Moreover, long-term use of L-DOPA therapy causes neurooxidative damage. However, this may be prevented by the antioxidant and metal-chelating properties of *Mucuna*

pruriens. Further research studies of the chemical composition of *Mucuna pruriens* revealed that it also has a high content of ursolic acid, which, in addition to L-DOPA, may be responsible for this powerful neuroprotective activity in PD [172–176]. For this reason, this plant has been extensively studied in preclinical rodent models using different neurotoxins such as MPTP, Paraquat, etc., and even in humans. In the MPTP-induced parkinsonian mouse model, the extract demonstrated an antioxidant effect against the oxidative stress of TH in the SN and striatal regions, increasing the level of antioxidant enzymes catalase and superoxide dismutase. In addition, normal levels of expression of iNOS and markers of neuroinflammation were recovered in the animals treated with MPTP [172,173]. *Withania somnifera* is another interesting medicinal plant that has shown a powerful antiparkinsonian effect in different preclinical models such as rotenone, 6-hydroxydopamine and MPTP [177–181]. Likewise, the ethanolic extract from the root of *W. somnifera* exerted a potent neuroprotective effect on dopaminergic neurons in the preclinical rodent model of Parkinson's induced with maneb-paraquat. Hence, it caused an increase in the expression of tyrosine hydroxylase and the levels of dopamine in the substantia nigra, while it reduced the expression of inducible NO synthase (iNOS), in addition to decreasing the glial activation process. Likewise, *W. somnifera* showed a powerful antiapoptotic effect through the increase of Bcl2 and the reduction of BAX (proapoptotic) [173–178].

These preclinical results underpin the importance of PTP1B inhibitors and natural compounds as promising therapies against PD.

7.5. Role of PTP1B in Rett syndrome

Rett syndrome (RTT) is a genetic neurological disorder that affects brain development and causes severe mental and physical disability. It is caused by mutations in the X-linked methyl CpG–binding protein (MECP2) gene, which was the first autism spectrum disorder-related gene to be identified [182]. Moreover, MECP2-deficient mice have markedly higher blood glucose levels, and these metabolic disorders were associated with significant upward expression of the *Ptpn1* gene, which encodes PTP1B [183]. Consistently, PTP1B levels are upregulated in RTT patients and murine models of RTT [183]. Therefore, PTP1B inhibitors could be a potential strategy for the RTT treatment.

In this regard, Krishnan and colleagues evaluated the effects of two characterized inhibitors of PTP1B in the *Mecp*2-mutant mice, reporting an improved symptomatology [184] (Table 1). This effect was mediated by TrkB phosphorylation and activation of receptor-signaling pathways such as RAS/MAPK, PI3K/AKT, and PLCγ/CaMKII, that are involved in neuronal survival, growth, differentiation, synaptic plasticity, and long-term potentiation (LTP). Accordingly, authors concluded that PTP1B inhibition could be a good therapeutic target for the treatment of RTT [184]. Nevertheless, this results still require to be validated in clinical studies.

7.6. Role of PTP1B in depression

Depression is a serious disorder affecting hundreds of millions of people worldwide. Its main symptoms are low or depressed mood, anhedonia (or inability to feel pleasure) and fatigue, but other symptoms such as sleep and gastrointestinal disturbances, among others, are often present [185]. Its pathophysiology is complex, and several mechanisms have been proposed, including the biogenic amine hypothesis, dysregulation of the hypothalamic-pituitary-adrenal axis, immunologic factors, abnormalities of second messenger systems and genetic and environmental factors [186].

Li and colleagues studied the role of miR-144 in the brain to provide a theoretical basis for the treatment of depression [187]. They used rats with depression induced by chronic mild unpredictable stress (CUMS), which is a widely used experimental model for the study of efficacy of new potential drugs for the treatment against depression. The authors demonstrated that miR-144 activates the TrkB / BDNF signalling

pathway by inhibiting the expression of PTP1B in the hippocampus of CUMS rats. Therefore, they associated the activation of TrkB / BDNF in the hippocampus with an antidepressant effect [187].

7.7. PTP1B as a therapeutic target for Spinal Cord Injury

Traumatic spinal cord injuries (SCI) are a leading cause of neurological disabilities and have a very important impact on the life quality and expectancy of affected patients. It has been proposed that in severe damage SCI, the adaptive response of the UPR fails to maintain the physiological protection [188]. Consequently, the ER begins a pro-apoptotic signalling through caspase-12 and CHOP. CHOP is a pro-apoptotic protein that is regulated by the activation of ATF4, which, as we have already mentioned, is upregulated in the PERK-eIF2 stress pathway.

A significant increase in the expression of PTP1B in the spinal cord after injury has been reported [189]. In this regard, Li and colleagues administered a miR-210 through the carrier of the AAV virus in rats with SCI [190]. They found that the treatment reported neuroprotective effects, including increased angiogenesis, inhibition of neuronal apoptosis, and regulation of inflammatory reactions [190]. The authors showed that the neuroprotective effect was due to the downregulation of PTP1B, hence supporting the potential therapeutic effect of PTP1B inhibition in SCI. However, miR-210 has additional potential targets including Efan3, Dapk1, and Ctgf [191]. The inhibition of these target genes by miR-210 may favour the functional improvement of cardiac function after myocardial infarction [191]. Likewise, miR-210 is involved in the regulation of mitochondrial respiration, iron metabolism, and reactive oxygen species generation [191].

8. Perspectives

The enzyme PTP1B phosphatase has been extensively studied for the treatment of metabolic disorders such as T2DM and obesity. However, it constitutes a therapeutic target that may not have been enough considered in the treatment of neurological diseases (Fig. 2). In this regard, most of the preclinical studies have been carried out in AD models, possibly because it is the most important neurodegenerative disease worldwide. However, the use of PTP1B inhibitors as a potential treatment in other neurological diseases cannot be ruled out, as we have already commented throughout the article. Given that PTP1B inhibition in brain is a powerful enhancer of the cognitive process, at least in preclinical studies, it would be interesting to compare its efficacy with other AD treatments that are currently on the market, such as inhibitors of the enzyme acetylcholinesterase or drugs that are under research for cognitive improvement also in AD or additional brain diseases.

The fact that the expression of the endogenous PTP1B inhibitor LMO4 is decreased in brain of AD patients, suggests that the activity of PTP1B is increased in this neurodegenerative disease [143]. Indeed, preclinical studies have shown that PTP1B is over-expressed in the brain after stress conditions such as aging process, in T2DM/obesity and in AD [34,35,192]. In previous studies, Pandey and colleagues reported that LMO4 loss, favors an increase in PTP1B activity in the hypothalamus [193]. Likewise, this inhibition is sensitive to metabolic stress, whereby the loss of the suppression of LMO4-dependent PTP1B activity can cause an alteration in insulin sensitivity and in the regulation of glucose levels. Although it remains to be elucidated how LMO4 inhibits PTP1B activity in different brain diseases, it has been proposed that the activity of PTP1B can be inhibited by the oxidation of a cysteine residue in the catalytic domain [18,19]. In any case, since PTP1B can inhibit three key hippocampal receptor pathways involved in the regulation of the cognitive process (the insulin pathway, leptin and BDNF / TrkB), we can speculate about a common mechanism involved in the pathogenesis of different neurological diseases with neurodegeneration (Fig. 1).

We have discussed in this paper, as well as in other manuscripts, the importance of targeting multiple pathways when fighting a multifaceted neurological disease such as AD. The ability to interact with and regulate a wide range of molecular targets, gives PTP1B a very promising therapeutic potential. In this regard, it has been demonstrated that PTP1B inhibition decreases the pro-inflammatory response in addition to reducing the secondary damage associated with inflammation in the neurological tissue. This is a matter of importance since a continuous inflammatory state can lead to an increase in deficient neurocognitive alterations. Inhibition of PTP1B also downregulates the UPR signalling pathways, including the proapoptotic process, hence constituting a promising ally to halt neurodegeneration. As already explained in this paper, inhibition of PTP1B increases TrkB phosphorylation, leading to an increase in BDNF signalling. The beneficial effect of this is obvious, bearing in mind that BDNF is a major regulator of synaptic transmission and plasticity in many regions of CNS. Finally, PTP1B inhibition also enhances hippocampal IR and leptin receptor, allowing targeting the metabolic disturbances associated with the neurodegenerative process. Hence, PTP1B emerges as a major regulatory enzyme in key physiological pathways involved not only in energy metabolism but also in
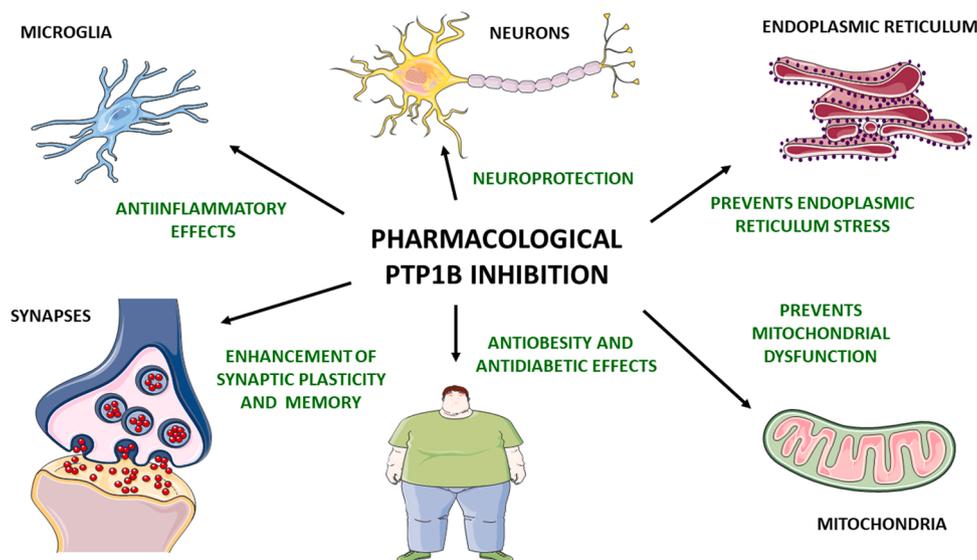

Fig. 2. PTP1 Inhibition as a multitarget therapeutic strategy. Inhibition of PTP1B has been shown to exert multiple beneficial effects, such as anti-inflammatory, neuroprotective, antidiabetic. It also prevents endoplasmic reticulum stress and mitochondrial dysfunction.

neuroprotection and synaptic improvement.

In this regard, as we discussed throughout the manuscript, the results in preclinical studies support the use of PTP1B inhibitors as a suitable therapeutic strategy in different neurological disorders. Hence, trodusquemine and UA have shown encouraging results for the treatment of AD, and PTP1B inhibition improves cognitive function, reduces tau hyperphosphorylation and protects against Aβ toxicity. A very interesting result is the fact that trodusquemine attenuates GSK3β hyperactivity in preclinical models of AD [153]. GSK3β has a key role in the aberrant phosphorylation of tau protein and its aggregation into neurofibrillary tangles. The reported results indicate that PTP1B is upstream of GSK3β activation; therefore, inhibition of PTP1B by trodusquemine could be a suitable target for the treatment of AD and other neurological diseases. Likewise, PTP1B has also been involved in the of microglial proinflammatory response.

Moreover, studies with rodents indicate that PTP1B inhibitors could prevent brain injury after an ischemic process and hence reduce the damage caused by a stroke. In addition, preclinical results also indicate that PTP1B inhibitors have a promising potential that should not be discarded in the treatment of RETT syndrome and Parkinson's disease.

Beyond the classical pharmacological inhibition of the enzyme, miRNAs therapy represents another therapeutic strategy that is being explored to regulate PTP1B at the post-transcriptional level. Hence, miRNA-144 exerts antidepressant effects by enhancing the neurotrophic process and, on another front, miR-34c inhibits the proliferation of human glioma cells, also through the PTP1B inhibition [187]. Other miRNAs that also inhibit PTP1B such as miR-338–3p, miR-193a-3p, miR-135a, miR-146-b and miR-206 have a role in tumour suppression and myocardial damage protection [194].

The advantage of inhibiting PTP1B in neurological disorders relies on the fact that this enzyme regulates different critical pathways. Hence, it is possible to achieve a simultaneous and robust action of many downstream pathways involved in neuroprotection, cognitive processing, and neurotransmitter regulation.

Currently, clinical trials based on the evaluation of PTP1B inhibitors for the treatment of neurological disorders have not been yet performed. Consequently, further studies are necessary to deepen our knowledge about the relation between PTP1B inhibition and brain diseases, as well as the neuroprotective pathways regulated by this phosphatase. However, considering the above explained, the potential of PTP1B, as a key therapeutic target for neurological disorders is undoubtable.

9. Conclusions

The evidence supporting the rationale for clinical targeting of PTP1B in neurological disorders are very limited and mainly based on preclinical animal models. On the other hand, the efficacy of PTP1B inhibitors in clinical trials on metabolic disorders, mainly T2DM, has been studied more extensively. Of note, the regulation of body weight is established through a fine regulation by the hypothalamus. There, PTP1B plays a prominent role through the regulation of insulin and leptin receptors. In addition to the hypothalamus, PTP1B is also found in hippocampus and other brain areas and has been characterized in neuronal and glial cells. Indeed, mounting evidence show that the overexpression of PTP1B could be involved in the pathophysiology of neurological disorders associated with a cognitive loss, neuroinflammation, activation of the UPR and neurotransmitter alterations, or mitochondrial dysfunction, among other mechanisms. Moreover, this may trigger other pathways that further worsen the condition, such as oxidative stress. This is important, since the brain is one of the most vulnerable organs to oxidative stress, given its limited antioxidant activity. PTP1B also is involved in synaptic plasticity and, additionally, it has a crosstalk with other pathways such as ERK1/2, c-Jun N-terminal kinases (JNK), NFκβ, not to mention that, through the UPR, can also modulate apoptotic responses.

Therefore, given that PTP1B regulates several pathways involved in

neurological and neurodegenerative disorders, therapeutic modulators targeting PTP1B have a wide scope in the management of these diseases.

Ethics approval and consent to participate

Not applicable.

Funding

Code availability

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

JO, AC, ME performed literature search and wrote the manuscript; EV, CA, MC helped in performing literature search and writing the neurodegenerative diseases section; JO, ME, A Cano, ESL, AF, and AC edited and revised the manuscript; JF, MB, JO and ME supervised the writing of manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Data Availability

No data was used for the research described in the article.

Acknowledgments

References

[1] F. Ardito, M. iuliani, D. Perrone, et al., The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy, Int. J. Mol. Med. 40 (2) (2017) 271–280.

[2] C.L. Welsh, P. Pandey, L.G. Ahuja, Protein Tyrosine Phosphatases: a new paradigm in an old signaling system? Adv. Cancer Res 152 (2021) 263–303.

[3] T. Hunter, Signaling–2000 and beyond, Cell 100 (1) (2000) 113–127.

[4] Z.Y. Zhang, Protein tyrosine phosphatases: structure and function, substrate specificity, and inhibitor development, Annu. Rev. Pharmacol. Toxicol. 42 (1) (2002) 209–234.

[5] A.J. Flint, T. Tiganis, D. Barford, N.K. Tonks, Development of "substrate-trapping" mutants to identify physiological substrates of protein tyrosine phosphatases, Proc. Natl. Acad. Sci. USA 94 (5) (1997) 1680–1685.

[6] G. Fan, S. Aleem, M. Yang, et al., Protein-tyrosine phosphatase and kinase specificity in regulation of SRC and breast tumor kinase, J. Biol. Chem. 290 (26) (2015) 15934–15947.

[7] Tonks N.K. Protein tyrosine phosphatases–from housekeeping enzymes to master regulators of signal transduction. FEBS J.; 280(2):346–378.

[8] W. Zhu, B.L. Zhou, L.J. Rong, Roles of PTBP1 in alternative splicing, glycolysis, and oncogensis, J. Zhejiang Univ. Sci. B. 21 (2) (2020) 122–136.

[9] D.J. Pagliarini, et al., Protein tyrosine phosphatases, in: W.J. Lennarz, M.D. Lane (Eds.), Encyclopedia of Biological Chemistry, Elsevier, New York, 2004, pp. 536–542.

[10] M. Streuli, N.X. Krueger, T. Thai, et al., Distinct functional roles of the two intracellular phosphatase like domains of the receptor-linked protein tyrosine phosphatases LCA and LAR, EMBO J. 9 (8) (1990) 2399–2407.

[11] M. Feldhammer, N. Uetani, D. Miranda-Saavedra, et al., PTP1B: a simple enzyme for a complex world, Crit. Rev. Biochem. Mol. Biol. 48 (5) (2013) 430–445.

[12] H. Cho, Protein tyrosine phosphatase 1B (PTP1B) and obesity, Vitam. Horm. 91 (2013) 405–424.

[13] N.K. Tonks, PTP1B: from the sidelines to the front lines, FEBS Lett. 546 (1) (2003) 140–148.

[14] Y.A. Puius, Y. Zhao, M. Sullivan, et al., Identification of a second aryl phosphate-binding site in protein-tyrosine phosphatase 1B: a paradigm for inhibitor design, Proc. Natl. Acad. Sci. USA 94 (25) (1997) 13420–13425.

[15] A.J. Barr, Protein tyrosine phosphatases as drug targets: strategies and challenges of inhibitor development, Future Med. Chem. 2 (10) (2010) 1563–1576.

[16] X. Li, L. Wang, D. Shi, The design strategy of selective PTP1B inhibitors over TCPTP, Bioorg. Med. Chem. 24 (16) (2016) 3343–3352.

[17] K.M. Doody, A. Bourdeau, M.L. Tremblay, T-cell protein tyrosine phosphatase is a key regulator in immune cell signaling: lessons from the knockout mouse model and implications in human disease, Immunol. Rev. 228 (1) (2009) 325–341.

[18] A. Salmeen, J.N. Andersen, M.P. Myers, et al., Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate, Nature 423 (2003) 769–773.

[19] R.L.M. van Montfort, M. Congreve, D. Tisi, et al., Oxidation state of the active-site cysteine in protein tyrosine phosphatase 1B, Nature 423 (2003) 773–777.

[20] Y.Y. Chen, Y.F. Huang, K.H. Khoo, et al., Mass spectrometry-based analyses for identifying and characterizing S-nitrosylation of protein tyrosine phosphatases, Methods 42 (2007) 243–249.

[21] Y.Y. Chen, H.M. Chu, K.T. Pan, et al., Cysteine S-nitrosylation protects protein-tyrosine phosphatase 1B against oxidation-induced permanent inactivation, J. Biol. Chem. 283 (2008) 35265–35272.

[22] S. Dadke, S. Cotteret, S.C. Yip, et al., Regulation of protein tyrosine phosphatase 1B by sumoylation, Nat. Cell Biol. 9 (2007) 80–85.

[23] B.L. Seely, P.A. Staubs, D.R. Reichart, et al., Protein tyrosine phosphatase 1B interacts with the activated insulin receptor, Diabetes 45 (10) (1996) 1379–1385.

[24] B.J. Goldstein, A. Bittner-Kowalczyk, M.F. White, M. Harbeck, Tyrosine dephosphorylation and deactivation of insulin receptor substrate-1 by protein-tyrosine phosphatase 1B. Possible facilitation by the formation of a ternary complex with the Grb2 adaptor protein, J. Biol. Chem. 275 (6) (2000) 4283–4289.

[25] M. Elchebly, P. Payette, E. Michaliszyn, et al., Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene, Science 283 (1999) 1544–1548.

[26] M. Delibegovic, D. Zimmer, C. Kauffman, et al., Liver-specific deletion of protein-tyrosine phosphatase 1B (PTP1B) improves metabolic syndrome and attenuates diet-induced endoplasmic reticulum stress, Diabetes 58 (2009) 590–599.

[27] J.L. Halaas, J.M. Friedman, Leptin and its receptor, J. Endocrinol. 155 (2) (1997) 215–216.

[28] J.M. Friedman, J.L. Halaas, Leptin and the regulation of body weight in mammals, Nature 395 (6704) (1998) 763–770.

[29] R.J. Perry, J.M. Resch, A.M. Douglass, et al., Leptin's hunger-suppressing effects are mediated by the hypothalamic-pituitary-adrenocortical axis in rodents, Proc. Natl. Acad. Sci. USA 116 (27) (2019) 13670–13679.

[30] M.W. Schwartz, E. Peskind, M. Raskind, E.J. Boyko, D. Porte Jr., Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans, Nat. Med 2 (5) (1996) 589–593.

[31] L.A. Campfield, F.J. Smith, Y. Guisez, et al., Recombinant mouse OB protein evidence for a Ozek peripheral signal linking adiposity and central neural networks, Science 269 (5223) (1995) 546–549.

[32] A. Cheng, N. Uetani, P.D. Simoncic, et al., Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B, Dev. Cell 2 (4) (2002) 497–503.

[33] W. Kaszubska, H.D. Falls, V.G. Schaefer, et al., Protein tyrosine phosphatase 1B negatively regulates leptin signaling in a hypothalamic cell line, Mol. Cell Endocrinol. 195 (1–2) (2002) 109–118.

[34] C.L. White, A. Whittington, M.J. Barnes, et al., HF diets increase hypothalamic PTP1B and induce leptin resistance through both leptin-dependent and -independent mechanisms, Am. J. Physiol. Endocrinol. Metab. 296 (2) (2009) E291–E299.

[35] M.N. Vieira, E. Lyra, N.M. Silva, S.T. Ferreira, De, F.G. Felice, Protein tyrosine phosphatase 1B (PTP1B): a potential target for alzheimer's therapy? Front Aging Neurosci. 9 (2017) 7.

[36] M. Miranda, J.F. Morici, M.B. Zanoni, P. Bekinschtein, Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain, Front Cell Neurosci. 13 (2019) 363.

[37] S. Bathina, U.N. Das, Brain-derived neurotrophic factor and its clinical implications, Arch. Med Sci. 11 (6) (2015) 1164–1178.

[38] M. Blurton-Jones, M. Kitazawa, H. Martinez-Coria, et al., Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease, Proc. Natl. Acad. Sci. USA 106 (32) (2009) 13594–13599.

[39] A. Osborne, A.X.Z. Wang, A. Tassoni, P.S. Widdowson, K.R. Martin, Design of a novel gene therapy construct to achieve sustained brain-derived neurotrophic factor signaling in neurons, Hum. Gene Ther. 29 (7) (2018) 828–841.

[40] C. Ozek, S.E. Kanoski, Z.Y. Zhang, et al., Protein-tyrosine phosphatase 1B (PTP1B) is a novel regulator of central brain-derived neurotrophic factor and tropomyosin receptor kinase B (TrkB) signaling, J. Biol. Chem. 289 (2014) 31682–31692.

[41] N.G. Hedrick, S.C. Harward, C.E. Hall, et al., Rho GTPase complementation underlies BDNF-dependent homo- and heterosynaptic plasticity, Nature 538 (7623) (2016) 104–108.

[42] M.R. Bennett, J. Lagopoulos, Stress and trauma: BDNF control of dendritic-spine formation and regression, Prog. Neurobiol. 112 (2014) 80–99.

[43] C. Chen, Z. Wang, Z. Zhang, X. Liu, S.S. Kang, Y. Zhang, K. Ye, The prodrug of 7,8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease, Proc. Natl. Acad. Sci. USA 115 (3) (2018) 578–583.

[44] N.A. Castello, M.H. Nguyen, J.D. Tran, D. Cheng, K.N. Green, F.M. LaFerla, 7,8-Dihydroxyflavone, a small molecule TrkB agonist, improves spatial memory and increases thin spine density in a mouse model of Alzheimer disease-like neuronal loss, PLoS One 9 (3) (2014), e91453.

[45] G. Paz-Filho, K. Esposito, B. Hurwitz, et al., Changes in insulin sensitivity during leptin replacement therapy in leptin-deficient patients, Am. J. Physiol. Endocrinol. Metab. 295 (6) (2008) E1401–E1408.

[46] C.D. Morrison, P. Huypens, L.K. Stewart, et al., Implications of crosstalk between leptin and insulin signaling during the development of diet-induced obesity, Biochim. Biophys. Acta 1792 (5) (2009) 409–416.

[47] B. Gray, F. Steyn, P.S. Davies, L. Vitetta, Liver function parameters, cholesterol, and phospholipid α-linoleic acid are associated with adipokine levels in overweight and obese adults, Nutr. Res 34 (5) (2014) 375–382.

[48] S.A. Farr, W.A. Banks, J.E. Morley, Effects of leptin on memory processing, Peptides 27 (6) (2006) 1420–1425.

[49] G.J. Biessels, L.P. Reagan, Hippocampal insulin resistance and cognitive dysfunction, Nat. Rev. Neurosci. 16 (11) (2015) 660–671.

[50] A. Ott, R.P. Stolk, A. Hofman, F. van Harskamp, D.E. Grobbee, M.M. Breteler, Association of diabetes mellitus and dementia: the Rotterdam Study, Diabetologia 39 (11) (1996) 1392–1397.

[51] C. Moran, T.G. Phan, J. Chen, et al., Brain atrophy in type 2 diabetes: regional distribution and influence on cognition, Diabetes Care 36 (12) (2013) 4036–4042.

[52] C.L. Masters, R. Bateman, K. Blennow, et al., Alzheimer's disease, Nat. Rev. Dis. Prim. 1 (2015) 15056.

[53] M.E. Belloy, V. Napolioni, M.D. Greicius, A quarter century of APOE and Alzheimer's disease: progress to date and the path forward, Neuron 101 (5) (2019) 820–838.

[54] V.T. Samuel, G.I. Shulman, Mechanisms for insulin resistance: common threads and missing links, Cell 148 (5) (2012) 852–871.

[55] J.R. Clarke, F.C. Ribeiro, R.L. Frozza, et al., Metabolic dysfunction in Alzheimer's disease: from basic neurobiology to clinical approaches, J. Alzheimers Dis. 64 (s1) (2018) S405–S426.

[56] M.N.N. Vieira, R.A.S. Lima-Filho, De, F.G. Felice, Connecting Alzheimer's disease to diabetes: underlying mechanisms and potential therapeutic targets. Neuropharmacology, 136(Pt B) (2018) 160–171.

[57] S.T. Ferreira, J.R. Clarke, T.R. Bomfim, et al., Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease, Alzheimers Dement 10 (1 Suppl) (2014) S76–S83.

[58] G. Morris, M. Berk, M. Maes, et al., Could Alzheimer's disease originate in the periphery and if so how so? Mol. Neurobiol. 56 (1) (2019) 406–434.

[59] S.M. de la Monte, M. Tong, Brain metabolic dysfunction at the core of Alzheimer's disease, Biochem Pharm. 88 (4) (2014) 548–559.

[60] M. Spinelli, S. Fusco, C. Grassi, Brain insulin resistance impairs hippocampal plasticity, Vitam. Horm. 114 (2020) 281–306.

[61] W.Q. Zhao, F.G. De Felice, S. Fernandez, et al., Amyloid beta oligomers induce impairment of neuronal insulin receptors, FASEB J. 22 (1) (2008) 246–260.

[62] S. Li, D.J. Selkoe, A mechanistic hypothesis for the impairment of synaptic plasticity by soluble Aβ oligomers from Alzheimer's brain, J. Neurochem 154 (6) (2020) 583–597.

[63] S. Hoyer, Glucose metabolism and insulin receptor signal transduction in Alzheimer disease, Eur. J. Pharm. 490 (1–3) (2004) 115–125.

[64] A.C. Cohen, M. Tong, J.R. Wands, S.M. de la Monte, Insulin and insulin-like growth factor resistance with neurodegeneration in an adult chronic ethanol exposure model, Alcohol Clin. Exp. Res 31 (9) (2007) 1558–1573.

[65] A. Apostolatos, S. Song, S. Acosta, et al., Insulin promotes neuronal survival via the alternatively spliced protein kinase CδII isoform, J. Biol. Chem. 287 (12) (2012) 9299–9310.

[66] Z. Arvanitakis, H.Y. Wang, A.W. Capuano, et al., Brain insulin signaling, alzheimer disease pathology, and cognitive function, Ann. Neurol. 88 (3) (2020) 513–525.

[67] C.A. Grillo, G.G. Piroli, R.C. Lawrence, S.A. Wrighten, A.J. Green, S.P. Wilson, R. R. Sakai, S.J. Kelly, M.A. Wilson, D.D. Mott, L.P. Reagan, Hippocampal Insulin Resistance Impairs Spatial Learning and Synaptic Plasticity, Diabetes 64 (11) (2015) 3927–3936.

[68] S.E. Arnold, Z. Arvanitakis, S.L. Macauley-Rambach, et al., Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums, Nat. Rev. Neurol. (2018) 168–181.

[69] K. Talbot, H.Y. Wang, H. Kazi, et al., Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline, J. Clin. Invest 122 (4) (2012) 1316–1338.

[70] T.R. Bomfim, L. Forny-Germano, et al., An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers, J. Clin. Invest 122 (4) (2012) 1339–1353.

[71] J.H. Ledo, E.P. Azevedo, J.R. Clarke, et al., Amyloid-β oligomers link depressive-like behavior and cognitive deficits in mice, Mol. Psychiatry 18 (10) (2013) 1053–1054.

[72] N. Kyrtata, H.C.A. Emsley, O. Sparasci, et al., A systematic review of glucose transport alterations in Alzheimer's disease, Front Neurosci. 15 (2021), 626636.

[73] X.L. Li, S. Aou, Y. Oomura, N. Hori, et al., Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents, Neuroscience 113 (3) (2002) 607–615.

[74] C.D. Morrison, P. Huypens, L.K. Stewart, T.W. Gettys, Implications of crosstalk between leptin and insulin signaling during the development of diet-induced obesity, Biochim Biophys. Acta 1792 (5) (2009) 409–416.

[75] S.J. Greco, S. Sarkar, G. Casadesus, et al., Leptin inhibits glycogen synthase kinase-3beta to prevent tau phosphorylation in neuronal cells, Neurosci. Lett. 455 (3) (2009) 191–194.

[76] D.J. Bonda, J.G. Stone, S.L. Torres, et al., Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance, J. Neurochem 128 (1) (2014) 162–172.

[77] M. Elchebly, P. Payette, E. Michaliszyn, et al., Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene, Science 283 (5407) (1999) 1544–1548, 5.

[78] L.D. Klaman, O. Boss, O.D. Peroni, et al., Increased energy expenditure, decreased adiposity, and tissue-specific insulin sensitivity in protein-tyrosine phosphatase 1B-deficient mice, Mol. Cell Biol. 20 (15) (2000) 5479–5489.

[79] J.L. Sobesky, H.M. D'Angelo, M.D. Weber, et al., Glucocorticoids mediate short-term high-fat diet induction of neuroinflammatory priming, the NLRP3 Inflammasome, and the Danger Signal HMGB1, eNeuro 3 (4) (2016 30) (ENEURO).

[80] S.J. Spencer, H. D'Angelo, A. Soch, et al., High-fat diet and aging interact to produce neuroinflammation and impair hippocampal- and amygdalar-dependent memory, Neurobiol. Aging 58 (2017) 88–101.

[81] J.P. Thaler, C.X. Yi, E.A. Schur, et al., Obesity is associated with hypothalamic injury in rodents and humans, J. Clin. Invest 122 (1) (2012) 153–162.

[82] S.C.B.R. Nakandakari, V.R. Muñoz, G.K. Kuga, et al., Short-term high-fat diet modulates several inflammatory, ER stress, and apoptosis markers in the hippocampus of young mice, Brain Behav. Immun. 79 (2019) 284–293.

[83] T. Tsunekawa, R. Banno, A. Mizoguchi, et al., Deficiency of PTP1B attenuates hypothalamic inflammation via activation of the JAK2-STAT3 pathway in microglia, EBioMedicine 16 (2017) 172–183.

[84] S. Bansal, S. Mahendiratta, M. Agrawal, et al., Role of protein tyrosine phosphatase 1B inhibitor in central insulin resistance and associated cognitive deficits, Brain Res Bull. 171 (2021) 113–125.

[85] H. Wang, X. Sun, N. Zhang, et al., Ferulic acid attenuates diabetes-induced cognitive impairment in rats via regulation of PTP1B and insulin signaling pathway, Physiol. Behav. 182 (2017) 93–100.

[86] J. Wu, X. Xue, G. Fan, et al., Ferulic acid ameliorates hepatic inflammation and fibrotic liver injury by inhibiting PTP1B activity and subsequent promoting AMPK phosphorylation, Front Pharm. 12 (2021), 754976.

[87] G. Leal, C.R. Bramham, C.B. Duarte, BDNF and Hippocampal Synaptic Plasticity, Vitam. Horm. 104 (2017) 153–195.

[88] G. Leal, P.M. Afonso, I.L. Salazar, C.B. Duarte, Regulation of hippocampal synaptic plasticity by BDNF, Brain Res 1621 (2015) 82–101.

[89] B. Connor, D. Young, Q. Yan, et al., Brain-derived neurotrophic factor is reduced in Alzheimer's disease, Brain Res Mol. Brain Res 49 (1–2) (1997) 71–81.

[90] V. Soontornniyomkij, G. Wang, C.A. Pittman, et al., Absence of brain-derived neurotrophic factor and trkB receptor immunoreactivity in glia of Alzheimer's disease, Acta Neuropathol. 98 (4) (1999) 345–348.

[91] S. Peng, J. Wuu, E.J. Mufson, M. Fahnestock, Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease, J. Neurochem 93 (6) (2005) 1412–1421.

[92] D. Camer, Y. Yu, A. Szabo, F. Fernandez, C.H.L. Dinh, X.F. Huang, Bardoxolone methyl prevents high-fat diet-induced alterations in prefrontal cortex signalling molecules involved in recognition memory, Prog. Neuropsychopharmacol. Biol. Psychiatry 59 (2015) 68–75.

[93] J.M. Zabolotny, Y.B. Kim, L.A. Welsh, et al., Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo, J. Biol. Chem. 283 (21) (2008) 14230–14241.

[94] E.C. Chiarreotto-Ropelle, L.S. Pauli, C.K. Katashima, et al., Acute exercise suppresses hypothalamic PTP1B protein level and improves insulin and leptin signaling in obese rats, Am. J. Physiol. Endocrinol. Metab. 305 (5) (2013) E649–E659.

[95] B. Borges, C. de, R.C. Rorato, E.T. Uchoa, et al., Protein tyrosine phosphatase-1B contributes to LPS-induced leptin resistance in male rats, Am. J. Physiol. Endocrinol. Metab. 308 (1) (2015) E40–E50.

[96] H. Ono, Molecular mechanisms of hypothalamic insulin resistance, Int. J. Mol. Sci. 20 (6) (2019) 1317.

[97] N.F. Mendes, N. Castro, D. Guadagnini, et al., Knocking down amygdalar PTP1B in diet-induced obese rats improves insulin signaling/action, decreases adiposity and may alter anxiety behavior, Metabolism 70 (2017) 1–11.

[98] Y. Wu, Y. Yu, A. Szabo, M. Han, X.F. Huang, Central inflammation and leptin resistance are attenuated by ginsenoside Rb1 treatment in obese mice fed a high-fat diet, PLoS One 9 (3) (2014), e92618.

[99] G.J. Song, M. Jung, J.H. Kim, et al., A novel role for protein tyrosine phosphatase 1B as a positive regulator of neuroinflammation, J. Neuroinflamm. 13 (1) (2016) 86.

[100] G.J. Song, J. Kim, J.H. Kim, et al., Comparative analysis of protein tyrosine phosphatases regulating microglial activation, Exp. Neurobiol. 25 (5) (2016) 252–261.

[101] J.V. Frangioni, P.H. Beahm, V. Shifrin, C.A. Jost, B.G. Neel, The nontransmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its 35 amino acid C-terminal sequence, Cell 68 (3) (1992) 545–560.

[102] D. Popov, Endoplasmic reticulum stress and the on site function of residentPTP1B, Biochem. Biophys. Res. Commun. 422 (2012) 535–538.

[103] F.G. Haj, P.J. Verveer, A. Squire, et al., Imaging sites of receptor dephosphorylation by PTP1B on the surface of the endoplasmic reticulum, Science 295 (5560) (2002) 1708–1711.

[104] F. Gu, D.T. Nguyên, M. Stuible, et al., Protein-tyrosine phosphatase 1B potentiates IRE1 signaling during endoplasmic reticulum stress, J. Biol. Chem. 279 (48) (2004) 49689–49693.

[105] C. Hetz, K. Zhang, R.J. Kaufman, Mechanisms, regulation and functions of the unfolded protein response, Nat. Rev. Mol. Cell Biol. 21 (8) (2020) 421–438.

[106] C. Hetz, The unfolded protein response: controlling cell fate decisions under ER stress and beyond, Nat. Rev. Mol. Cell Biol. 13 (2) (2012) 89–102.

[107] X. Wei, A.S. Howell, X. Dong, et al., The unfolded protein response is required for dendrite morphogenesis, Elife 4 (2015), e06963.

[108] V. Sharma, R. Sood, A. Khlaifia, et al., eIF2α controls memory consolidation via excitatory and somatostatin neurons, Nature 586 (7829) (2020) 412–416.

[109] R. Sano, J.C. Reed, ER stress-induced cell death mechanisms, Biochim Biophys. Acta 1833 (12) (2013) 3460–3470.

[110] R. Paxman, L. Plate, E.A. Blackwood, et al., Pharmacologic ATF6 activating compounds are metabolically activated to selectively modify endoplasmic reticulum proteins, Elife 7 (2018), e37168.

[111] A. Agouni, N. Mody, C. Owen, et al., Liver-specific deletion of protein tyrosine phosphatase (PTP) 1B improves obesity- and pharmacologically induced endoplasmic reticulum stress, Biochem J. 438 (2) (2011) 369–378.

[112] Y.M. Jeon, S. Lee, S. Kim, Y. Kwon, K. Kim, C.G. Chung, S. Lee, S.B. Lee, H.J. Kim, Neuroprotective effects of protein tyrosine phosphatase 1B inhibition against ER stress-induced toxicity, Mol. Cells 40 (2017) 280–290.

[113] F. Foufelle, B. Fromenty, Role of endoplasmic reticulum stress in drug-induced toxicity, Pharm. Res Perspect. 4 (1) (2016), e00211.

[114] E. Panzhinskiy, Y. Hua, B. Culver, et al., Endoplasmic reticulum stress upregulates protein tyrosine phosphatase 1B and impairs glucose uptake in cultured myotubes, Diabetologia 56 (3) (2013) 598–607.

[115] B. Liu, G. Ou, Y. Chen, J. Zhang, Inhibition of protein tyrosine phosphatase 1B protects against sevoflurane-induced neurotoxicity mediated by ER stress in developing brain, Brain Res Bull. 146 (2019) 28–39.

[116] A. Arachiche, O. Augereau, M. Decossas, et al., Localization of PTP-1B, SHP-2, and Src exclusively in rat brain mitochondria and functional consequences, J. Biol. Chem. 283 (36) (2008) 24406–24411.

[117] E. Hébert Chatelain, J.W. Dupuy, et al., Functional impact of PTP1B-mediated Src regulation on oxidative phosphorylation in rat brain mitochondria, Cell Mol. Life Sci. 68 (15) (2011) 2603–2613.

[118] J. Lyu, G. Zheng, Z. Chen, et al., Sepsis-induced brain mitochondrial dysfunction is associated with altered mitochondrial Src and PTP1B levels, Brain Res 1620 (2015) 130–138.

[119] H. Hussain, I.R. Green, G. Abbas, S.M. Adekenov, W. Hussain, I. Ali, Protein tyrosine phosphatase 1B (PTP1B) inhibitors as potential anti-diabetes agents: patent review (2015-2018), Expert Opin. Ther. Pat. 29 (9) (2019) 689–702.

[120] A.K. Tamrakar, C.K. Maurya, A.K. Rai, PTP1B inhibitors for type 2 diabetes treatment: a patent review (2011 - 2014), Expert Opin. Ther. Pat. 24 (10) (2014) 1101–1115.

[121] S. Lee, Q. Wang, Recent development of small molecular specific inhibitor of protein tyrosine phosphatase 1B, Med Res Rev. 27 (4) (2007) 553–573.

[122] N. Krishnan, K.F. Konidaris, G. Gasser, et al., A potent, selective, and orally bioavailable inhibitor of the protein-tyrosine phosphatase PTP1B improves insulin and leptin signaling in animal models, J. Biol. Chem. 293 (5) (2018) 1517–1525.

[123] N. Krishnan, N.K. Tonks, Anxious moments for the protein tyrosine phosphatase PTP1B, Trends Neurosci. 38 (8) (2015) 462–465.

[124] N. Krishnan, D. Koveal, D.H. Miller, et al., Targeting the disordered C terminus of PTP1B with an allosteric inhibitor, Nat. Chem. Biol. 10 (7) (2014) 558–566.

[125] H. Cho, Protein tyrosine phosphatase 1B (PTP1B) and obesity, Vitam. Horm. 91 (2013) 405–424.

[126] K.A. Lantz, S.G. Hart, S.L. Planey, et al., Inhibition of PTP1B by trodusquemine (MSI-1436) causes fat-specific weight loss in diet-induced obese mice, Obesity 18 (8) (2010) 1516–1523.

[127] R. Limbocker, S. Errico, D. Barbut, et al., Squalamine and trodusquemine: two natural products for neurodegenerative diseases, from physical chemistry to the clinic, Nat. Prod. Rep. (2021), https://doi.org/10.1039/d1np00042j.

[128] R. Limbocker, R. Staats, S. Chia, et al., Squalamine and its derivatives modulate the aggregation of amyloid-β and α-synuclein and suppress the toxicity of their oligomers, Front Neurosci. 15 (2021), 680026.

[129] S. Errico, H. Ramshini, C. Capitini, et al., Quantitative measurement of the affinity of toxic and nontoxic misfolded protein oligomers for lipid bilayers and of its modulation by lipid composition and trodusquemine, ACS Chem. Neurosci. 12 (2021) 3189–3202.

[130] R. Limbocker, B. Mannini, F.S. Ruggeri, et al., Trodusquemine displaces protein misfolded oligomers from cell membranes and abrogates their cytotoxicity through a generic mechanism, Commun. Biol. 3 (1) (2020 13) 435.

[131] Z. Qin, et al., Functional properties of Claramine: a novel PTP1B inhibitor and insulin-mimetic compound, Biochem. Biophys. Res. Commun. 458 (2015) 21–27.

[132] Genaera Corporation. GENAERA: Presents Preliminary Phase 1b Data for Trodusquemine (MSI-1436). Website: https://www.marketscreener.com/GENAERA-9416/news/GENAERA-.

[133] Presents-Preliminary-Phase-1b-Data-for-Trodusquemine- MSI-1436–13123592/. Accessed November 10, 2018.

[134] Bio Space. Genaera Corporation Presents Preliminary Phase 1b Data for Trodusquemine (MSI-1436). Website: ⟨https://www.biospace.com/article/releases/genaera-corporation-presents-phase-1-data-for-trodusquemine-msi-1436-/⟩. Accessed November 10, 2018.

[135] W. Zhang, D. Hong, Y. Zhou, Y. Zhang, Q. Shen, J.Y. Li, L.H. Hu, J. Li, Ursolic acid and its derivative inhibit protein tyrosine phosphatase 1B, enhancing insulin receptor phosphorylation and stimulating glucose uptake, Biochim Biophys. Acta 1760 (2006) 1505–1512.

[136] W. Xue, J. Tian, X.S. Wang, J. Xia, S. Wu, Discovery of potent PTP1B inhibitors via structure-based drug design, synthesis and in vitro bioassay of Norathyriol derivatives, Bioorg. Chem. 86 (2019) 224–234.

[137] G.S. Kumar, R. Page, W. Peti, The mode of action of the Protein tyrosine phosphatase 1B inhibitor Ertiprotafib, PLoS One 15 (10) (2020), e0240044.

[138] S. Shrestha, B.R. Bhattarai, H. Cho, J.K. Choi, H. Cho, PTP1B inhibitor Ertiprotafib is also a potent inhibitor of IkappaB kinase beta (IKK-beta), Bioorg. Med Chem. Lett. 17 (10) (2007) 2728–2730.

[139] M.M. Swarbrick, P.J. Havel, A.A. Levin, et al., Inhibition of protein tyrosine phosphatase-1B with antisense oligonucleotides improves insulin sensitivity and increases adiponectin concentrations in monkeys, Endocrinology 150 (4) (2009) 1670–1679.

[140] L.K. Huang, S.P. Chao, C.J. Hu, Clinical trials of new drugs for Alzheimer disease, J. Biomed. Sci. 27 (1) (2020) 18.

[141] Y.Y. Syed, Sodium Oligomannate: First Approval, Drugs 80 (4) (2020) 441–444.

[142] X. Wang, G. Sun, T. Feng, et al., Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression, Cell Res 29 (10) (2019) 787–803.

[143] G. Leuba, A. Vernay, D. Vu, et al., Differential expression of LMO4 protein in Alzheimer's disease, Neuropathol. Appl. Neurobiol. 30 (1) (2004) 57–69.

[144] L. Zhang, Z. Qin, F. Sharmin, et al., Tyrosine phosphatase PTP1B impairs presynaptic NMDA receptor-mediated plasticity in a mouse model of Alzheimer's disease, Neurobiol. Dis. 156 (2021), 105402.

[145] F. Fuentes, D. Zimmer, M. Atienza, et al., Protein tyrosine phosphatase PTP1B is involved in hippocampal synapse formation and learning, PLoS One 7 (7) (2012), e41536.

[146] L. Macklin, C.M. Griffith, Y. Cai, et al., Glucose tolerance and insulin sensitivity are impaired in APP/PS1 transgenic mice prior to amyloid plaque pathogenesis and cognitive decline, Exp. Gerontol. 88 (2017) 9–18.

[147] A. King, A. Brain, K. Hanson, J. Dittmann, J. Vickers, C. Fernandez-Martos, Disruption of leptin signalling in a mouse model of Alzheimer's disease, Metab. Brain Dis. 33 (4) (2018) 1097–1110.

[148] G.K. Kuga, V.R. Muñoz, R.C. Gaspar, et al., Impaired insulin signaling and spatial learning in middle-aged rats: the role of PTP1B, Exp. Gerontol. 104 (2018) 66–71.

[149] Z. He, S. Han, H. Zhu, et al., The protective effect of vanadium on cognitive impairment and the neuropathology of Alzheimer's disease in APPSwe/PS1dE9 mice, Front Mol. Neurosci. 13 (2020) 21.

[150] Z. He, S. Han, C. Wu, et al., Bis(ethylmaltolato)oxidovanadium(iv) inhibited the pathogenesis of Alzheimer's disease in triple transgenic model mice, Metallomics 12 (4) (2020) 474–490.

[151] Z. He, X. Li, S. Han, et al., Bis(ethylmaltolato)oxidovanadium (IV) attenuates amyloid-beta-mediated neuroinflammation by inhibiting NF-kappaB signaling pathway via a PPARgamma-dependent mechanism, Metallomics 13 (7) (2021) mfab036, 2.

[152] S. Kumar, S. Ivanov, A. Lagunin, R.K. Goel, Attenuation of hyperhomocysteinemia induced vascular dementia by sodium orthovanadate perhaps via PTP1B: Pertinent downstream outcomes, Behav. Brain Res. 364 (2019) 29–40.

[153] K.M. Ricke, S.A. Cruz, Z. Qin, K. Farrokhi, F. Sharmin, L. Zhang, M.A. Zasloff, A.R. Stewart, H.H. Chen, Neuronal Protein Tyrosine Phosphatase 1B Hastens Amyloid beta-Associated Alzheimer's Disease in Mice, J. Neurosci. 40 (7) (2020) 1581–1593.

[154] T.A. Kanno, A. Tsuchiya, A. Tanaka, Combination of PKCε and PTP1B inhibition effectively suppresses Aβ-induced GSK3β activation and Tau phosphorylation, Mol. Neurobiol. 53 (2016) 4787–4797.

[155] R.S. Keefe, W.S. Fenton, How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr. Bull. 33 (2007) 912–920.

[156] A. Reichenberg, A. Caspi, H. Harrington, R. Houts, R.S. Keefe, R.M. Murray, et al., Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30- year study, Am. J. Psychiatry 167 (2010) 160–169.

[157] Z. Qin, L. Zhang, S.A. Cruz, A.F.R. Stewart, H.H. Chen, Activation of tyrosine phosphatase PTP1B in pyramidal neurons impairs endocannabinoid signaling by tyrosine receptor kinase trkB and causes schizophrenia-like behaviors in mice, Neuropsychopharmacology 45 (11) (2020) 1884–1895.

[158] Z. Qin, et al., LIM domain only 4 (LMO4) regulates calcium-induced calcium release and synaptic plasticity in the hippocampus, J. Neurosci. 32 (2012) 4271–4283.

[159] Z. Qin, et al., Chronic stress induces anxiety via an Amygdalar intracellular cascade that impairs endocannabinoid signaling, 2015, Neuron 85 (2015) 1319–1331.

[160] H.C. Lu, K. Mackie, An introduction to the endogenous cannabinoid system, Biol. Psychiatry 79 (7) (2016) 516–525.

[161] Z. Qin, L. Zhang, M.A. Zasloff, et al., Ketamine's schizophrenia- like effects are prevented by targeting PTP1B, Neurobiol. Dis. 155 (2021), 105397.

[162] A.C. Lahti, M.A. Weiler, B.A. Tamara Michaelidis, et al., Effects of ketamine in normal and schizophrenic volunteers, Neuropsychopharmacology 25 (4) (2001) 455–467.

[163] M.W. Salter, L.V. Kalia, Src kinases: a hub for NMDA receptor regulation, Nat. Rev. Neurosci. 5 (4) (2004) 317–328.

[164] S. Yoo, M.Y. Kim, J.Y. Cho, Syk and Src-targeted anti-inflammatory activity of aripiprazole, an atypical antipsychotic, Biochem Pharm. 148 (2018) 1–12.

[165] M. Katan, A. Luft, Global burden of stroke, Semin Neurol. 38 (2) (2018) 208–211.

[166] M. Sun, Y. Shinoda, K. Fukunaga, KY-226 protects blood-brain barrier function through the Akt/FoxO1 signaling pathway in brain ischemia, Neuroscience 399 (2019) 89–102.

[167] M. Sun, H. Izumi, Y. Shinoda, K. Fukunaga, Neuroprotective effects of protein tyrosine phosphatase 1B inhibitor on cerebral ischemia/reperfusion in mice, Brain Res 1694 (2018) 1–12.

[168] Y. Zhu, J. Yu, J. Gong, et al., PTP1B inhibitor alleviates deleterious microglial activation and neuronal injury after ischemic stroke by modulating the ER stress-autophagy axis via PERK signaling in microglia, Aging (Albany NY) 13 (3) (2021) 3405–3427.

[169] S.A. Cruz, Z. Qin, K.M. Ricke, et al., Neuronal protein-tyrosine phosphatase 1B hinders sensory-motor functional recovery and causes affective disorders in two different focal ischemic stroke models, Neural Regen. Res 16 (1) (2021) 129–136.

[170] C.W. Feng, N.F. Chen, T.F. Chan, W.F. Chen, Therapeutic role of protein tyrosine phosphatase 1B in Parkinson's Disease via antineuroinflammation and Neuroprotection In Vitro and In Vivo, Park. Dis. 2020 (2020) 8814236.

[171] Y.M. Jeon, S. Lee, S. Kim, et al., Neuroprotective effects of protein tyrosine phosphatase 1B inhibition against ER stress-induced toxicity, Mol. Cells 40 (4) (2017) 280–290.

[172] S.K. Yadav, J. Prakash, S. Chouhan, S.P. Singh, Mucuna pruriens seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced Parkinsonian mouse model, Neurochem Int 62 (8) (2013) 1039–1047.

[173] S.K. Yadav, J. Prakash, S. Chouhan, S. Westfall, M. Verma, T.D. Singh, S.P. Singh, Comparison of the neuroprotective poten_tial of Mucuna pruriens seed extract with estrogen in 1-methyl_4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced PD mice model, Neurochem Int 1 (65) (2014) 1–3.

[174] S.N. Rai, S.K. Yadav, D. Singh, S.P. Singh, Ursolic acid attenuates oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in MPTP-induced Parkinsonian mouse model, J. Chem. Neuroanat. 1 (71) (2016) 41–49.

[175] S.N. Rai, W. Zahra, S.S. Singh, H. Birla, C. Keswani, H. Dilnashin, A.S. Rathore, R. Singh, R.K. Singh, S.P. Singh, Anti-inflammatory activity of ursolic acid in MPTP-induced parkinsonian mouse model, Neurotox. Res 36 (3) (2019) 452–462.

[176] W. Zahra, S.N. Rai, H. Birla, S.S. Singh, A.S. Rathore, H. Dilnashin, R. Singh, C. Keswani, R.K. Singh, S.P. Singh, Neuroprotection of rotenone-induced Parkinsonism by ursolic acid in PD mouse model, CNS Neurol. Disord. Drug Targets 19 (7) (2020) 527–540.

[177] J. Prakash, S.K. Yadav, S. Chouhan, S.P. Singh, Neuroprotective role of Withania somnifera root extract in maneb-paraquat induced mouse model of parkinsonism, Neurochem Res 38 (5) (2013) 972–980.

[178] J. Prakash, S. Chouhan, S.K. Yadav, S. Westfall, S.N. Rai, S.P. Singh, Withania somnifera alleviates parkinsonian phenotypes by inhibiting apoptotic pathways in dopaminergic neurons, Neurochem Res 39 (12) (2014) 2527–2536.

[179] N.J. Dar, A. Hamid, M. Ahmad, Pharmacologic overview of Withania somnifera, the Indian Ginseng, Cell Mol. Life Sci. 72 (23) (2015) 4445–4460.

[180] S. Rajasankar, T. Manivasagam, S. Surendran, Ashwagandha leaf extract: a potential agent in treating oxidative damage and physiological abnormalities seen in a mouse model of Parkinson's disease, Neurosci. Lett. 454 (2009) 11–15.

[181] J. Prakash, S.K. Yadav, S. Chouhan, S.P. Singh, Neuroprotective role of Withania somnifera root extract in maneb_paraquat induced mouse model of parkinsonism, Neurochem Res 38 (2013) 972–980.

[182] R.C. Samaco, J.L. Neul, Complexities of Rett syndrome and MeCP2, J. Neurosci. 31 (22) (2011) 7951–7959.

[183] L. Tautz, PTP1B: a new therapeutic target for Rett syndrome, J. Clin. Invest 125 (8) (2015) 2931–2934.

[184] N. Krishnan, K. Krishnan, C.R. Connors, et al., PTP1B inhibition suggests a therapeutic strategy for Rett syndrome, Clin. Invest. 125 (2015) 3163–3177.

[185] B. Brigitta, Pathophysiology of depression and mechanisms of treatment, Dialog-. Clin. Neurosci. 4 (1) (2002) 7–20.

[186] E. Jesulola, P. Micalos, I.J. Baguley, Understanding the pathophysiology of depression: from monoamines to the neurogenesis hypothesis model - are we there yet? Behav. Brain Res 341 (2018) 79–90.

[187] Y. Li, N. Wang, J. Pan, et al., Hippocampal miRNA-144 modulates depressive-like behaviors in rats by targeting PTP1B, Neuropsychiatr. Dis. Treat. 17 (2021) 389–399.

[188] M. Oñate, A. Catenaccio, G. Martínez, et al., Activation of the unfolded protein response promotes axonal regeneration after peripheral nerve injury, Sci. Rep. 6 (2016) 21709.

[189] X. Zhu, Y. Zhou, R. Tao, J. Zhao, J. Chen, C. Liu, Z. Xu, G. Bao, J. Zhang, M. Chen, J. Shen, C. Cheng, D. Zhang, Upregulation of PTP1B after rat spinal cord injury, Inflammation 38 (5) (2015) 1891–1902.

[190] R. Li, L. Bao, W. Hu, et al., Expression of miR-210 mediated by adeno-associated virus performed neuroprotective effects on a rat model of acute spinal cord injury, Tissue Cell 57 (2019) 22–33.

[191] S. Hu, M. Huang, Z. Li, F. Jia, Z. Ghosh, M.A. Lijkwan, P. Fasanaro, N. Sun, X. Wang, F. Martelli, R.C. Robbins, J.C. Wu, MicroRNA-210 as a novel therapy for treatment of ischemic heart disease, Circulation 122 (11 Suppl) (2010) S124–S131.

[192] M. García-San Frutos, T. Fernández-Agulló, J.M. Carrascosa, et al., Involvement of protein tyrosine phosphatases and inflammation in hypothalamic insulin resistance associated with ageing: effect of caloric restriction, Mech. Ageing Dev. 133 (7) (2012) 489–497.

[193] N.R. Pandey, X. Zhou, Z. Qin, et al., The LIM domain only 4 protein is a metabolic responsive inhibitor of protein tyrosine phosphatase 1B that controls hypothalamic leptin signalling, J. Neurosci. 33 (31) (2013) 12647–12655.

[194] Y. Yan, H. Dang, X. Zhang, et al., The protective role of MiR-206 in regulating cardiomyocytes apoptosis induced by ischemic injury by targeting PTP1B, Biosci. Rep. 40 (1) (2020). BSR20191000.