REVIEW

Neuroprotective and anti-ageing role of leptin

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Abstract

Leptin (Lep), an adipose-derived hormone, exerts very important functions in the body mainly on energy storage and availability. The physiological effects of Lep controlling the body weight and suppressing appetite are mediated by the long form of Lep receptor in the hypothalamus. Lep receptor activates several downstream molecules involved in key pathways related to cell survival such as STAT3, PI3K, MAPK, AMPK, CDK5 and GSK3β. Collectively, these pathways act in a coordinated manner and form a network that is fully involved in Lep physiological response. Although the major interest in Lep is related to its role in the regulation of energy balance, and since resistance to Lep affects is the primary risk factor for obesity, the interest on their effects on brain cognition and neuroprotection is increasing. Thus, Lep and Lep mimetic compounds now await and deserve systematic exploration as the orchestrator of protective responses in the nervous system. Moreover, Lep might promote the activation of a cognitive process that may retard or even partially reverse selected aspects of Alzheimer's disease or ageing memory loss.

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Introduction

It is well documented that hormones play a vital role in the regulation of numerous biochemical pathways throughout the body (Fernandez & Torres-Alemán 2012). In recent years it has been demonstrated that a range of hormones can be found within the CNS jointly with its receptors and this is evidence of an existence of physiological effects in the brain under regulation of hormonal signalling (Scott *et al.* 2009). Although a wide number of hormonal systems can be potential candidates to study the effects on the brain, the largest bodies of work concentrate mainly around leptin (Lep) and insulin due to their modulation on hippocampal function (Plum *et al.* 2005, Signore *et al.* 2008). Likewise, there are other potential targets regulated by Lep such as brain-derived neurotrophic factor (BDNF), which is a neurotrophin also involved in hypothalamic food intake regulation and represents a potential target for developing new anti-obesity therapies. Furthermore, cytokines such as interleukin 6 and other hormones also regulate the physiological actions of Lep (Sadagurski *et al.* 2010, Rosas-Vargas *et al.* 2011).

Alterations in lipid metabolism have been related to neurodegenerative disorders, in particular Alzheimer's disease (AD; Lieb *et al.* 2009, Tezapsidis *et al.* 2009). Interestingly, clinical studies have also shown that patients with diabetes mellitus have an increased risk of suffering from AD, which reveals the link between hormonal diseases and neurodegenerative processes (Salminen *et al.* 2011, Li *et al.* 2012). Furthermore, the association between obesity and altered signalling mechanisms of insulin implies a greater susceptibility to neurodegenerative processes (Fig. 1).

However, controversy exists in determining the specific relationships between obesity and Alzheimer's disease (AD). Although some authors consider that obesity in middle age is due to a risk of dementia, others questioned the existence of a relationship between the two processes, particularly in humans (Doruk *et al.* 2010, Arab *et al.* 2011). On the other hand, it is well known that both insulin resistance, associated with an

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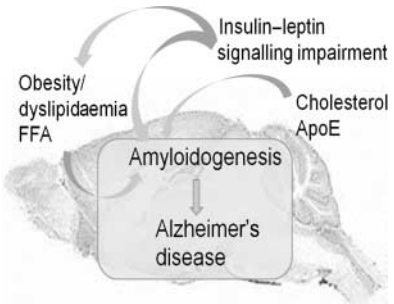

Figure 1 Factors involved in the amyloidogenesis: free fatty acids (FFA), cholesterol, lipoproteins (Apo lipoprotein E), obesity and dislipidaemia status and impairment of insulin and leptin signalling (adapted from Merlo S, Spampinato S, Canonico PL, Copani A & Sortino MA 2010 Alzheimer's disease: brain expression of a metabolic disorder? *Trends in Endocrinology & Metabolism* **21** 537–544).

increase in plasmatic levels of fatty acids, and high VLDL content contribute to amyloidogenesis (Arab *et al.* 2011).

Probably, the main characteristic and important problem to solve in AD is memory loss. It is well known that the hippocampus has been recognized to play a fundamental role in the process of learning and memory (Bonda *et al.* 2011). Thus, hormonal modulation of hippocampal neuronal function by insulin and Lep has great interest and numerous implications (Bjørbaek & Kahn 2004, Harvey *et al.* 2006, Harvey 2007, Carro 2009).

The aim of the present review is to discuss the potential beneficial effects of the hormone Lep in neurological disorders basically in two aspects: its neuroprotective role and beneficial effects on memory (Tezapsidis *et al.* 2009).

Physiological functions of Lep in the CNS

The Lep gene (*OB* (*LEP*)) encodes a polypeptide of 16 kDa. The primary sequence and the crystallographic data suggest that Lep adopts a helical three-dimensional structure, which is reminiscent of some cytokines such as interleukin 2 (Elmquist *et al.* 1998, Elias *et al.* 2000).

The physiological functions of Lep are known to be mediated through the binding to Lep receptor (Ob-R), and elicit an array of subsequent intracellular signalling cascades (Guo *et al.* 2008). For instance, previous studies demonstrated that mice with a deficiency in Lep develop morbid obesity and diabetes and plasma levels of Lep are highly correlated with the amount of body fat (Thio *et al.* 2006, Coccurello *et al.* 2009, Doruk *et al.* 2010).

Within the CNS, Lep receptors are located in the hypothalamus, where they are known to be involved in the control of energy homeostasis. Besides the regulation of body energy homeostasis and neuroendocrine functions in the hypothalamus, Lep may have more widespread actions in the brain. Examples of Lep functions in the brain are the modulation of the excitability of hippocampal neurons by activating potassium channels. Another interesting point is that, since Lep receptor-deficient mice have impaired spatial learning ability, it was suggested that Lep signalling may influence neuronal excitability and synaptic plasticity (Oomura *et al.* 2006).

The regulation of appetite and energy expenditure by Lep takes place by inhibiting serotonin synthesis and releasing it in brainstem neurons. Therefore, the brain regulation of serotonin is an important biological and medical function of Lep. This effect is due to the localization of Lep receptors, which are found in brainstem serotonergic neurons. Besides, the presence of Ob-Rb mRNA expression has been demonstrated in the substantia nigra. Neurochemical effects of Lep on dopaminergic neurons also include the increase of tyrosine hydroxylase content and the regulation of dopamine transporter activity (Scott *et al.* 2009). Therefore, Lep is able to modulate the mesolimbic dopaminergic system (Bjørbaek & Kahn 2004, Scott *et al.* 2009).

On the other hand, Lep receptors have been shown to be expressed in neuronal cell cultures of hippocampal and glial cells (Marwarha *et al.* 2012). As Lep is a modulator of hippocampal function, the study of the effects of Lep in this brain area on glutamate receptors, especially *N*-methyl-D-aspartate (NMDA) and AMPA, is therefore of particular interest, because they are potential modulators of not only learning and memory processes but also with regard to CNS-driven diseases such as epilepsy (Moult & Harvey 2008, 2011, Morley & Banks 2010). These roles are interesting, because it has been demonstrated that Lep exerts an important role in protecting from kainate excitoxicity and modulating synaptic plasticity and dendritic morphology (Shanley *et al.* 2002).

Lep receptor signalling in neurons

From the Lep receptor gene a total of six different isoforms are synthesized. All are membrane proteins with the exception of the soluble isoform, Ob-Re. The Ob-R form is the longest isoform and is solely responsible for signalling induced by ligand binding. The best-described signalling pathway used by Lep involves the coordinated activation of JAK2/STAT3. The binding of Lep, or an agonist, to its receptor stimulates the activation of JAK2, which in turn phosphorylates tyrosine residues in the intracellular domain of the Lep receptor. STAT3 is a transcriptional factor that, upon phosphorylation, dimerizes and is transported to the nucleus, where it controls

the transcription of target genes (Guo *et al.* 2008, Signore *et al.* 2008). This favours the activation of different molecular mechanisms critical for Lep effects on body weight, control the route of phosphatidylinositol 3 kinase (PI3K), the kinase AKT, MAPK and protein kinase activated by 5′-AMP (Shanley *et al.* 2002). The signalling mechanism of the Lep receptor is negatively regulated by the molecule suppressor of cytokine signalling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B). In particular, SOCS3 is a member of cytokine-inducible signalling inhibitors, which inhibits LepR signalling by blocking JAK2 activity (Hubschle *et al.* 2001, Avraham *et al.* 2010; Fig. 2).

More recently, it has been suggested that Cdk5/p35 modulate signalling triggered by Lep (He *et al.* 2009). Thus p35, a co-activator of p35, favours Lep signalling manifested by STAT3 and SOCS3 activation. Moreover, cdk5 was co-localized with Lep receptor in the same cells in the hypothalamus (He *et al.* 2009).

Another downstream target of Lep signalling is peroxisome proliferator-activated receptor γ (PPARγ (PPARG)). Lep is involved in the regulation of PPARγ levels both *in vivo* in peripheral tissues and in neuronal cultures of human neuroblastoma SH-SY5Y (Greco *et al.* 2009*a*,*b*, 2011).

Moreover, Lep modulates activation of endogenous cellular energy sensors in neurons such as AMP and NAD^+, AMPK and sirtuin 1 (SIRT1; Avraham *et al.* 2010). It is well known that AMPK is an important enzyme involved in the regulation of cellular metabolic activity (Marwarha *et al.* 2010, Greco *et al.* 2011). Among them, AMPK regulates the cellular uptake of glucose, the β-oxidation of fatty acids and the biogenesis of glucose transporter 4 (GLUT4) and mitochondria (Greco *et al.* 2009*a*,*b*, 2011, Salminen *et al.* 2011). Thus, through changes in hypothalamic AMPK activity, Lep could regulate human metabolism. Furthermore, downstream targets of AMPK, such as the mammalian target of rapamycin pathway, are important not only in food intake regulation but also in the control of the ageing process and autophagia (Greco *et al.* 2011).

Lep as a neuroprotective agent

Different studies conducted in *in vitro* models show that Lep is neuroprotective not only in dopaminergic cells but also in other cell types and brain areas (Dicou *et al.* 2001, Tezapsidis *et al.* 2009, Oury and Karsentry 2011). These data suggest the potential application of Lep in the treatment of neurological disorders such as AD and Parkinson's disease (PD; discussed below).

Role of Lep in AD

AD has been well characterized as a multifactorial neurodegenerative process characterized by progressive neuronal loss, gliosis and accumulation of two markers of disease: senile plaques (aggregates of β-amyloid peptides) and neurofibrillary tangles (hyperphosphorylated tau protein) (Greco *et al.* 2008, 2009*a*). The formation of β-amyloid aggregates is the result of an abnormal amyloid precursor protein cleavage by β- and γ-secretases. It seems that the presence of free fatty acids, cholesterol, lipoprotein and APOE

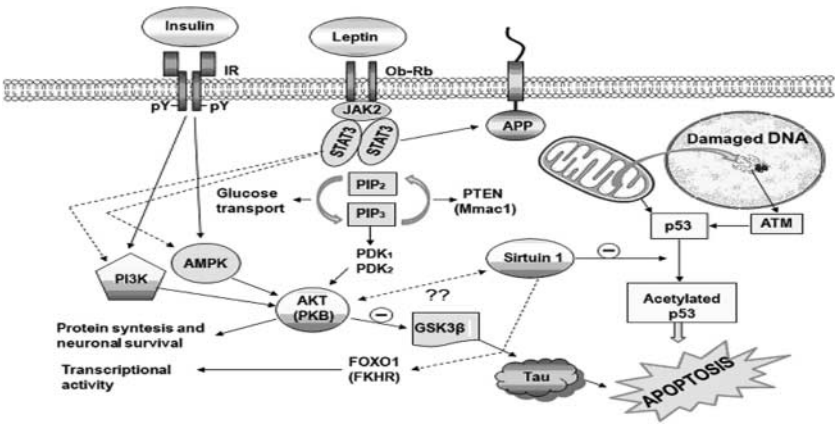

Figure 2 Proposed anti-apoptotic mechanisms of leptin. The leptin signalling pathway can contribute to reduce the neuronal apoptosis through, hypothetically, the activation of sirtuin 1 activity that, in turn, would reduce the stabilization of p53 by an acetylation process. Currently it is unknown how SIRT1 regulates AKT (??). Activation of p53 is promoted by mitochondrial metabolism impairment and the concomitant generation of reactive oxygen species. The oxidative species damage DNA and activate ataxia telangiectasia mutated (ATM) protein, which also acts due to the activation of p53.

promotes amyloidogenesis, whereas Lep facilitates their elimination. Intervention in one or more of these factors could slow or limit the process of amyloidogenesis. In the context of the β-amyloid hypothesis for AD, Lep may interfere with the pathogenesis of AD in different ways by a) inhibiting the amyloidogenic process (Greco *et al.* 2008); b) decreasing the activity of glycogen synthase kinase-3β (GSK3β) and, thus, reducing the levels of tau protein phosphorylation (Greco *et al.* 2009*b*) and c) improving the cognitive function (Tezapsidis *et al.* 2009).

Firstly, it appears that Lep may reduce amyloidogenesis, decreasing the activity of the enzyme responsible for the breakdown of the β site APP (BACE) in neurons and, thus, decreasing the amount of protein β-amyloid formed (Marwarha *et al.* 2010). It has been suggested that this effect may be indirect, and is related to the lipolytic activity of Lep. Similarly, Lep may also enhance the elimination of β-amyloid protein through the effect of APOE-dependent uptake. It has been demonstrated that Lep signalling is probably related to changes in *Apoe* gene expression and Lep would exert this effect on removal of β-amyloid aggregates with the same intensity. These observations have been confirmed in *in vitro* and *in vivo* experiments using a transgenic mice model for AD in which mice have been administered Lep chronically (Greco *et al.* 2010, Marwarha *et al.* 2010). It was shown that the treatment of a murine model of AD (TgCRND8) with Lep significantly improves all parameters of experimental AD such as decrease in β-amyloid and phospho-tau levels and cognitive function improvement (Tezapsidis *et al.* 2009).

Another mechanism involved in the neuroprotective effects of Lep may be the activation of AMPK and SIRT1, because these enzymes constitute potential targets associated with AD (Fig. 2; Greco *et al.* 2011). Low levels of Lep contribute to an insufficient stimulation of AMPK which, in turn, favours an increase in β-amyloid levels and phosphorylated tau. SIRT1 activation exerts beneficial effects in AD probably by upregulation of α-secretase production (Bonda *et al.* 2011). Moreover, additional neuroprotective effects in AD of SIRT1 may also be mediated, at different levels, through the acetylation state (and thus the localization and activity) of basic transcription factors like *p53* (*TP53*), *NF-κB*, *FOXO* and *KU70* (*XRCC6*), and this might trigger pro-survival pathways in the neuronal cell (Camins *et al.* 2010).

Published data suggest that Lep regulates tau phosphorylation through a pathway involving both AMPK and GSK3β, leading the enzyme to this inactive form by the activation of serine-9 phosphorylation (Greco *et al.* 2008, 2009*a*,*b*). Thus, Lep, which ameliorates both amyloid β- and τ-related pathological pathways, holds promise as a therapeutic for AD (Fig. 3).

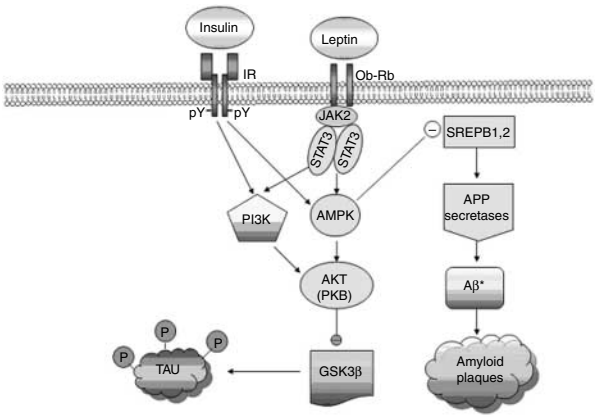

Figure 3 Insulin and leptin signalling. Leptin inhibits the hyperphosphorylation of tau protein through PI3K and AKT activation that, in turn, promotes the formation of inactive form Ser-9 GSK3β. Leptin also inhibits GSK3β activity acting on AMPK, and reducing the activity of transcription factors SREPB1,2 and the formation of amyloid deposits (Aβ*).

Effects of Lep on memory

Recent evidence indicates that Lep plays an important role in modulating hippocampal synaptic plasticity and affecting glutamate receptor trafficking, mainly NMDA and AMPA receptors (Moult *et al.* 2010).

The regulation of NMDA by Lep is important because receptor-dependent long-term potentiation (LTP) induced in the hippocampal CA1 region has been implicated in spatial learning and memory. It is well established that the synaptic activation of NMDA receptors is associated with a postsynaptic rise in intracellular Ca^{2+}, which is crucial for the induction of LTP in hippocampal CA1 synapses. Treatment of hippocampal neurons with Lep stimulates CaMKII phosphorylation and facilitates the development of LTP. It has been shown that neonatal Lep administration in rodents is able to increase the expression of the NR1 subunit of NMDA receptors in the hippocampus (Walker *et al.* 2007). Subsequently, this treatment increases the density of hippocampal synapses. This process is dependent on the synaptic activation of NR2A-containing NMDA receptors. The role of Lep in regulating dendritic morphogenesis has important implications in hippocampal synaptic plasticity and neuronal development (Moult *et al.* 2010, O'Malley *et al.* 2007). These effects of Lep are not limited to hippocampal neurons, as Lep receptors are expressed in cerebellar neurons and treatment of these neurons with Lep facilitated NR2B NMDA receptor-mediated calcium influx. Therefore, these effects could explain, in part, the beneficial effects of Lep on memory.

Lep promotes an increase in the synaptic expression of GLUR2-lacking AMPA receptors in adult hippocampal slices resulting in a persistent increase in the efficacy of excitatory synaptic transmission (Moult & Harvey 2011). AMPA receptors are permeable to Ca^{2+}, which allows the activation of specific intracellular signalling pathways required for synaptic efficacy.

Role of Lep in PD

Several reports show that weight loss is a common characteristic in patients with PD (Fiszer *et al.* 2010). The relationship between serum body weight with Lep in PD patients has been studied (Loreflät *et al.* 2009, Aziz *et al.* 2011). However, a decreased body fat mass is probably the better parameter to be correlated with lower Lep levels in PD patients (Novakova *et al.* 2011).

It was reported that Lep exerts a cytoprotective effect against the mitochondrial neurotoxin MPP^+, an experimental model of PD (Lu *et al.* 2006). In these studies two neuroprotective pathways are mainly proposed. The first one suggests that the activation by Lep of PI3K/AKT favours the survival of SH-SY5Y neuroblastoma cells (Lu *et al.* 2006, Ho *et al.* 2010). Another study suggests that Lep neuroprotective effects are mediated through the expression of mitochondrial uncoupling protein 2 (UCP2). Thus, Lep favours an increase of UCP2 that restores ATP levels *in vitro* and *in vivo* and preserves energy supply, as has been observed in the neuroblastoma SH-SY5Y cell line. These data are interesting as they show the association between Lep and the increase in mitochondrial efficiency (Ho *et al.* 2010).

6-hydroxydopamine (6-OHDA) is another well known neurotoxin. In the MN9D dopaminergic cell line, subjected to the toxic action of 6-OHDA, the administration of Lep reverses cell loss (Weng *et al.* 2007). The neuroprotective effect is related to the modulation of the route of mitogenic extracellular kinase and ERK. Lep treatment has shown significant protective effects by rescuing dopaminergic neurons from 6-OHDA toxicity *in vivo* due to pCREB increased BDNF levels. Lep-induced increase of BDNF levels may be the main potential mechanism that mediates neuroprotection and gives support to the application of Lep as a neuroprotective drug in experimental PD models.

Lep and epilepsy

The interest in Lep as anti-epileptogenic therapy has emerged after the observation that the ketogenic diet, an effective anticonvulsant therapy used to treat intractable epilepsy, elevates serum Lep levels in rodents (Thio *et al.* 2006). Thus, current data suggest that Lep will be an endogenous anticonvulsant (Shanley *et al.* 2002). This hypothesis is based on the observation that mice deficient in Lep receptors (*ob/ob* mice) are more susceptible to seizures induced by pentylenetetrazol (PTZ), an experimental proconvulsant agent used as experimental model of epilepsy (Erbayat-Altay *et al.* 2008). Moreover, it was evidenciated that the *ob/ob* mice are more susceptible to PTZ-induced generalized seizures and cell death than wild-type mice. These data suggest that elevated blood Lep levels may decrease neuronal excitability and also provide an anticonvulsant effect. Likewise, Lep treatment also significantly diminished seizure activity induced by other chemical models, such as i.c. injections of 4-aminopyridine (voltage-gated potassium channel inhibitor), and i.p. injections of PTZ (a non-competitive GABA antagonist) in mice (Xu *et al.* 2008).

Furthermore, in Lep-deficient *ob/ob* mice model, Lep was able to protect hippocampal neurons against kainate excitotoxicity, another experimental model of epilepsia. This experimental model favours seizure activity by activation of glutamate receptors (Guo *et al.* 2008).

How Lep exerts this anticonvulsant effect in this model is unknown. However, several hypotheses have been proposed. The anticonvulsant effect of Lep may result from NMDA receptor modulation or via activation of large conductance calcium-activated potassium channels (Walker *et al.* 2007). Calcium-activated potassium channels are important in determining the excitability of hippocampal neurons and may contribute to aberrant firing such as during seizure activity (Moult & Harvey 2011).

The inhibition of AMPAR-mediated synaptic transmission constitutes another potential mechanism involved in Lep anti-epileptic properties. This effect on AMPA synaptic responses is mediated by binding to its receptor and activating the JAK2/PI3K pathway.

In addition, previous studies demonstrated that Lep has an *in vitro* neuroprotective effect against NMDA receptor-induced excitotoxicity (a receptor implicated in kainate-induced hippocampal cell death) and oxidative stress favours neuronal damage (Dicou *et al.* 2001). The mechanisms involved in these neuroprotective mechanisms may be the induction of Bcl-xL and Mn-SOD, through a STAT3-dependent manner. Mn-SOD is a mitochondrial antioxidant enzyme, whereas Bcl-xL stabilizes mitochondrial membranes, and both proteins favour mitochondrial protection mediated by Lep. This hormone has also shown neuroprotective effects against death induced by trophic factor withdrawal, a model relevant to natural developmental cell death.

Neuroprotective effects of Lep in models of ischaemia

In addition to the beneficial effects on the potential treatment of neurodegenerative diseases, Lep exerts a neuroprotective role in rodent models of cerebral ischaemia. In these studies, it has been demonstrated that Lep neuroprotective mechanisms involve ERK1/2, AKT, NF-κβ transcription and STAT3 signalling pathways (Weng *et al.* 2007, Zhang & Chen 2008, Guo *et al.* 2008), which are all downstream signalling events of Lep receptor activation. With respect to the transcription factor NF-κB, activation is typical of neuroprotective molecules and is associated with the induction of the Bcl-xL gene, an anti-apoptotic protein which is member of the BCL-2 family (valerio *et al.* 2009). Therefore, the anti-apoptotic properties of Lep in ischaemia could be explained by modification of the Bcl-xL/Bax ratio towards an anti-apoptotic state. Likewise, the neuroprotective properties of Lep could be also explained by the activation of ERK1/2 that can phosphorylate Bad at Ser-112 and, thus, prevent its apoptotic activity. The nuclear translocation of p65 and p50, which then form a complex with c-Rel that is also involved in cell survival, is another neuroprotective effect of Lep.

Conclusions and future perspectives

It has been demonstrated that Lep plays an important role in neuroprotection and cognitive improvement against some experimental neuropathological conditions such as ischaemia, AD, PD and epilepsy. Evidence suggests that Lep, through binding to its receptor, modulates key pathways namely CDK5, AMPK, GSK3β, STAT3 and others involved in neuroprotection (Tezapsidis *et al.* 2009). In addition, Lep modulates glutamate receptors and improves cognition (Moult & Harvey 2011). The regulation or modulation of the mitochondria function is another area of interest in the neuroprotective functions of this hormone. AMPK, and the PPARγ coactivator (PGC)/PPAR are pathways activated by Lep which supports mitochondrial function. Lep-dependent mitochondrial metabolic activation and regulation may exert a trophic and protective effect that contributes to the restoration of energetic status in neurons altered in neurological disorders. The molecular mechanisms driving these mitochondrial changes induced by Lep should be investigated in depth, because the regulation of BCL-2 family of proteins is a key factor involved in apoptotic neuronal cell death.

Finally, the development of peptides designed as potential agonists of Lep could be relevant for the treatment of diseases associated with the Lep receptor. In reference to this, an area of pharmacological interest is the treatment of rheumatoid arthritis, where antagonists of Lep receptor probably could be of therapeutic use (Otvos *et al.* 2008, 2011).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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