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REVIEW

Targeting midkine and pleiotrophin signalling pathways in addiction and neurodegenerative disorders: recent progress and perspectives

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Midkine (MK) and pleiotrophin (PTN) are two neurotrophic factors that are highly up-regulated in different brain regions after the administration of various drugs of abuse and in degenerative areas of the brain. A deficiency in both MK and PTN has been suggested to be an important genetic factor, which confers vulnerability to the development of the neurodegenerative disorders associated with drugs of abuse in humans. In this review, evidence demonstrating that MK and PTN limit the rewarding effects of drugs of abuse and, potentially, prevent drug relapse is compiled. There is also convincing evidence that MK and PTN have neuroprotective effects against the neurotoxicity and development of neurodegenerative disorders induced by drugs of abuse. Exogenous administration of MK and/or PTN into the CNS by means of non-invasive methods is proposed as a novel therapeutic strategy for addictive and neurodegenerative diseases. Identification of new molecular targets downstream of the MK and PTN signalling pathways or pharmacological modulation of those already known may also provide a more traditional, but probably effective, therapeutic strategy for treating addictive and neurodegenerative disorders.

LINKED ARTICLES
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Abbreviations
ALDH1A1, aldehyde dehydrogenase family 1 member A1; ALK, anaplastic lymphoma kinase; ANXA7, annexin; BBB, blood brain barrier; CKMT1, creatine kinase U-type; COPS5, COP9 signalosome subunit 5; CPP, conditioned place preference; KA, kainic acid; MK, midkine; NGF, nerve growth factor; PD, Parkinson's disease; PTK, protein tyrosine kinase; PTN, pleiotrophin; PTP, protein tyrosine phosphatase; PTPRZ, protein tyrosine phosphatase type Z

Introduction

The neurotoxic effects of drugs of abuse underlie not only drug-seeking behaviours but also the neurodegeneration processes associated with chronic drug consumption (Herradon *et al.*, 2009). For example, chronic alcohol consumption is associated with an increase in the incidence of a variety of diseases, including CNS degeneration (Collins and Neafsey, 2012). These addictive and neurotoxic effects of psychostimulants and other drugs of abuse have been associated with enhanced damage of dopaminergic neurons in the nigrostriatal pathway (Ferrucci *et al.*, 2008; Valverde and Rodríguez-Árias, 2013). Drugs of abuse promote the intracellular accumulation of dopamine (Kalivas and O'Brien, 2008), which could elicit neuronal death by blocking mitochondrial complex 1, as occurs, for example, with Parkinsonian agents (Fahn and Sulzer, 2004). In addition, cocaine has been shown to cause significant increases in α-synuclein levels in dopaminergic neurons (Mash *et al.*, 2003). Interestingly, α-synuclein is known to be the main component of Lewy bodies in patients with Parkinson's disease (PD) (Spillantini *et al.*, 1997). Furthermore, it was recently found that

α-synuclein can induce dose-dependent toxic effects and neurodegeneration in dopaminergic neurons and other neuronal populations (Sanchez-Guajardo *et al.*, 2013). Thus, preclinical evidence suggests that PD is one of the possible long-term neurological consequences of abusing psychostimulants. Interestingly, Callaghan *et al.* (2012) have recently obtained the first epidemiological evidence showing a significant increase in the prevalence of PD among methamphetamine abusers.

There is much preclinical and epidemiological evidence to support the search for common factors with potential roles in the development of neurodegenerative and addictive disorders in an effort to identify new pharmacological targets for the treatment of both types of disorder, but also to elucidate the connection between drug addiction and neurodegeneration processes. In this regard, two neurotrophic factors with important functions in catecholaminergic neurons, midkine (MK) and pleiotrophin (PTN), have been found to be up-regulated in different brain areas after administration of drugs of abuse and in the degenerating substantia nigra in patients with PD (Gramage and Herradon, 2011). PTN is significantly up-regulated in the nucleus accumbens after acute administration of amphetamine (Le Greves, 2005) and in the cingulate cortex, frontoparietal cortex and caudate putamen after injection of the psychoactive component of cannabis, Δ-9-tetrahydrocannabinol (Mailleux *et al.*, 1994). MK has been also found to be up-regulated in the hippocampus of morphine-treated rats (Ezquerra *et al.*, 2007) and in the prefrontral cortex of alcoholics and smokers (Flatscher-Bader and Wilce, 2008). More interestingly, PTN has been found to be highly up-regulated in the substantia nigra of patients with PD (Marchionini *et al.*, 2007). L-Dopa, still the drug of choice for treating the motor symptoms of PD, alone or in combination with other drugs has been found to increase the levels of expression of PTN in the striatum (Ferrario *et al.*, 2004). The existing evidence together with the knowledge that PTN and MK are significantly redundant in structure and function (Herradon *et al.*, 2005) and regulate the survival and function of dopaminergic neurons (Jung *et al.*, 2004; Prediger *et al.*, 2011), support the hypothesis that both neurotrophic factors are up-regulated in neurodegenerative and addictive disorders in order to induce trophic or neuroprotective effects on dopaminergic neurons.

The receptor nomenclature conforms to BJP's Concise Guide to PHARMACOLOGY (Alexander *et al.*, 2013).

MK and PTN: cytokines with important roles in neural repair and differentiation

MK is a heparin-binding growth factor or cytokine that promotes growth, survival, differentiation and migration of different target cells (Kadomatsu *et al.*, 1988). MK has an important role in development and repair of the CNS (Muramatsu, 2011). PTN, initially cited as heparin-binding growth factor-8 (Milner *et al.*, 1989), and heparin-binding growth-associated molecule (Rauvala, 1989) is a secreted, highly conserved cytokine which shares over 50% identity in amino acid sequence with MK, the only other member of the PTN/MK developmentally-regulated gene family (Kadomatsu and Muramatsu, 2004).

The expression of the MK gene is induced by retinoic acid (Matsubara *et al.*, 1994). The PTN gene is induced by PDGF and basic fibroblast growth factor (Li *et al.*, 1992). The PTN and MK genes are widely expressed at different times in different cell types during development (Silos-Santiago *et al.*, 1996; Deuel *et al.*, 2002; Muramatsu, 2011). However, the expression of both PTN and MK genes is constitutive and limited to only a few cell types in adults (Herradon and Ezquerra, 2009; Muramatsu, 2010). Both genes are up-regulated at sites of injury and repair in inflammatory macrophages, microglia, dermal fibroblasts, endothelial cells and other cells (Jin *et al.*, 2009; Martin *et al.*, 2011; Muramatsu, 2011), suggesting PTN and MK signalling may be critical in different steps of differentiation of different cells both in development and in wound repair. Accordingly, PTN and MK have been shown to induce and stimulate neuronal differentiation (Jung *et al.*, 2004; Ishikawa *et al.*, 2009; Luo *et al.*, 2012). In addition, PTN was found to play a significant role in injury-induced and activity-dependent plasticity in the rat hippocampus (Rauvala and Peng, 1997), to be part of the supportive environment for regeneration of axons after injury (Iseki *et al.*, 2002), to be a source of trophic support for neurons in the brain (Dugas *et al.*, 2008) and to exert key trophic effects on donor cells in neural transplantation *in vivo* and save nigral dopaminergic neurons from degeneration (Hida *et al.*, 2007; Moses *et al.*, 2008). In contrast, MK is involved in the regeneration of injured peripheral nerves (Sakakima *et al.*, 2009) and protects against ischaemia-related brain injury (Ooboshi, 2011).

Mechanism of action of midkine and pleiotrophin

MK and PTN share common receptors such as receptor protein tyrosine phosphatase type Z (PTPRZ; also called RPTPbeta/zeta) (Maeda *et al.*, 1996; 1999; Meng *et al.*, 2000), syndecan-3 (Rauvala *et al.*, 2000) and anaplastic lymphoma kinase (ALK) (Stoica *et al.*, 2001). PTPRZ, also known as PTPRB and PTPRZ1 (Krueger and Saito, 1992), is a receptor-like protein tyrosine phosphatase, which is abundantly expressed in the CNS as a chondroitin sulfate proteoglycan (Krueger and Saito, 1992).

MK and PTN bind in a similar manner to PTPRZ (Maeda *et al.*, 1996; 1999). Maeda *et al.* (1999) showed that the MK terminal domain with neurite promoting activity, the C-terminal domain, was sufficient for the binding to PTPRZ. After removal of the chondroitin sulfate chain, the affinity of MK for PTPRZ decreases (Maeda *et al.*, 1999), suggesting that MK is likely to bind mostly to the chondroitin sulfate portion of PTPRZ. Although binding of MK to PTPRZ has been shown to be key for MK-dependent survival of embryonic neurons, the mechanisms triggered by the formation of the complex PTN/PTPRZ are better known. The interaction of PTPRZ with PTN inactivates the intrinsic tyrosine phosphatase activity of PTPRZ; this inactivation of PTPRZ is presumed to result from a PTN-induced conformational change in this receptor that prevents substrates from accessing the active site in the D1

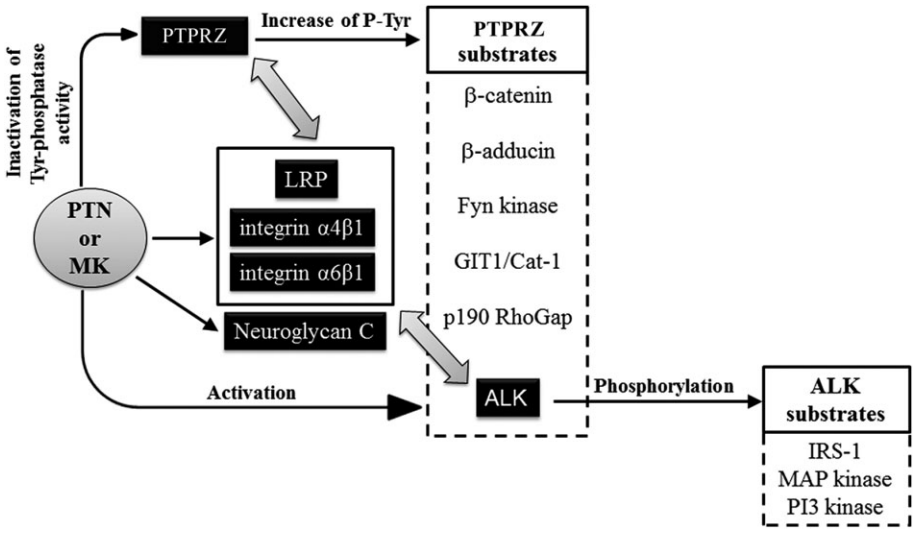

Figure 1

The receptor complex for pleiotrophin (PTN) and midkine (MK): receptor protein tyrosine phosphatase (PTPR) B/Z1 and anaplastic lymphoma kinase (ALK) and their interaction. The binding of PTN or MK with receptor protein tyrosine phosphatase type Z (PTPRZ) inactivates the intrinsic tyrosine (Tyr) phosphatase activity of PTPRZ resulting in an increase of Tyr phosphorylation (P-Tyr) of the substrates of PTPRZ, among which is ALK. ALK can also be directly activated by PTN or MK, leading to the phosphorylation of ALK substrates. PTPRZ and ALK also form a complex with other identified MK-binding proteins such as lipoprotein receptor-related protein (LRP) and integrins. Neuroglycan C also serves as a functional MK receptor. IRS-1, insulin receptor substrate-1.

domain of PTPRZ, a mechanism supported by the demonstration that PTN directly impedes the phosphotyrosine phosphatase activity of PTPRZ (Meng *et al.*, 2000). This hypothesis for the mechanism of action of PTN was confirmed by Fukada *et al.* (2006). They managed to induce the oligomerization of PTPRZ using an artificial dimerizer, polyclonal antibodies against the extracellular region of PTPRZ and PTN. The PTN/PTPRZ signalling pathway (Figure 1) regulates tyrosine phosphorylation of downstream targets including β-catenin (Meng *et al.*, 2000), β-adducin (Pariser *et al.*, 2005a,b), Fyn (Pariser *et al.*, 2005c), GIT1/Cat-1 (Kawachi *et al.*, 2001) and p190 RhoGap (Tamura *et al.*, 2006), which are important players in cell-cell adhesion, cell motility and migration, cell division, and, importantly, for an epithelial-mesenchymal transition (Perez-Pinera *et al.*, 2007). The robust evidence demonstrating the significant structural and functional redundancy between PTN and MK, that has been compiled for the last two decades (Kadomatsu *et al.*, 2013), suggest that binding of MK to PTPRZ could trigger similar mechanisms to those triggered by the PTN/PTPRZ complex (Figure 1).

MK and PTN are also activating ligands for the ALK receptor (Stoica *et al.*, 2001). PTN exerts a higher binding affinity for ALK (K_D = 30 pM) than MK (K_D ~100 pM), although both exert physiological roles through ALK (Wellstein, 2012). However, it has been determined that ALK is also a substrate of PTPRZ (Perez-Pinera *et al.*, 2007) suggesting the possibility that MK and PTN could trigger signalling pathways by direct activation of ALK or by regulating ALK phosphorylation levels through their capacity to inhibit the phosphatase activity of PTPRZ (Figure 1). Similarly to MK and PTN, ALK is also highly expressed in the nervous system during development and it has been suggested that there is connection between the PTN/ALK axis and neuronal repair in adult rats (Mi *et al.*, 2007).

MK has been also shown to bind proteoglycans such as syndecans (Nakanishi *et al.*, 1997), glypican-2 (Kurosawa *et al.*, 2001) and versican/PG-M (Zou *et al.*, 2000). Neuroglycan C also serves as an MK receptor for the promotion of neurites in oligodendrocyte precursor-like cells (Ichihara-Tanaka *et al.*, 2006). In addition, low density lipoprotein receptor-related protein (LRP), integrin α4β1 and integrin α6β1 were identified as MK-binding proteins in embryonic mouse brain (Muramatsu *et al.*, 2000; 2004). PTPRZ and ALK also form a complex with LRP and the integrins, suggesting the possibility that LRP and integrins may form the core of the receptor complex for MK, and other molecules such as PTPRZ and ALK are recruited to the complex (Figure 1) (Muramatsu, 2011; Kadomatsu *et al.*, 2013).

Roles of MK and PTN in addiction and neurodegeneration

Drug addiction

Drug-induced neurotoxicity. Methamphetamine and 3,4-methylenedioxymethamphetamine, amphetamine derivatives that are more neurotoxic than amphetamine, have been shown to cause dopaminergic cell death in the substantia nigra (Ares-Santos *et al.*, 2013). In contrast, amphetamine is widely known to induce striatal denervation without causing any toxic effects on dopaminergic neurons in the substantia nigra (Krasnova *et al.*, 2005). Surprisingly, it was shown that amphetamine causes dopaminergic cell loss in the substantia nigra of PTN knockout (PTN-/-) mice (Gramage *et al.*, 2010a) suggesting PTN is a single genetic factor that critically

modulates previously unknown amphetamine neurotoxic effects (Gramage and Herradon, 2011). Several different drugs of abuse, including amphetamine and its derivatives, have been shown to induce neuroinflammation (Coelho-Santos *et al.*, 2012). Sustained neuroinflammation and/or exacerbated neuroinflammatory responses, including astrocytosis and microglia activation, have been linked to neurodegenerative processes (Qin *et al.*, 2007; Sanchez-Guajardo *et al.*, 2013). Interestingly, amphetamine-induced astrocytosis in the nigrostriatal pathway is significantly enhanced in PTN-/- mice (Gramage *et al.*, 2010a; 2010b). However, amphetamine-induced striatal astrocytosis is also enhanced in MK-/- mice, although loss of dopaminergic terminals in the striatum was found to be similar to that observed in wild type (WT+/+) mice (Gramage *et al.*, 2011). These data suggest that both cytokines have neuroprotective roles against drug-induced neurotoxicity and this hypothesis is supported by results from *in vitro* studies (Gramage *et al.*, 2008; 2010b). These different responses to amphetamine treatment in PTN-/-, MK-/- and WT+/+ mice led us to use these animal models to identify druggable downstream targets in the PTN/MK signalling pathways that could modulate the amphetamine-induced neurotoxic effects (Gramage *et al.*, 2013a). In proteomic studies, we identified 13 differentially expressed phosphoproteins that are judged to be relevant in the neuroprotective roles of PTN and MK against amphetamine-induced neurotoxicity. It is very interesting to note that four of these phosphoproteins, annexin A7 (ANXA7), COP9 signalosome subunit 5 (COPS5), aldehyde dehydrogenase family 1 member A1 (ALDH1A1) and creatine kinase U-type (CKMT1), are known to be involved in PD. This result is significant, as PTN and MK have also been demonstrated to limit the progression of PD (Prediger *et al.*, 2011; Taravini *et al.*, 2011) and have been suggested to be among the important genetic factors that could prevent the development of PD in methamphetamine abusers (Gramage and Herradon, 2011; Callaghan *et al.*, 2012). Studies designed to confirm or to reject each of those four identified phosphoproteins as new pharmacological targets in the treatment or prevention of amphetamine-induced neurotoxicity (and, possibly, PD) are in progress.

Drug-induced addictive effects. MK and PTN also regulate drug-induced addictive behaviours (Gramage and Herradon, 2011) and pharmacological effects (Gramage and Herradon, 2010; Gramage *et al.*, 2012). The rewarding properties of drugs can be tested in animal models by self-administration studies and the conditioned place preference (CPP) paradigm. CPP is a simple non-invasive procedure, which is compatible with the Pavlovian conditioning serving the drug as an unconditioned stimulus that is repeatedly paired with a specific environment that serves as conditioned stimulus. Environmental cues previously associated with reinforcing drugs can play an important role in relapse to drug seeking behaviours in humans (Dackis and O'Brien, 2005). This conditioning in which previously neutral cues acquire secondary reinforcing properties when paired with a primary reinforce can be tested in the CPP paradigm (Tzschentke, 2007), which is traditionally used to identify novel genetic factors possibly underlying the induction and extinction of drug addictive behaviours, particularly in genetically modified mouse models (Tzschentke, 2007). Morphine-induced CPP is enhanced in PTN-/- mice compared to MK-/- and WT+/+ mice (authors' personal observation). Acquisition of amphetamine-induced CPP was found to be similar in PTN-/-, MK-/- and the control, WT+/+, mice (Gramage *et al.*, 2010b; 2011). However, in those studies it was shown that PTN-/- mice maintain amphetamine-induced CPP 5 days after the last injection of amphetamine whereas WT+/+ and MK-/- mice did not maintain amphetamine-induced CPP (Gramage *et al.*, 2010b; Martín *et al.*, 2013), suggesting a role for endogenous PTN in the loss of amphetamine-induced CPP. In contrast, we recently found that genetic deletion of MK strikingly decreases the capacity of mice to eradicate cocaine-induced CPP (Gramage *et al.*, 2013b). The data support the notion that the absence of endogenous PTN or MK is a risk factor for amphetamine or cocaine relapse, respectively, after drug withdrawal and suggest that mutations on the PTN/MK genes leading to a loss of their functions or low levels of their expression in humans could underlie an individual increased vulnerability to amphetamine and cocaine relapse.

The evidence presented here and summarized in Table 1 suggests that the potentiation of MK and/or PTN signalling

Table 1

Proposed roles and effects of pleiotrophin (PTN) and midkine (MK) in drug addiction, Parkinson's disease and Alzheimer's disease

	Drug addiction		Neurodegenerative disorders	
	Neurotoxicity	**Addictive behaviour**	**Parkinson's Disease**	**Alzheimer's Disease**
PTN	↓ Amphetamine nigrostriatal toxicity ↓ Cocaine neurotoxicity	↓ Amphetamine relapse ↓ Morphine reward	↓ nigrostriatal degeneration ↑ functional nigrostriatal recovery	
MK	↓ Amphetamine striatal toxicity	↓ Cocaine relapse	↓ neurochemical and behavioural dysfunctions in nigrostriatal pathways ↓ olfactory and cognitive dysfunctions of early stages	↓ amyloid β-peptide plaques cytotoxicity ↓ amyloid β-peptide plaques deposition

This table summarizes the actions of PTN and MK in preclinical models

pathways could be a novel therapeutic strategy to treat, prevent or limit drug-induced neurotoxic and addictive effects.

Parkinson's disease

MK and PTN, their receptors syndecan-3 and PTPRZ, and associated intracellular signalling molecules, are highly expressed in the striatum during nigrostriatal development (Marchionini *et al.*, 2007), suggesting important roles for these cytokines in dopaminergic systems in normal and pathological states. Accordingly, PTN has been found to increase the levels of expression of TH, the rate-limiting enzyme in the dopamine synthesis in cell cultures (Jung *et al.*, 2004). The dopamine precursor, L-Dopa, used as a drug of choice in PD, up-regulates the expression levels of PTN in the nigrostriatal pathways of Parkinsonian rats (Ferrario *et al.*, 2004). L-Dopa is known to act as an exogenous precursor to increase dopamine synthesis in the remaining dopaminergic neurons of patients with PD, but also to contribute to a trophic environment for dopaminergic terminals in the striatum, which may turn lead to the development of aberrant striatal circuits and the appearance of L-Dopa-induced dyskinesias (Dicaudo *et al.*, 2012). PTN has been identified as a growth factor with significant trophic effects on dopaminergic neurons *in vitro* (Jung *et al.*, 2004) and as a critical survival factor for the catecholaminergic PC12 cell line (Gramage *et al.*, 2008). Whether or not, L-Dopa's ability to up-regulate PTN levels of expression is involved in the development of L-Dopa-induced dyskinesia remains to be established. Importantly, PTN was shown to exert key trophic effects on donor cells after neural transplantation *in vivo* and elicit functional recovery of nigrostriatal pathways (Hida *et al.*, 2007; Moses *et al.*, 2008). In addition, striatal PTN overexpression to an extent similar to the level of PTN expression found in the area during development provides functional and morphological neuroprotection against the Parkinsonian insult in rats (Taravini *et al.*, 2011; Gombash *et al.*, 2012).

MK has previously been shown to promote survival of mesencephalic TH-immunoreactive neurons (Kikuchi *et al.*, 1993). It has also been found that activation of MK and PTN signalling is required for the neuritogenic activity of chondroitin sulfate proteoglycans in dopaminergic neurons (Sotogaku *et al.*, 2007). In addition, MK deficiency has been related to neurochemical and behavioural dysfunctions in the dopaminergic system (Ohgake *et al.*, 2009), confirming the potential importance of this cytokine in the nigrostriatal pathways in physiological and pathological conditions (Marchionini *et al.*, 2007). Furthermore, genetic deletion of MK causes a partial loss of dopaminergic neurons and depletion of dopamine, resulting in olfactory and memory deficits with no major motor impairments (Prediger *et al.*, 2011). Taking into account that impairments in olfactory and cognitive functions are associated with early onset of disruption of dopaminergic neurotransmission in different brain areas, Prediger *et al.* (2011) suggested that the MK-/- mouse may represent a promising animal model for the study of the early stages of PD and for testing new therapeutic strategies to restore sensorial and cognitive processes in PD.

The evidence compiled *in vivo* and *in vitro*, summarized in Table 1, support the possibility of using PTN or MK as new therapeutics for PD.

Alzheimer's disease

MK and PTN have been found to be expressed in senile plaques in the brain of patients with Alzheimer's disease (Yasuhara *et al.*, 1993; Wisniewski *et al.*, 1996). Despite the presence of PTN in the cerebral amyloidoses of patients with Alzheimer's disease and other disorders also characterized by deposition of amyloid β, Down's syndrome (Wisniewski *et al.*, 1996), the role of PTN in the neurodegenerative process inherent to Alzheimer's disease has been studied to a lesser extent than that of MK. In contrast, the study demonstrating the expression of MK in nearly all amyloid β-peptide plaques in the cerebral cortex of eight Alzheimer's disease patients, but not in the control tissues (Yasuhara *et al.*, 1993), led to further studies on the role of MK in this neurodegenerative disorder. For example, elevated serum levels of MK were also detected in nearly half of patients with Alzheimer's disease (Salama *et al.*, 2005). More importantly, MK was found to inhibit cytotoxicity (Yu *et al.*, 1998) and polymerization (Monji *et al.*, 2000) of amyloid β-peptide, suggesting that MK by counteracting the deposition of amyloid β-peptide plaques has a neuroprotective role in this disease. Accordingly, the deposition of amyloid β-peptide plaques derived from transgene was more extensive in MK-/- mice than in WT+/+ mice (Muramatsu *et al.*, 2011). This effect was found to be related to the ability of MK to bind amyloid β-peptide, presumably to inhibit its polymerization, because mice lacking endogenous PTN, which binds with much lower affinity to amyloid β-peptide, did not show enhanced deposition of amyloid β-peptide plaques (Muramatsu *et al.*, 2011).

In summary, these data suggest that MK could be a new therapy to prevent and to limit the progression of Alzheimer's disease. However, further studies are needed to clarify the significance of the expression of PTN in senile plaques of patients with Alzheimer's disease before being able to postulate it as a new therapeutic target in Alzheimer's disease.

Activation of MK/PTN signalling pathways: a novel therapeutic strategy to treat addictive and neurodegenerative disorders

The existing evidence here strongly suggests that the potentiation of the MK/PTN signalling cascades could be a new pharmacological treatment to halt the progression of neurodegenerative conditions, to limit or prevent drug-induced neurotoxic effects and neurodegenerative sequelae, to reduce the rewarding effects of drugs of abuse and to prevent drug relapse. In addition to gene and cellular therapies as a long-term strategy, exogenous administration of MK and/or PTN as well as pharmacological modulation of their known signalling effectors deserve consideration for midterm treatments.

Administration of MK and PTN proteins

In addition to the beneficial effects of MK or PTN overexpression, induced by gene-transfer, observed in preclinical models for the treatment and prevention of neural injury and neurodegeneration induced by different causes, including cerebral infarction, Alzheimer's disease and PD (Gramage and

Herradon, 2011; Muramatsu, 2011; Taravini *et al.*, 2011; Gombash *et al.*, 2012), the neuroprotective effects of exogenous administration of MK have also been observed in animal models. In order to evaluate *in vivo* activity of MK in preventing neuronal death, Yoshida and colleagues (2001) administered MK into the brain ventricle immediately before occlusion of the bilateral common carotid artery of Mongolian gerbils. MK administration (0.5–2 μg) was found to ameliorate delayed neuronal death in the hippocampal CA1 region caused by transient ischaemia. In addition, it has been shown that i.c.v. administration of MK (0.4 μg) significantly reduced neuronal loss in the kainic acid (KA)-injected mouse hippocampus and the intensity and duration of KA-induced seizures (Kim *et al.*, 2010).

Although promising, these results were obtained after intracranial administration of MK, a route of administration that should be avoided in humans whenever possible. Exogenous administration of MK has been recently patented for the treatment of various forms of ischaemia, including heart attack (US patent number 8288343). This patent covers the stimulation of nitric oxide (NO) synthesis by MK injection in order to facilitate blood flow, vasodilatation and angiogenesis in the damaged tissue. Whether or not this novel mechanism triggered by MK is also involved in the neuroprotective effects of MK in neurotoxic or neurodegenerative processes remains to be clarified. However, drug delivery to the CNS is highly problematic because the blood–brain barrier (BBB) acts through a variety of mechanisms to prevent the unregulated entry of blood-borne substances into the brain (Pardridge, 2012). There are ongoing clinical trials that involve intracerebral administration of growth factors such as glial-derived neurotrophic factor and nerve growth factor (NGF) to treat Alzheimer's disease and PD (Allen *et al.*, 2013); however, the inherent risks of this route of administration limit its general use in these patient populations.

Many groups are currently working to overcome these limitations using other routes of administration and advanced pharmaceutical technology. For instance, strategic drug delivery to the brain, an approach that considers in depth the relationship among the BBB, the candidate therapeutic, the CNS target and the disease state to be treated, has been successfully applied to deliver a leptin analogue into the CNS (Banks *et al.*, 2011). In addition, the convenient intranasal administration of different growth factors such as NGF and acidic fibroblast growth factor has been successful at inducing neurogenesis and angiogenesis after brain ischaemic stroke (Cheng *et al.*, 2011), attenuating the progression of Alzheimer's disease (Capsoni *et al.*, 2012) and reducing the oedema subsequent to traumatic brain injury (Lv *et al.*, 2013). Thus, intranasal delivery is emerging as a non-invasive option for delivering drugs to the CNS. This method also facilitates the delivery of large and/or charged therapeutics, which fail to effectively cross the BBB (Chapman *et al.*, 2012). In addition, it is very important to note that the existence of the nose-to-cerebral spinal fluid pathway has been verified in humans and, furthermore, there is abundant indirect evidence for the nose-to-brain pathway as determined by the efficacy of intranasally administered neuroproteins, such as insulin, oxytocin, and vasopressin in clinical trials (Zhu *et al.*, 2012). The evidence summarized in this review strongly supports the preclinical evaluation of intranasal administration of MK and/or PTN as a critical preliminary step before testing the clinical application of MK and PTN in treating chronic CNS diseases.

Other emerging techniques, such as non-invasive disruption of the BBB using focused ultrasound, have been successfully employed to systemically administer neurotrophic factors and trigger neuronal downstream signalling effects in a highly localized region in the brain (Baseri *et al.*, 2012). Non-invasive ultrasound delivered to the brain through the intact skull combined with preformed microbubbles, can safely induce transient, localized and reversible disruption of the BBB, allowing therapeutics to be delivered into the CNS; this has recently been demonstrated in rodent models of Alzheimer's disease and humans (O'Reilly and Hynynen, 2012). Protein carriers for brain-targeting delivery of therapeutic proteins are producing promising results as well in animal models (Fu *et al.*, 2013). Nanotechnology has patented new formulations and is evolving as a promising new technique for delivering drugs needed to treat brain diseases, especially those arising from neurodegenerative conditions (Jain *et al.*, 2013). The ideal method for transporting drugs across the BBB should be controllable and should not damage the barrier and amongst the various approaches that are available, nanobiotechnology-based delivery has been judged to be the best (Jain *et al.*, 2013).

All in all, when thinking of exogenous administration of growth factors, potential side effects derived from their carcinogenic properties have to be considered (Muramatsu, 2010). It should be noted that MK and PTN exhibit angiogenic potential, which is important in the tissue remodelling and repair capacity of both cytokines after injury (Weckbach *et al.*, 2012; Fang *et al.*, 2013). In addition, MK/PTN may alter the vascular tone of large vessels, such as aorta, as it may affect the regulation of catecholamine synthesis and the renin-angiotensin II system in this tissue (Herradon *et al.*, 2004; Ezquerra *et al.*, 2005; Hobo *et al.*, 2009), effects which have been associated with the known capacity of MK to induce hypertension (Kadomatsu, 2010). However, the potential peripheral side effects of PTN/MK can be diminished by the choice of method used to administer the substances to the CNS. For instance, with regard to the possible peripheral effects using intranasal administration, experience with NGF has shown that intranasal delivery minimizes the build-up of peripheral NGF, even though residual leakage and absorption of NGF into the blood stream occurs from the nasal compartment (Malerba *et al.*, 2011).

Pharmacological modulation of the MK/PTN/PTPRZ signalling pathway

The cellular phosphatase activity of PTPs is precisely balanced by the kinase activity of other family of enzymes, the protein tyrosine kinases (PTKs). Disruption of this balance underlies different diseases (Hendriks *et al.*, 2008). For this reason, PTPs (including the receptor-like class) are currently being considered as prime targets for drug design (Wong *et al.*, 2013) following the path opened by selective PTK inhibitors that were previously developed and reached clinical use (Ventura and Nebreda, 2006). Pharmaceutical development of therapeutics targeting PTPs has been proposed to treat a wide variety of diseases including diabetes mellitus, neural diseases

Table 2

Potential common targets related to midkine (MK) and pleiotrophin (PTN) for the treatment of neurodegenerative disorders and amphetamine neurotoxicity

Protein (Abbreviation)	Function	Role in neurodegenerative disorders
Aldehyde dehydrogenase family 1 member A1 (ALDH1A1)	Metabolism of biogenic aldehydes and amines, and its potentially toxic metabolites (Anderson *et al.*, 2011).	• Its expression is reduced in substantia nigra of PD patients (Westerlund *et al.*, 2005). • Candidate biomarker for PD diagnosis (Grünblatt *et al.*, 2010). • Its deletion results in a Parkinsonian phenotype in mice (Wey *et al.*, 2012). • ALDH inhibition has been described as a new pathogenic mechanism in PD (Fitzmaurice *et al.*, 2013).
Annexin A7 (ANXA7)	Calcium/phospholipid-binding protein involved in exocytosis (Liemann and Lewit-Bentley, 1995).	• Changes of expression related to PD (Lessner *et al.*, 2010).
COP9 signalosome subunit 5 (COPS5)	Regulates the cellular ubiquitin/proteasome pathway (Li *et al.*, 2008).	• Ubiquitin/proteasome pathway disruptions have a role in neurodegenerative diseases such as PD (Huang and Figueiredo-Pereira, 2010).
Creatine kinase U-type (CKMT1)	Reversibly convert creatine into phosphocreatine and shielding effects on the opening of transition permeability pores in the mitochondria, thus affecting necrotic and apoptotic processes (Adhihetty and Beal, 2006).	• Its alterations may play a role in neurodegenerative diseases, such as Alzheimer's disease or PD (Adhihetty and Beal, 2006; Nersesova, 2011).

This table shows the phosphoproteins related to amphetamine neurotoxicity differently expressed in MK-/- and PTN-/- mice and their relationship with neurodegenerative disorders. These phosphoproteins have been suggested as potential new pharmacological targets involved in PTN or MK neuroprotection (Gramage *et al.*, 2013a).

such as PD and Alzheimer's disease, inflammatory diseases and allergy (Herradon and Ezquerra, 2009; Heneberg, 2009).

In the case of the MK/PTN receptor, PTPRZ, reports of PTPR inhibitors are usually from PTP-1B programme screening panels. For example, PTPRZ is often found in selection panels in PTP inhibitor screens (Hoffman *et al.*, 2004). Following this path, Huang and colleagues (2003) designed a trifluoromethyl sulfone (4-trifluoromethylsulfonylbenzyl 4-trifluoromethylsulfonylphenyl ether) inhibitor of PTPRZ with an IC_{50} of 3.5 μM that is twofold selective versus PTPRE and ~10-fold selective versus PTPRD. To the best of our knowledge, this is the only PTPRZ inhibitor synthesized with relative selectivity, although we should expect, in the short term, a number of this type of compounds since methods designed to specifically test inhibitors of PTPRZ have been recently patented (i.e. US patent number 20100287626).

Fyn kinase, β-catenin and β-adducin, known substrates of PTPRZ, the levels of phosphorylation of which are regulated by the ability of PTN to inhibit the phosphatase activity of PTPRZ, have been linked to the development and progression of neurodegenerative and addictive disorders (see review by Gramage and Herradon, 2011). Thus, pharmacological modulation of PTN and MK signalling cascades for these indications could be achieved by acting downstream of PTPRZ. Because β-catenin and β-adducin show a wide variety of functions, many of them critical at the cellular level, their pharmacological modulation is anticipated to be problematic. However, different rational drug design programmes targeting Fyn kinase are currently being developed because of the demonstrated implication of this kinase in cancer and brain diseases such as PD and Alzheimer's disease (Schenone *et al.*, 2011). However, a significant obstacle needs to be overcome before modulation of Fyn kinase activity can be used to regulate PTN and MK functions: the specific residues in Fyn that are specifically modulated by PTN/MK need to be identified. PTN has been shown to increase tyrosine phosphorylation of Fyn by inhibiting PTPRZ phosphatase activity (Pariser *et al.*, 2005c), but, to the best of our knowledge, specific residues phosphorylated in Fyn by PTN have not been identified. This is of critical importance because depending on the residue that is phosphorylated the kinase activity of Fyn may be activated or inhibited. For instance, activation of the kinase activity of Fyn by phosphorylation of its residue Y417 leads to the phosphorylation of the NR2B subunit of the NMDA receptor which is involved in alcohol dependence (Wang *et al.*, 2007).

The recent application of phosphoproteomic techniques to identify proteins that may be relevant mediators of PTN/MK neuroprotective effects against amphetamine-induced neurotoxicity (Gramage *et al.*, 2013a) has revealed several new compounds: ANXA7, COPS5, ALDH1A1 and CKMT1. Table 2 summarizes the cellular function of these proteins and existing evidence supporting their possible roles in neurodegenerative diseases. Since the phosphorylation pattern of these proteins was found to be differentially regulated by amphetamine treatment and the presence/absence of endogenous MK and PTN (Gramage *et al.*, 2013a), the data not only confirm the connection between the molecular mechanisms of amphetamine-induced neurotoxicity and

those involved in neurodegenerative processes but suggest these four proteins could be new pharmacological targets involved in the neuroprotective effects of MK and PTN. Interestingly, some of these proteins, such as ALDH1A1, are already in screening panels for drug discovery. The current development of aldehyde dehydrogenase inhibitors (Koppaka *et al*., 2013) provides a rationale for the continued development of ALDH isozyme-selective modulators (including activators) with potential applications in addictive and neurodegenerative disorders.

Conclusion

There is robust evidence demonstrating that MK and PTN limit the rewarding effects of drugs of abuse and, potentially, prevent drug relapse. There is also convincing evidence that MK and PTN provide neuroprotective effects against the neurotoxicity and development of neurodegenerative disorders induced by drugs of abuse. The next step, achievable in the midterm, is to identify a suitable method for MK and PTN delivery into the CNS by a non-invasive technique. Based on existing evidence with different growth factors, intranasal administration of MK/PTN or nanobiotechnology-based delivery techniques are suggested as prime methods to test MK/PTN delivery to the CNS; i.c.v. administration of MK (or PTN) could serve as a control since it has been successfully used in animal models. Identification of new molecules, downstream of MK/PTN/PTPRZ or pharmacological modulation of those already known provide a more traditional, but probably effective, therapeutic strategy for treating addictive and neurodegenerative disorders.

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Conflict of interest

None to declare.

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