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Nuclear Receptors in Neurodegenerative Diseases

Rebecca Skerrett[a], **Tarja Malm**[a,b], and **Gary Landreth**[a]

[a]Department of Neurosciences, Case Western Reserve University, School of Medicine, Cleveland, OH 44106 [b]A.I. Virtanen Institute for Molecular Sciences, Department of Neurobiology, University of Eastern Finland, Neulaniementie 2 70211 Kuopio, Finland

Abstract

Nuclear receptors have generated substantial interest in the past decade as potential therapeutic targets for the treatment of neurodegenerative disorders. Despite years of effort, effective treatments for progressive neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and ALS remain elusive, making non-classical drug targets such as nuclear receptors an attractive alternative. A substantial literature in mouse models of disease and several clinical trials have investigated the role of nuclear receptors in various neurodegenerative disorders, most prominently AD. These studies have met with mixed results, yet the majority of studies in mouse models report positive outcomes. The mechanisms by which nuclear receptor agonists affect disease pathology remain unclear. Deciphering the complex signaling underlying nuclear receptor action in neurodegenerative diseases is essential for understanding this variability in preclinical studies, and for the successful translation of nuclear receptor agonists into clinical therapies.

Keywords

nuclear receptors; peroxisome proliferator-activated receptors; liver X receptors; retinoid X receptors; microglia; inflammation; neurodegeneration; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; Huntington's disease

Nuclear receptors are ligand activated transcription factors that act globally to regulate a diverse array of homeostatic processes (Chawla et al., 2001; Castrillo and Tontonoz, 2004). The best characterized of these are the type I receptors, which include estrogen and progesterone receptors. This review will focus on the more recently discovered type II nuclear receptors, which act as regulators of lipid and energy metabolism, and specifically on their actions in the brain. The predominant type II nuclear receptors in the brain are the peroxisome proliferator-activated receptors (PPAR) α, β/δ and γ, and liver X receptors

Corresponding Author: Gary Landreth, Alzheimer Research Laboratory, Department of Neurosciences, School of Medicine, Case Western Reserve University, 10900 Euclid Ave., Cleveland, OH 44106-4928, gel2@case.edu, 216 368-6101.

(LXR) α and β. PPARs function as lipid sensors which bind dietary lipids or their metabolites, most prominently fatty acids and eicosanoids. LXRs act as cholesterol sensors, binding hydroxylated forms of cholesterol. Through association of the receptors with sequence specific promoter elements of genes of lipid and energy metabolism, PPARs and LXRs couple the size of the metabolic machinery to metabolic demand. These receptors play critical roles in CNS biology because the brain has a very high lipid content and is the most metabolically active organ in the body.

Nuclear receptors (type II) form obligate heterodimers with retinoid X receptors (RXR) α,β and γ to create a functional transcription factor (Figure 1A). In the nucleus, ligand bound or unbound receptor heterodimers associate with DNA response elements comprised of two direct repeat motifs. Unliganded dimeric receptors are transcriptionally silenced by their association with the corepressors NCoR or SMRT and HDAC3 (Figure 1B). Upon ligand binding, the corepressor complexes are dismissed and coactivator complexes then associate with the heterodimeric receptor, resulting in changes in local chromatin structure and the subsequent transcription of the target gene (Saijo et al., 2012). Unique exceptions to this mechanism are the NR4A receptors, including Nurr1, which are ligand independent receptors that can also signal as heterodimers with RXR. This review will focus on the PPARs and LXRs, as they are highly expressed in the brain, and discuss new data on the NR4A receptor Nurr1 that link it to CNS metabolism and disease.

Regulation of microglial phenotype and anti-inflammatory actions

Neurodegenerative diseases all exhibit a robust inflammatory component, reflective of the response of the innate immune system to disease-related perturbations in the brain (Mosher and Wyss-Coray, 2014). The brain is densely and uniformly populated by resident innate immune cells, the microglia (Nayak et al., 2014). The diseased brain is characterized by an increase in microglial number and their transformation from a surveillant, tissue maintenance mode to a protective host-defense mode and induction of proinflammatory genes. Typically, these ‘activated’ microglia are found associated with disease-related lesions or focal accumulations of abnormally folded proteins which stimulate host-defense responses normally directed to pathogens (Czirr and Wyss-Coray, 2012). This phenotypic conversion of microglia to a proinflammatory or ‘M1’ state is linked to the elaboration of a diverse array of immune mediators, including proinflammatory cytokines (Colton, 2009; Gordon and Martinez, 2010).

In the context of neurodegenerative diseases, this proinflammatory milieu within the brain acts to impair normal neuronal functions and synaptic activity and has coincident effects on CNS glia, including autocrine regulation of microglial and astrocyte phenotypes. Proinflammatory activation of microglia impedes their normal tissue surveillance and maintenance functions, prominently inhibiting their active monitoring of neuronal homeostasis and synapses (Morris et al., 2013). Inflammatory cytokines also act to impair neuronal integrity and have been postulated to mediate the loss of neurons at late stages of disease. The disease-related stimulation of the microglial inflammatory response is responsible for ‘bystander damage’ in the brain and contributes to disease pathogenesis and progression.

Examination of the brain in many neurodegenerative diseases reveals that activated microglia are generally unable to efficiently clear the initiating stimulus. An evolutionary adaption to this type of situation (e.g. parasitic infections) in other organ systems has been the ability of macrophages to acquire an 'alternative activation' phenotype, termed 'M2' (Gordon and Martinez, 2010). The M2 phenotype is associated with the inhibition of inflammatory gene expression and resolution of inflammation as well as the induction of a genetic program associated with tissue repair and enhanced phagocytosis. Importantly, it has only recently been appreciated that nuclear receptors act as master regulators of macrophage/microglia phenotype, governing the acquisition of 'alternative activation' states (Odegaard and Chawla, 2011). Macrophages in which PPARγ (Odegaard et al., 2007), PPARδ (Mukundan et al., 2009), LXRs (A-Gonzalez et al., 2009) and RXRα (Nunez et al., 2010) have been genetically inactivated exhibit reduced phagocytosis and are unable to acquire an M2 phenotype (Odegaard and Chawla, 2011). Each of these receptors has been shown to transactivate genes associated with the resolution of inflammation including anti-inflammatory cytokines such as IL-10 and TGFβ. This mechanism explains why phagocytosis of apoptotic cells by macrophages or microglia does not elicit an inflammatory response. There is a coincident stimulation of genes promoting phagocytosis.

Importantly, nuclear receptor activation also acts to suppress proinflammatory gene expression. Elegant work by Glass and colleagues have demonstrated that PPARs and LXRs undergo sumoylation upon ligand binding, allowing their targeted interaction with NFκB and AP1 positioned on the promoters of proinflammatory genes (Figure 1B) (Glass and Saijo, 2010). This interaction stabilizes the binding of NCoR/HDAC3 complexes with NFkB, repressing target proinflammatory gene expression. The phagocytic ingestion of the apoptotic corpse is associated with the catabolism of its membranes, yielding high levels of nuclear receptor ligands, most prominently fatty acids and cholesterol. Upon ligand binding, the receptors act to suppress NFκB-dependent inflammatory gene expression. This adaptive response is central to normal development and ongoing tissue maintenance.

It is now evident that nuclear receptors can be enlisted to intervene in disease pathogenesis, owing to the salutary effects of agonists of these receptors in a number of CNS disorders, including neurodegenerative diseases. The mechanisms subserving these effects in the brain are poorly understood. However, studies in other organ systems have revealed a complex interplay between the innate immune response and tissue metabolism (Odegaard and Chawla, 2013). The diseased brain has a well-documented alteration in metabolic state, with reduced glucose utilization and production associated with a broad range of metabolic changes. The innate immune system is an exquisitely responsive sensor of the metabolic state of the tissue in which these cells reside (Odegaard et al., 2007; Odegaard and Chawla, 2013). In the liver, muscle and fat, metabolic perturbations associated with obesity and type II diabetes result in an increased abundance of macrophages in the tissues and elevated inflammatory cytokines reflective of a low grade inflammatory state. The cytokines in turn elicit insulin resistance and impaired glucose uptake by the tissue. These reciprocal interactions between the tissue and its endogenous macrophages contribute to disease pathogenesis. It is of particular importance that nuclear receptor agonists act to normalize both metabolism and inflammation. This may account for their ability to attenuate disease-related pathologies and reverse behavioral impairment in animal models of

neurodegenerative disease. These types of interactions have yet to be explored in the brain and this is clearly an area in need of investigation.

PPARγ

PPARγ plays critical roles in lipid homeostasis through its ability to interact with fatty acids and other lipid metabolites (Beaven and Tontonoz, 2006). Its activation leads to the induction of genes associated with lipid uptake and storage. In the periphery PPARγ activation is associated with enhanced insulin sensitivity and thus two PPARγ agonists have been FDA approved (pioglitazone, ActosTM; rosiglitazone, Avandia™) for the treatment of type II diabetes. In addition, PPARγ activation is reported to improve mitochondrial metabolism and biogenesis (Alaynick, 2008).

The first report of the neurodegenerative disease-relevant actions of PPARγ agonists was published in 2000 (Combs et al., 2000) and was quickly followed by a flurry of studies in animal models of AD (Mandrekar-Colucci and Landreth, 2011), PD (Carta and Pisanu, 2013), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) (Kiaei, 2008), stroke (Ouk et al., 2013), and traumatic injuries (Semple and Noble-Haeusslein, 2011; Mandrekar-Colucci et al., 2013). The therapeutic relevance of targeting PPARγ has been documented in animal models for a number of neurodegenerative diseases and has resulted in several clinical trials for these disorders.

Alzheimer's disease

The actions of PPARγ and its agonists in *in vitro* and murine models of AD have been well documented over the past decade and this work has been extensively reviewed (Heneka et al., 2007; Jiang et al., 2008a; Landreth et al., 2008; Nicolakakis and Hamel, 2010; Mandrekar-Colucci and Landreth, 2011; Sodhi et al., 2011; Mandrekar-Colucci et al., 2013). In 17 independent studies, oral administration of PPARγ agonists have been shown to be effective in many mouse models of AD, as measured by improved memory and cognition, suppression of inflammation and reduction of amyloid levels (Table I). There has been significant new work that has focused on the underlying mechanisms.

PPARγ agonist treatment of murine models of AD has been associated with the reversal of transgene-induced behavioral impairments, as evaluated in a number of different assays of cognition, memory and neural network function. It remains enigmatic exactly how the PPARγ-mediated improvement of behavior is effected. One proposed mechanism is that the robust anti-inflammatory effects of PPARγ suppress the levels of proinflammatory cytokines that have been linked to cognitive impairment. Whether anti-inflammatory effects are entirely responsible for reversal of the behavioral deficits remains to be convincingly demonstrated. Recent studies of PPARγ signaling in neurons argue that other mechanisms likely participate in the PPARγ-mediated enhancement of cognition and memory. The actions of PPARγ agonists on neurons have received comparatively little attention. PPARγ agonists are reported to stimulate Wnt signaling (Toledo and Inestrosa, 2010). Recent work by Dinely and colleagues have dissected the neuronal effects of PPARγ agonists and their underlying mechanisms which are summarized in this volume (Rodriguez-Rivera et al., 2011; Denner et al., 2012; Nenov et al., 2014). It has also been reported that PPAR agonists

act to normalize synaptic function in AD mouse models (Searcy et al., 2012). The salutary effects of PPARγ agonists in AD mice have been postulated to arise from their ability to improve peripheral insulin sensitivity in type II diabetes and by extension work in analogous ways in the brain (Craft et al., 2013). However, there is no direct evidence to support the view that neurons are insensitive to insulin action, but they have been reported to exhibit changes in signal transduction pathways reflective of impaired insulin receptor signaling in AD models of rodents monkeys and in humans. Ferreira and colleagues have argued the insulin resistance results from the actions of microglia-derived TNFα. TNFa is elevated in the AD brain and causes the inactivation of elements necessary for insulin signaling (Ferreira et al., 2014).

One of the most compelling effects of chronic PPARγ agonist treatment documented in earlier work is the reduction of amyloid plaque burden owing to induction of microglial phagocytosis of Aβ deposits (Pedersen et al., 2006; Escribano et al., 2009; Toledo and Inestrosa, 2009; Escribano et al., 2010; Rodriguez-Rivera et al., 2011; Denner et al., 2012; Masciopinto et al., 2012; O'Reilly and Lynch, 2012; Searcy et al., 2012; Yamanaka et al., 2012). Recently, Mandrekar–Collucci reported that pioglitazone treatment as brief as 9 days was sufficient to clear up to 50% of plaques in 6 or 12 month old APP/PS1 mice and was associated with the appearance of amyloid-laden microglia in the cortex and hippocampus of the drug-treated mice (Mandrekar-Colucci et al., 2012). Similarly, Yamanaka reported that pioglitazone and a new PPARγ agonist, DSP-8658, stimulated the recruitment of microglia to plaques and promoted their clearance (Yamanaka et al., 2012). *In vitro* studies demonstrated that PPARγ agonists stimulated Aβ phagocytosis through induction of CD36 expression. The effect of the PPARγ agonists was dependent upon RXRa expression, and was additively enhanced by simultaneous treatment with an RXR agonist. The same study observed that DSP-8658 was also able to stimulate microglial recruitment to plaques and increase their phagocytosis of Aβ in an AD mouse model. In each of these latter studies behavioral improvement was observed.

A frequent comorbidity and contributor to AD pathogenesis is cerebral amyloidosis, or the accumulation of Aβ peptides within the vasculature, which is associated with impaired vascular function (Park et al., 2011). PPARγ agonist treatment of mouse models also restored vascular reactivity and improved blood flow to the brain (Nicolakakis and Hamel, 2010; Papadopoulos et al., 2013). Thus, PPARγ-mediated improvements in vascular function could provide another mechanism of therapeutic action.

There have been several phase I/II trials of pioglitazone and rosiglitazone in AD patients. A large phase III trial of rosiglitazone in mild/moderate AD failed to show clinical benefit (Gold et al., 2010). Currently, a phase III trial of pioglitazone is underway.

Parkinson's disease

The initial report of the effects of PPARγ agonists in an MPTP model of PD by Breidert and colleagues found that pioglitazone prevented dopaminergic cell loss and suppressed the inflammatory response seen in this model (Breidert et al., 2002). Subsequently, there have been several studies implicating PPARγ in disease etiology. Many studies in murine models of PD (Schintu et al., 2009; Swanson et al., 2013) have found drug-induced prevention of

dopaminergic terminal and cell loss as well as prevention of functional deficits. In an MPTP model in monkeys, Swanson et al. reported that pioglitazone treatment ameliorated behavioral deficits and prevented the loss of several markers of dopaminergic function. Importantly, pioglitazone prevented dopaminergic cell loss, with a reduction in inflammation, similar to the effects observed in rodents (Swanson et al., 2011). The underlying mechanisms that subserve these effects remain controversial and have been postulated to be due to anti-oxidant effects (Martin et al., 2012), MAO-B inhibition (Quinn et al., 2008), or the antiinflammatory effects of PPARγ activation (Breidert et al., 2002; Dehmer et al., 2004; Carta and Pisanu, 2012).

A principal cofactor and regulator of PPAR action is PPARγ-coactivator 1α (PCG-1a) (Katsouri et al., 2012). PCG-1α participates in transcriptional complexes mediating the activation of PPARγ and other nuclear receptor-responsive genes. PCG-1α has been shown to play critical roles in insulin sensitivity, mitochondrial biogenesis, energy production, and neuronal viability. In MPTP treated mice, transgenic expression of PCG-1α prevented the loss of dopaminergic neurons (Mudo et al., 2012). PGC-1α levels are reduced in genetic models of PD (Katsouri et al., 2012) and in parkin mutant mice (Shin et al., 2011). PPARγ agonists have been shown to stimulate the expression of PGC-1α (Hondares 2006), providing another possible mechanism for PPARγ action in PD. There is currently a phase II trial of pioglitazone in early stage Parkinson's underway.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by extensive loss of motor neurons. Treatment of mouse SOD1 models of ALS with pioglitazone resulted in prevention of neuronal loss, preservation of neurological function and longer survival (Kiaei et al., 2005; Schutz, 2005; Shibata et al., 2008). Pioglitazone treatment was also shown to reduce inflammation. However, a clinical trial of pioglitazone in ALS patients showed no clinical benefit (Dupuis et al., 2012).

Huntington's disease

Chiang et al. reported that PPARγ levels were reduced both in Huntington's disease (HD) patient lymphocytes and the R6/2 HD mouse model. Treatment of HD mice with a PPARγ agonist prevented functional impairments in these mice, extended their survival, and also normalized the reduced expression of PCG-1α (Chiang et al., 2010). Administration of a pan-PPAR agonist resulted in elevation of PCG-1α levels, amelioration of behavioral deficits, and increased survival (Johri et al., 2012). A recent study using a different HD model found that rosiglitazone prevented neuronal loss, improved mitochondrial function and restored PGC-1α levels in the brain (Jin et al., 2013). These studies have led to the conclusion that PGC-1α deficiency underlies the mitochondrial dysfunction observed in HD (Johri et al., 2013).

LXR

LXRs are cholesterol sensors that play an essential modulatory role in cholesterol metabolism, lipogenesis, and the regulation of inflammation. Two isoforms of LXR exist,

LXRα, which is prominently expressed in liver, adipose tissue, adrenal glands, intestine, kidney, and macrophages, and LXRβ , which is expressed 2–5 times higher than LXRα in the brain (Whitney et al., 2002) and ubiquitously expressed at low levels throughout the body. The two isoforms are activated by the same endogenous ligands, namely 24(S)-hydroxycholesterol, 22(R)-hydroxycholesterol 24(S),25-epoxycholesterol, and 27-hydroxycholesterol, and transcriptionally regulate genes involved in reverse cholesterol transport. The principal LXR ligand in the brain is 24(S)-hydroxycholesterol. Activated LXRs also exhibit antiinflammatory action, as they are sumoylated and repress transcription at NFκB target genes by a mechanism similar to that of PPARγ (Lee et al., 2009).

LXRs have been shown to play an essential role in the normal CNS. Neuronal development, synaptogenesis, and learning and memory are dependent on cholesterol, and dysregulation of cholesterol metabolism has been implicated in several neurodegenerative disorders (Brown 3rd et al., 2004). LXR double knockout mice have CNS abnormalities, including increased lipid deposition and neurodegeneration (Wang et al., 2002), and LXRβ knockout mice exhibit adult-onset motor neuron degeneration (Andersson et al., 2005). Two widely used synthetic ligands, T0901317 and GW3965, have been developed as tools for the study of LXRs. LXRs have been studied in a number of neurodegenerative diseases and CNS injury models and the development of new LXR agonists with acceptable side effect profiles remains an active area of interest.

Alzheimer's disease

The elevated risk associated with possession of the apolipoprotein e4 allele for sporadic AD indicates the importance of cholesterol metabolism in AD. LXRs act to regulate the expression of the *APOE* gene and its lipid transporters, *ABCA1* and *ABCG1*. Apolipoprotein E (apoE) is the most prominent apolipoprotein in the brain, where it functions as an acceptor of cholesterol and phospholipids effluxed from cells and facilitates their transport as HDL-like particles throughout the brain. Nascent apoE is lipidated by the lipid transporter ABCA1 and subsequently by ABCG1, which acts to transfer additional lipids to already lipidated apoE particles. Although the mechanism by which apoE isoforms confer AD risk remains unclear, it is generally thought that the comparatively poor lipid-carrying ability of apoE4 impairs its ability to facilitate soluble Aβ clearance, leading to accumulation of soluble amyloid species in the brain. Other mechanisms have also been postulated, reflective of a toxic gain of function associated with the E4 allele (Kim et al., 2009). ApoE has also been argued to play a role in clearance of amyloid from the brain into the peripheral vasculature and apoE4 is implicated in compromise of vascular integrity (Zlokovic, 2013). LXR, as a direct transcriptional regulator of apoE, ABCA1, and ABCG1, is an attractive therapeutic target and acts to increase Aβ clearance in mouse models of AD.

In the past 10 years, LXR agonists have been investigated in twelve separate studies (Table 1) which demonstrate their efficacy in improving behavioral impairments and amyloid clearance in AD models, with some mixed results in the stimulation of plaque clearance (Koldamova et al., 2005; Lefterov et al., 2007; Riddell et al., 2007; Jiang et al., 2008b; Donkin et al., 2010; Fitz et al., 2010; Terwel et al., 2011; Wesson et al., 2011; Vanmierlo et al., 2011; Cui et al., 2012; Hu et al., 2013; Fitz et al., 2014). Vanmierlo et al. observed

improvements in hippocampal dependent memory but no change in plaque load with T0901317 treatment in APPSLxPS1mut mice (Vanmierlo et al., 2011). However, Riddell et al. only observed decreases in hippocampal Aβ42 with no change in cortical Aβ levels, although T0901317 treatment of Tg2576 mice mediated behavioral improvement (Riddell et al., 2007). The ability of LXR agonists to stimulate Aβ clearance and behavioral improvements is dependent on ABCA1 (Donkin et al., 2010; Fitz et al., 2010), indicating that LXR-mediated regulation of apoE lipidation state plays an important role in amyloid pathology.

Several groups have also shown that LXRs are able to modulate neuroinflammation in AD models primarily by modifying the responses of microglia and astrocytes (Zelcer et al., 2007; Cui et al., 2012). LXR-mediated transrepression of the expression of neurotoxic pro-inflammatory cytokines could be an additional mechanism for the behavioral improvements LXR agonists effect in AD models (Zhang-Gandhi and Drew, 2007; Ghisletti et al., 2009). The long-studied role of LXRs in peripheral macrophage inflammatory phenotype (Zelcer and Tontonoz, 2006; Hong and Tontonoz, 2008) and phagocytosis (A-Gonzalez et al., 2009) has recently sparked interest in the role of LXRs in microglia (Saijo et al., 2012) and the therapeutic value of LXR's anti-inflammatory effect in AD models (Lefterov et al., 2007; Zhang-Gandhi et al., 2007; Cui et al., 2012).

Their anti-inflammatory properties and stimulation of reverse cholesterol transport makes LXRs an attractive therapeutic candidate for AD treatment, and one that is supported by an extensive literature in AD models. However, the poor side effect profile of LXR ligands precludes their clinical use. Better targeted or tissue-specific agonists of LXRs are currently in development (Hu et al., 2013) as potential AD therapeutics.

Parkinson's disease

A novel role for LXRs in the developmental differentiation of dopaminergic neurons has recently been proposed by the Gustafsson group. Developmental midbrain neurogenesis is decreased in LXR double knockouts (Sacchetti et al., 2009). Moreover, activation of LXRs is important for *in vivo* development as well as sufficient for inducing ESCs to differentiate into dopaminergic neurons (Sacchetti et al., 2009; Theofilopoulos et al., 2012). This agrees with the observation that LXR double knockout mice have decreased neuronal numbers in the substantia nigra (Wang et al., 2002). Additionally, LXRβ knockout mice have increased death of dopaminergic neurons in the substantia nigra upon challenge with MPTP (Dai et al., 2012) and β-sitosterol (Kim et al., 2008), which is attributed to increased activation of microglia. Dai et al. also report that treatment with LXR agonist GW3965 can protect against loss of dopaminergic neurons induced by MPTP (Dai et al., 2012).

PPARδ

The role of PPAR β/δ (hereafter referred to as PPARδ) in neurodegeneration is far less studied than that of its related family member, PPARγ. PPARδ is ubiquitously expressed in all cell types in the central nervous system (CNS) (Moreno et al., 2004) and has the highest CNS expression of the three PPARs (Braissant et al., 1996). Several synthetic PPARδ

activators have been produced and used in the research of CNS diseases although none are currently approved for clinical use.

PPARδ has important roles in neuronal function. Studies using mice deficient in PPARδ have revealed its vital role in many physiological processes, especially in the control of central and peripheral inflammatory reactions. PPARδ deficient mice are viable but show several defects in normal CNS biology and exhibit augmented inflammatory reactions. Specifically, PPARδ deficient mice show altered myelination (Peters et al., 2000) and impaired performance in memory tests with associated increases in inflammatory markers, astrogliosis and tau hyperphosphorylation (Barroso et al., 2013). PPARδ deficient mice show increased vulnerability to ischemic insults (Arsenijevic et al., 2006; Pialat et al., 2007) due to defects in antioxidant responses (Arsenijevic et al., 2006). PPARδ is also abundantly expressed in brain endothelia and controls vascular functions. Specific deletion of PPARδ in vascular smooth muscle cells leads to increased ischemic infarct size by increasing matrix metalloproteinase (MMP)-9 activity and by increasing the expression of several proinflammatory mediators (Yin et al., 2011).

The data generated from the use of PPARδ agonists show that PPARδ activation provides protection in many pathological CNS conditions largely due to its potent anti-inflammatory and antioxidant properties. PPARδ agonists have been shown to provide protection against neuronal degeneration in the MPTP model of Parkinson's disease (Iwashita et al., 2007; Martin et al., 2013), stroke (Iwashita et al., 2007; Yin et al., 2010), EAE (Polak et al., 2005), spinal cord injury (Paterniti et al., 2010) and in a streptozotocin-induced experimental type 3 diabetes (La Monte et al., 2006), all mainly via reducing inflammation and oxidative stress. However, it should be noted that one study reported that a PPARδ agonist was not able to reduce 6-OHDA induced neuron loss *in vivo* even though it reduced microgliosis (Sadeghian et al., 2012). The protection elicited by PPARδ activation has several possible underlying mechanisms. PPARδ interferes with NFκB signaling, thus leading to a dampened inflammatory milieu and decreased oxidative stress (Paterniti et al., 2010; Barroso et al., 2013). PPARδ activation has been shown to decrease intracellular calcium concentration and reduce ROS production *in vitro* (Jin et al., 2012). In ischemic conditions PPARδ reduces MMP-9 activity, possibly by binding directly to the PPAR response element site in the MMP-9 promoter region (Yin et al., 2011). In addition, PPARδ activation has also been shown decrease apoptotic cell death by promoting the expression of bcl-2 (Paterniti et al., 2010; Yin et al., 2010) and attenuating caspase-3 activity both *in vitro* (Iwashita et al., 2007; Yin et al., 2010) and *in vivo* in ischemic conditions (Yin et al., 2010) as well as in spinal cord injury (Paterniti et al., 2010). Interestingly, PPARδ upregulation in SRC-3 deficient mice has been shown to promote alternative activation of microglia in a mouse model of EAE, indicating another mechanism by which it modulates microglial activity (Xiao et al., 2010).

So far only one study has assessed the possible protection of PPARδ agonists in a transgenic mouse model of Alzheimer's disease. In a paper by Kalinin et al. (Kalinin et al., 2009) long term PPARδ agonist treatment reduced the subicular Aβ load and reduced astrocytic activation in 5xFAD mice. The reduction in the levels of Aβ was associated with increased expression of Aβ degrading enzymes neprilysin and insulin degrading enzyme, however, the

role of microgliosis in this context was not analyzed. An additional *in vitro* study indicates that PPARδ agonists also protect primary neurons from Aβ induced cell death (Madrigal et al., 2007).

The majority of studies have attributed the neuroprotective properties of PPARδ to its role in ameliorating inflammatory reactions. Indeed, the most well defined effect of PPARδ is its ability to suppress inflammation in macrophages. The evidence for a direct neuroprotective role of PPARδ *in vitro* (Smith et al., 2004) is somewhat controversial. In one study PPARδ ligand GW0742 alone was not able to rescue SH-SY5Y cells from MPP+ induced cell death as measured by LDH release, although *in vivo* administration attenuated MPTP induced neurotoxicity (Martin et al., 2013). In contrast, other PPARδ activators L-165041 and GW501516 were shown to be directly neuroprotective *in vitro* at very high concentrations (Iwashita et al., 2007). Treatment with GW0742 protected cerebellar granule neurons from low-KCl induced toxicity only during a 12-hour exposure period in high concentrations (Smith et al., 2004) and also protected a mouse hippocampal cell line against glutamate toxicity during the same 12 hour period of exposure (Jin et al., 2012). The treatment during a longer exposure period was no longer protective and longer exposure times (48 hours) to GW0742 actually induced cell death (Smith et al., 2004).

Overall, accumulating data supports the role for PPARδ in controlling inflammatory reactions. Whether PPARδ activation is directly neuroprotective or if its neuroprotective effects are mediated through suppression of inflammation needs clarification.

RXR

The actions of RXR agonists are diverse, owing to the ability of RXR to form permissive heterodimers with other type II nuclear receptors, and their complexity is poorly understood. In addition to acting as heterodimerization partners for type II nuclear receptors, RXRs can act as homotetramers to modulate DNA 3D architecture or as homodimers that associate with their target genes in the presence or absence of ligand (Dawson and Xia, 2012).

Only a few genes have been shown to be regulated by the RXR homodimer complex (IJpenberg et al., 2004), most prominently a subset of chemokines (Nunez et al., 2010). RXR heterodimers are characterized as ‘permissive’ or ‘non-permissive’ based on whether ligation of either member of the heterodimer can elicit transcription. In the brain, permissive receptors include the PPARs, LXRs and the NR4A receptors (Rőszer et al., 2013) while non-permissive complexes are formed with RARs, thyroid and vitamin D receptors. Thus, RXR agonists can elicit pleiotropic actions through their actions on RXR homodimers as well as heterodimers containing permissive receptors. Recent work has shown that RXR agonists only regulate a subset of genes controlled by permissive receptors and that this subset is cell type-specific (Szeles et al., 2010). The basis for this restriction is not understood but explains why a broader range of effects of RXR agonists in the brain is not observed.

Alzheimer's disease

There are a limited number of studies investigating RXR actions in neurodegenerative disease, although these receptors have well established roles during development. The literature on RXR activation is confused by a number of studies which investigate the actions of docasohexanoic acid (DHA), an omega 3 –polyunsaturated fatty acid, and attribute its actions to its binding to RXRs (de Urquiza et al., 2000). However, DHA also binds to PPARs (Kliewer et al., 1997) and two GPCRs (Im, 2012), thus it is not possible to conclude that these are RXR-specific actions. RXRα levels have been found to be elevated in dementia in a manner correlated with cognitive impairment (Akram et al., 2010). Cramer et al. (Cramer et al., 2012) reported that the RXR agonist bexarotene resulted in the rapid reduction in soluble forms of Aβ in the brains of mouse models of AD, owing to the induction of the LXR target genes *apoE* and *Abca1* and elevation of brain high density lipoprotein levels (Ulrich et al., 2013). The reduction in soluble Aβ species was associated with improved neural network function and reversal of behavioral deficits. This effect on soluble Aβ levels was also reported by Fitz (Fitz et al., 2013a), Veeraraghavalu (Veeraraghavalu et al., 2013) and Ulrich (Ulrich et al., 2013), but not others (Table I; see below). Importantly, bexarotene-mediated behavioral improvement was observed by Fitz (Fitz et al., 2013b), Boehm-Cagan (Boehm-Cagan and Michaelson, 2014) and Tesseur (Tesseur et al., 2013). Cramer et al. reported that bexarotene treatment also resulted in the rapid reduction in amyloid plaque burden (Cramer et al., 2012) and this finding has been controversial (Landreth et al., 2013) (see below).

Parkinson's disease

In a remarkable paper, McFarland reported that in two rodent models of Parkinson's bexarotene acted to prevent neuronal loss and prevented functional impairment (McFarland et al., 2013). These effects were achieved at very low drug levels. Bexarotene was postulated to act through the ability of RXRs to heterodimerize with Nurr1 and drive its transcriptional activities.

Nurr1

The NR4A receptors were first identified as immediate-early genes induced in the nervous system in response to a wide variety of extracellular stimuli such as seizures (de Ortiz and Jamieson, 1996), stress (Garcia-Yague et al., 2013) and neurotransmitters (Barneda-Zahonero et al., 2012; Debernard et al., 2012). The NR4A family, including Nur77 (NR4A1; NGF-IA), Nurr1 (NR4A2; NGF-IB) and Nor-1 (NR4A3), are unique among type II nuclear receptors because the steric hindrance in their nominal ligand binding domains prevents them from accepting ligands. They were long thought to be constitutively active, but it has been recently shown that they can also play a role in transcriptional repression in a context dependent manner. NR4A transcriptional activity depends mainly on gene expression, miRNA targeting, alternative splicing, posttranslational modification, subcellular localization, and interactions with other nuclear receptors (Michelhaugh et al., 2005; Maxwell and Muscat, 2006; Sacchetti et al., 2006; Mohan et al., 2012; Yang et al., 2012).

All three family members can signal at NBREs (or NurREs) as monomers or homo- or heterodimers with other NR4As. Importantly, Nurr1 and Nur77 can also signal in complex with RXRs at DR5 repeats, and NR4A/RXR heterodimers can be activated by RXR ligands. Synthetic ligands that bind directly to NR4A:RXR heterodimers and drive transcriptional activity have also been described (Morita et al., 2005; Ishizawa et al., 2012). Development of specific ligands for NR4As could be therapeutically relevant for a variety of diseases. Aside from their critical role in nervous system function, NR4As are implicated as regulators of glucose homeostasis (Close et al., 2013), fatty acid metabolism (Volakakis et al., 2009; Holla et al., 2011), cellular proliferation (Sirin et al., 2010), cancer (Mohan et al., 2012), and immune regulation both in the periphery and in the brain.

Parkinson's disease

Nurr1 mutations are associated with rare genetic forms of PD, but are not a major genetic risk factor for PD (see Decressac 2013 for an excellent review of Nurr1 in PD) (Decressac et al., 2013). A substantial body of evidence indicates that Nurr1 is downregulated in sporadic PD patients. This downregulation is selective for neurons with α-synuclein inclusions, and decreased Nurr1 correlates with decreased dopaminergic signaling markers in these cells. Rodents highly express Nurr1 in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) throughout development and into adulthood (Saucedo-Cardenas and Conneely, 1996; Zetterstrom et al., 1996). Nurr1 overexpression directs the differentiation of mesodiencephalic dopaminergic neurons (mdDAs) *in vitro* by controlling transcription of the dopaminergic genes tyrosine hydroxylase (TH), dopamine transporter (DAT), vesicular monoamine transporter 2 (VMAT2), and RET receptor tyrosine kinase (cRET) (Decressac et al., 2013). *In vivo*, Nurr1 knockouts develop mdDAs, but these neurons exhibit dysfunctional neurotransmission during embryogenesis and are not maintained in newborn animals. Interestingly, mdDAs in Nurr1 heterozygous mice have an increased vulnerability to stressors including MPTP and also exhibit an age-dependent dysfunction that correlates with decreasing motor abilities (Jiang et al., 2005). Studies utilizing conditional knockouts of Nurr1 in mature dopaminergic neurons indicate that these effects cannot entirely be attributed to developmental Nurr1, but that Nurr1 plays an important ongoing role in the maintenance of mdDAs.

The role of Nurr1 in mdDA neuronal survival is probably due to a combination of factors, including maintenance of dopaminergic neurotransmission machinery expression and facilitating the response of mdDAs to GDNF (Decressac et al., 2012). Nurr1 has also been shown to mediate cAMP-response element binding protein (CREB)-induced neuroprotection in response to stress, by upregulating an anti-apoptotic gene program in hippocampal neurons (Volakakis et al., 2010) and increasing BDNF expression in cerebellar granule cells (CGCs) (Barneda-Zahonero et al., 2012). In fact, Nurr1 is transcriptionally regulated in a CREB-dependent manner (Altarejos and Montminy, 2011). Additionally, Nurr1 plays a role in DNA repair of double strand breaks in neurons (Malewicz et al., 2011) and nucleotide excision repair in melanoma cells (Jagirdar et al., 2013). In both cell types Nurr1 is recruited to nuclear foci containing DNA repair proteins via a mechanism involving poly(ADP-ribose) polymerase-1 (PARP-1) and has a non-transcriptional critical role in DNA repair. Nurr1 is also induced by inflammatory stimuli in microglia and astrocytes and

downregulates inflammatory gene transcription by CoREST-dependent transrepression at NFκB target gene promoters (Saijo et al., 2009). Knockdown of Nurr1 in the SN resulted in an enhanced glial inflammatory response to LPS or α-synuclein and increased death of dopaminergic neurons, suggesting that anti-inflammatory activities of Nurr1 may also be important for PD pathogenesis.

McFarland et al. reported that bexarotene, acting though its ability to stimulate Nurr1:RXR heterodimers, prevented dopaminergic cell loss, and impairment of both motor and cognitive function in two different rodent models of PD (McFarland et al., 2013).

Alzheimer's disease

Recent evidence from the Saura group indicates that Nurr1 levels are decreased in an AD mouse model as well as in late-stage AD patients (España et al., 2010; Parra-Damas et al., 2014), and it has been reported that Nur77 levels decrease with age in an APP/PS1 mouse model of AD (Dickey et al., 2003). However, a direct role of Nurr1 in AD pathogenesis has yet to be studied. The involvement of Nurr1 in regulating neuronal survival, neuroinflammation, and hippocampal function and plasticity (Volakakis et al., 2010; Hawk et al., 2012; Bridi and Abel, 2013), however, makes it an attractive target for further study in AD and other neurodegenerative diseases.

Reproducibility of nuclear receptor effects in mouse models of neurodegenerative disease

The first study of the effects of nuclear receptor agonists in AD models was published in 2003 (Yan et al., 2003). Subsequently, 39 additional studies have been reported in 14 genetic animal models using agonists to PPARγ, LXRs and RXRs. From this body of work it is quite clear that, in the context of AD models, nuclear receptor agonists have their most consistent and robust effects on cognition and learning. Of the studies that have evaluated behavioral endpoints, there are 31 reports of behavioral improvements, one report where drug toxicity precluded interpretation of behavior (Tesseur et al., 2013) and 5 reports of failure to observe behavioral improvements. Similarly, these agents reproducibly reduced inflammation and the number and activation status of microglia, and in some cases, astrocytes. In the 17 studies which examined this endpoint, only two did not observe these effects.

Other endpoints were less consistent and have generated substantial controversy. Aβ reduction following nuclear receptor agonist treatment was observed in 61% of the 36 studies that measured deposited amyloid burden in 12 animal models of AD and 72% of 33 studies found reductions in soluble Aβ species. A clear example of the variability of plaque reduction is provided by the 12 studies examining the effect of LXR agonists. Plaque loss varied from 0–65% in these studies. These studies differed in the animal models used, the LXR agonist, and the formulation used to treat the mice, as well as the length of the treatment period, but in all but one study behavioral improvement was observed. Recently, the ability of the RXR agonist bexarotene to reduce plaque burden has been called into question. Cramer et al. reported that brief treatments with bexarotene reduced plaque

burden, however, chronic drug treatment was not associated with plaque loss (Cramer et al., 2012). Five reports have challenged the former finding in 3 different mouse AD models (LaClair et al., 2013; Price et al., 2013; Tesseur et al., 2013; Veeraraghavalu et al., 2013; Fitz et al., 2013a). These studies used a very different drug formulation in their treatments, in which bexarotene was administered solubilized in DMSO (or in a cyclodextrin vehicle) rather than as the clinical formulation (TargretinTM) as micronized crystals used by Cramer et al. (Cramer et al., 2012). New work has compared these preparations and shown that they yield very different pharmacodynamics and overall drug exposure (Chen et al., 2013).

Amyloid plaques are removed from the brain principally by microglial-mediated phagocytosis and there is now good evidence that nuclear receptor agonists promote phagocytosis. However, we currently have no reliable markers for drug action within these cells in the brain. Phagocytosis of fAβ is stimulated by bexarotene and this effect is reliant upon RXRα (Yamanaka et al., 2012). Clearly, sustained activation of RXR fails to maintain a phagocytically active population of microglia, as plaque loads rebound to normal levels after several months of drug treatment and the basis of this effect is unknown. Importantly, plaque burden is unrelated to cognitive improvement in both mice and men.

It should be noted that LaClair et al. reported that bexarotene failed to improve behavior in APP/PS1 mice, but the conclusions of this study are invalidated by the absence of any behavioral deficits in their untreated AD transgenic model (LaClair et al., 2013). Indeed, cognition and learning are the most critical measure of efficacy for AD-directed therapies and the highly reproducible effects of nuclear receptor agonists on behavior support the translation of these studies into clinical trials in AD.

The outcomes of nuclear receptor treatment in rodent models of other neurodegenerative diseases have been less variable. For instance, of 27 studies using agonists for PPARγ, PPARα, PPARδ, LXR, or Nurr1 in the treatment of Parkinson's mouse or rat models, 23 reported a positive outcome. One additional study in MPTP-treated monkeys (Swanson et al., 2011) reported no effects at 2.5mg/kg/day Pioglitazone, but a positive outcome was seen when that dose was doubled. The small number of studies performed in ALS and Huntington's mouse models using nuclear receptor agonists also show promise, with all three studies in ALS models and 2 of 3 studies in Huntington's models reporting positive outcomes.

While some outcome variability exists in nuclear receptor agonist studies, a strong persistence of positive outcomes in animal studies indicates that nuclear receptor agonists may be of therapeutic benefit in several neurodegenerative diseases. Many questions about the role of nuclear receptors in neurodegenerative disease remain unanswered, and further studies are required to elucidate the complex mechanisms behind the salutary actions of nuclear receptor agonists.

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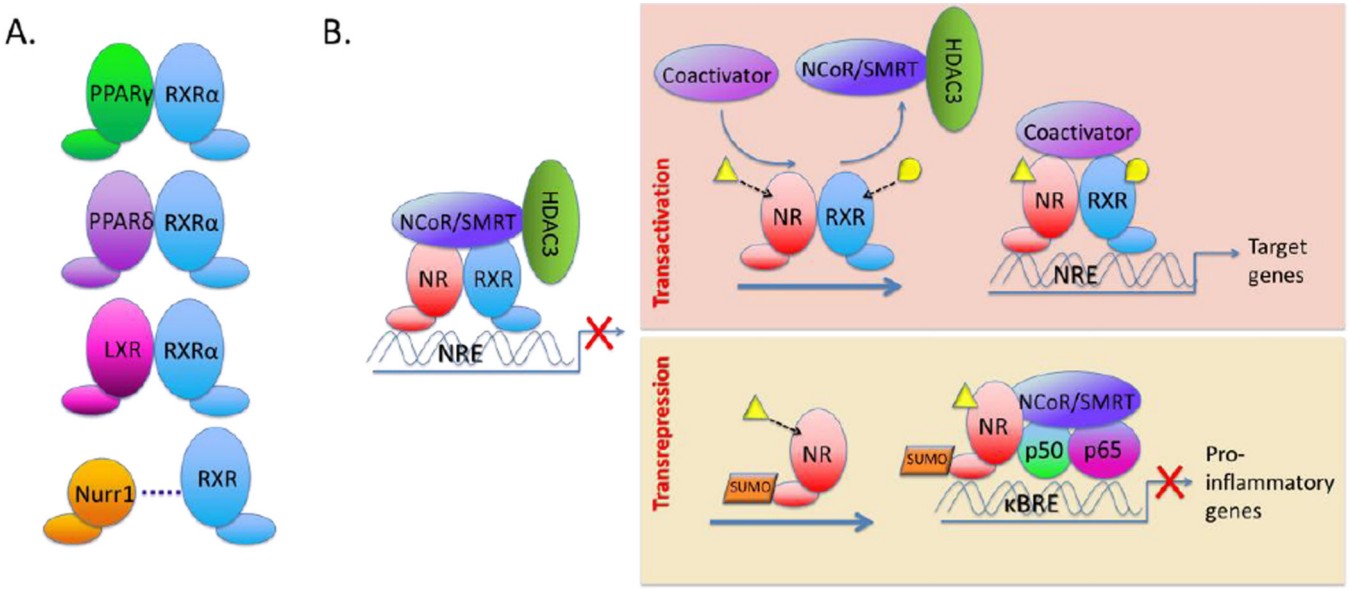

Figure 1. Nuclear receptors are ligand-activated transcription factors

Nuclear receptors (type II) form obligate heterodimers with RXR and comprise the functional transcription factor. The nuclear receptor complex transactivates its target genes by binding to sequence specific elements in their promoters. Ligand binding results in dismissal of a corepressor complex and association with coactivators, resulting in transcription of the target gene. Nuclear receptors can also act as transrepressors. Sumoylation induces their direct association with NFkB positioned on the promoters of proinflammatory genes, preventing the dismissal of corepressor complexes and the initiation of transcription.

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Table 1

Effects of nuclear receptor agonists in neurodegenerative disease models.

Neurodegenerative disease	Nuclear Receptor target	Ligand	Dosage	Length of treatment	Route of Administration	Animal model	Pathology effects	Inflammatory Effects	Behavioral Outcomes
Alzheimer's disease									
Yan et al., 2003	PPARγ	Pioglitazone	20 mg/kg/day	16 wks	oral: chow	Tg2576	↓ sol Aβ		
Lacombe et al. 2004		Pioglitazone	18 mg/kg/day	2 months	oral: chow	TGFbeta OE	↓ sol Aβ42	↓	
Heneka et al., 2005		Pioglitazone	40 mg/kg/day	7 days	oral: chow	APPV717I	↓ plaques, sol Aβ	↓	
Sastre et al., 2006		Pioglitazone	40 mg/kg/day	7 days	oral: chow	APPV717I	↓ intracellular Aβ		
Nicolakakis et al., 2008		Pioglitazone	20 mg/kg/day	6–8 wks	oral: chow	hAPP swe-ind	no effect	↓	n.c. MWM
Mandrekar-Collucci et al., 2012		Pioglitazone	80 mg/kg/day	9 days	oral: gavage	APPswe/PSEN1dE9	↓ plaques, sol Aβ	↓	↑ CFC
Searcy et al. 2012		Pioglitazone	18 mg/kg/day	14 wks	oral: chow	3xTg-AD	↓ intracellular Aβ, ↓ p-tau		↑ active avoidance learning
Masciopinto et al., 2012		Pioglitazone	20 mg/kg/day	9 months	oral: chow	PS1-KIm146v			↑ MWM, NOR in females
		Pioglitazone	20 mg/kg/day	9 months	oral: chow	3xTg-AD			n.c.
Papadopoulos et al., 2013		Pioglitazone	20 mg/kg/day	6 months	oral: chow	hAPP swe-ind/TGF-b1	n.c.	↓	n.c.
		Pioglitazone	20 mg/kg/day	3 months	oral: chow	hAPP swe-ind/TGF-b1	n.c.	↓	n.c.
Pedersen et al., 2006		Rosiglitazone	4 mg/kg/day	15 wks	oral: chow	Tg2576	↓ sol Aβ42		↑ radial arm maze
Escribano et al. 2009		Rosiglitazone	5 mg/kg/day	10 wks	oral: chow	hAPP swe-ind			↑ NOR
		Rosiglitazone	5 mg/kg/day	4 wks	oral: chow	hAPP swe-ind			↑ NOR
Toledo and Inestrosa, 2010		Rosiglitazone	3 mg/kg/day	12 wks	oral: gavage	APPswe/PSEN1dE9	↓ plaques	↓	↑ MWM
Escribano et al., 2010		Rosiglitazone	5 mg/kg/day	4–16 wks	oral: gavage	hAPP swe-ind	↓ plaques, sol Aβ, p-tau	↓	↑ NOR, MWM
Rodriguez-Rivera et al., 2011		Rosiglitazone	0.18 mg/day	1 month	oral: chow	Tg2576			↑ CFC, age dependent (9m only)
O'Reilly and Lynch, 2012		Rosiglitazone	6 mg/kg/day	4 wks	oral	APPswe/PSEN1dE9	↓ plaques, insol Aβ42	↓	↑ MWM
Denner et al., 2012		Rosiglitazone	0.18 mg/day	1 month	oral: chow	Tg2576	n.c.		↑ CFC
Yamanaka et al., 2012		DSP-8658	150 mg/kg/day	3 months	oral: chow	APPswe/PSEN1dE9	↓ plaques, sol Aβ	↑ phagocytosis	↑ MWM
Inestrosa et al., 2013	PPARα	WY-14643	0.2 g/l	60 days	oral: water	APPswe/PSEN1dE9	↓ plaques, p-tau	↓	↑ MWM
		4-PB	10 mg/l	60 days	oral: water	APPswe/PSEN1dE9	↓ plaques, p-tau	↓	↑ MWM
Kalinin et al., 2009	PPARδ	GW742				5XFAD	↓ plaques	↓	
Dumont et al. 2012	pan-PPAR	bezafibrate	0.5% chow	9 months	oral: chow	P301S	↓ tau pathology, p-tau	↓	↓ locomotor deficits and anxiety
Jiang et al., 2008	LXR	GW3965	33 mg/kg/day	4 months	oral: chow	Tg2576	↓ plaques, sol Aβ		↑ CFC
Donkin et al., 2010		GW3965	2.5 mg/kg/day	8 or 24 wks	oral: chow	APPswe/PSEN1dE9	↑ sol Aβ		↑ NOR/MWM

Neurodegenerative disease	Nuclear Receptor target	Ligand	Dosage	Length of treatment	Route of Administration	Animal model	Pathology effects	Inflammatory Effects	Behavioral Outcomes
		GW3965	33 mg/kg/day	8 wks	oral: chow	APPswe/PSEN1dE9	↓ plaques, ↑ sol Aβ		↑ NOR/MWM
Wesson et al., 2011		GW3965	33 mg/kg/day	2 wks	oral: gavage	Tg2576	↓ plaques, sol Aβ		↑ olfactory behavior
Koldamova et al., 2005		TO901317	50 mg/kg/day	6 days	oral: gavage	APP23	↓ sol Aβ		
Riddell et al., 2007		TO901317	10 mg/kg/day	7 days	oral: gavage	Tg2576	n.c.		
		TO901317	30 mg/kg/day	7 days	oral: gavage	Tg2576	↓ sol Aβ42		
		TO901317	50 mg/kg/day	7 days	oral: gavage	Tg2576	↓ sol Aβ42		↑ CFC
Lefterov et al., 2007		TO901317	50 mg/kg/day	1 day	oral: gavage	APP23		n.c.	
		TO901317	20 mg/kg/day	4 wks	oral: gavage	APP23	↓ insol Aβ	↓	
Fitz et al., 2010		TO901317	25 mg/kg/day	4 months	oral: chow	APP23	↓ plaques, sol Aβ		↑ MWM
Vanmierlo et al., 2011		TO901317	30 mg/kg/day	6–9 wks	oral: chow	APPSLxPS1mut	n.c. in plaques		↑ NOR and object location
Terwel et al., 2011		TO901317	50 mg/kg/day	7 wks	oral: gavage	APP23	↓ plaques, sol Aβ		(↑) MWM
		TO901317	50 mg/kg/day	6 days	oral: gavage	APP23		↑ glia/plaque association	
Cui et al., 2012		TO901317	30 mg/kg/day	30 days	oral: gavage	APPswe/PSEN1dE9	↓ plaques	↓	↑ MWM
Fitz et al., 2014		TO901317	25 mg/kg/day	15 days	oral: chow	APP23	↓ ISF Aβ42		
		TO901317	25 mg/kg/day	50 days	oral: chow	APP23	n.c. in plaques, sol Aβ		↑ CFC and RWM
Hu et al., 2013		19	10 mg/kg; 3x/wk	6 wks	IP	APPswe/PSEN1dE9	↓ plaques, sol Aβ		
Cramer et al., 2012	RXR	bexarotene	100 mg/kg/day	3, 7 or 14 days	oral: gavage	APPswe/PSEN1dE9	↓ plaques, ↓sol Aβ		↑ CFC/MWM
		bexarotene	100 mg/kg/day	90 days	oral: gavage	APPswe/PSEN1dE9	↓ sol Aβ, n.c. plaques		↑ CFC/MWM
		bexarotene	100 mg/kg/day	20 days	oral: gavage	APPPS1-21	↓ plaques, sol Aβ		↑ CFC/MWM
		bexarotene	100 mg/kg/day	3 or 9 days	oral: gavage	Tg2576			↑ olfactory behavior/nesting
Price et al., 2013		bexarotene	100 mg/kg/day	3 or 7 days	oral: gavage	APPswe/PSEN1dE9	n.c. in plaques or sol Aβ		
Fitz et al., 2013		bexarotene	100 mg/kg/day	15 days	oral: gavage	APPswe/PSEN1dE9	↓ ISF Aβ, n.c. in plaques		↑ RWM
Veeraraghavalu et al., 2013		bexarotene	100 mg/kg/day	7 days	oral: gavage	APPswe/PSEN1dE9	(↓) sol Aβ, n.c. in plaques ↓ sol Aβ40, (↓) sol Ab4β,		
		bexarotene	100 mg/kg/day	7 days	oral: gavage	5XFAD	n.c. in plaques		
		bexarotene	100 mg/kg/day	7 days	oral: gavage	APPPS1-21	(↓) sol Aβ, n.c. in plaques		
Tesseur et al., 2013		bexarotene	100 mg/kg/day	19 days	oral: gavage	APPPS1-21	n.c. plaques/sol Aβ40		unclear, possibly due to drug toxicity
Ulrich et al., 2013		bexarotene	100 mg/kg/day	1 day 3, 7 or 14	oral: gavage	APPswe/PSEN1dE9	↓ ISF Aβ40		

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LaClair et al., 2013		bexarotene	100 mg/kg/day	days	oral: gavage	APPswe/PSEN1dE9	n.c. plaques	n.c.	n.c. in CFC
Boehm-Cagan and Michaelson, 2014		bexarotene	2.5mg/day	10 days	oral: gavage	ApoE4-TR	↓ neuronal Aβ42, tau		↑ MWM, NOR
Parkinson's disease									
Breidert et al., 2002	PPARγ	Pioglitazone	20 mg/kg/day	6–14 days	oral: chow	MPTP	↓ TH+ neuron loss	↓	
Dehmer et al., 2004		Pioglitazone	20 mg/kg/day	6–16 days	oral: chow	MPTP	↓ TH+ neuron loss	↓	
Quinn et al., 2008		Pioglitazone	20 mg/kg; 2x/day	7 days	oral: gavage	MPTP	↓ TH+ neuron loss		↑ motor performance
Kumar et al., 2009		Pioglitazone	10 or 30 mg/kg/day	35 days	oral: gavage	MPTP (rat)	↓ oxidative stress		↑ MWM/passive avoidance
Swanson et al., 2011		Pioglitazone	2.5 mg/kg/day	3 months	oral	MPTP (monkey)	n.c.	n.c.	n.c.
		Pioglitazone	5 mg/kg/day	3 months	oral	MPTP (monkey)	↓ TH+ neuron loss	↓	↑ motor performance
Ulusoy et al., 2011		Pioglitazone	10 mg/kg/day	15 days	IP	rotenone	↑ striatal DA		↑ motor performance
Laloux et al, 2012		Pioglitazone	50 mg/kg/day	14 days	oral: gavage	MPTP	↓ TH+ neuron loss		↑ motor performance
		Pioglitazone	50 mg/kg/day	14 days	oral: gavage	6-OHDA (rat)	n.c.		n.c.
Sadeghian et al., 2012		Pioglitazone	20 mg/kg; 2x/day	7 days	oral: gavage	6-OHDA (rat)	↓ TH+ neuron loss	↓	
		GW855266X	15 mg/kg; 2x/day	7 days	oral: gavage	6-OHDA (rat)	↓ TH+ neuron loss	↓	
Schintu et al., 2009		Rosiglitazone	10 mg/kg/day	5 wks	IP	MPTPp	↓ TH+ neuron loss	↓	↑ motor/olfactory performance
Carta et al., 2011		Rosiglitazone	10 mg/kg/day	1.5 wk	IP	MPTPp	↓ TH+ neuron loss	↓	
Martin et al., 2012		Rosiglitazone	10 mg/kg/day	29 days	IP	MPTP			
Lee et al., 2012		Rosiglitazone	3 mg/kg; 2x/day	1 day	IP	6-OHDA (rat)	↓ TH+ neuron loss	↓/↑	
Swanson et al., 2013		LSN862	30 mg/kg/day	29 days	oral: gavage	MPTP	↓ TH+ neuron loss	↓	
Barbiero et al., 2014	PPARα	fenofibrate	100 mg/kg/day	1 day	oral: gavage	MPTP (rat)	↓ TH+ neuron loss		↑ motor performance
Uppalapati et al., 2014		fenofibrate	10 mg/kg/day	30 days	oral: gavage	MPTP (rat)	↓ TH+ cell loss	↓	
		fenofibrate	30 mg/kg/day	30 days	oral: gavage	MPTP (rat)	↓ TH+ cell loss	↓	↑ MWM
		fenofibrate	100 mg/kg/day	30 days	oral: gavage	MPTP (rat)	↓ TH+ cell loss	↓	↑ passive avoidance, MWM
Sadeghian et al., 2012	PPARδ	GW610742X	10 mg/kg/day	7 days	oral: gavage	6-OHDA (rat)	n.c.	↓	
Martin et al., 2013		GW0742	84 ug/day	14 days	intra-striatal	MPTP	↓ TH+ neuron loss		
Iwashita et al., 2007		L-165041	24 or 240 ug/day	2 days	i.c.v. infusion	MPTP	↑ striatal DA		

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		GW501516	24 or 240 ug/day	2 days	i.c.v. infusion	MPTP	↑ striatal DA		
Dai et al., 2012	LXR	GW3965	20 mg/kg/day	7 days	s.c.	MPTP	↓ TH+ neuron loss	↓	
McFarland et al., 2013	RXR/Nurr1	bexarotene	6 ug/kg/day	28 days	i.c.v. infusion	6-OHDA (rat)	↓ TH+ neuron loss		↑ motor performance
		bexarotene	0.3 mg/kg/day	28 days	oral: gavage	6-OHDA (rat)			n.c.
		bexarotene	1 or 3 mg/kg/day	28 days	oral: gavage	6-OHDA (rat)	↓ TH+ neuron loss		↑ motor performance
ALS									
Kiaei et al., 2005	PPARγ	Pioglitazone	1200 ppm	6 wks - death	oral: chow	G93A SOD1	↓ motor neuron loss	↓	↑ motor performance
Schutz et al., 2005		Pioglitazone	40 mg/kg/day	day 57 - death	oral: chow	G93A SOD1	↓ motor neuron loss	↓	↑ motor performance
Shibata et al., 2008		Pioglitazone	1200 ppm	6 wks - death	oral: chow	G93A SOD1	↓ motor neuron loss	↓	
Huntington's disease									
Chiang et al., 2010	PPARγ	Rosiglitazone	0.01% in chow	4 wks - death	oral: chow	R6/2	n.c. in neuronal death		↑ motor performance/survival
Jin et al., 2013		Rosiglitazone	10 mg/kg/day	24 wks	oral: gavage	N171-82Q	↓ neurodegeneration		↑ motor performance
Johri et al., 2012	pan-PPAR	bezafibrate	0.5% in chow	9 wks	oral: chow	R6/2	↓ neurodegeneration		↑ motor performance/survival

Key: IP: intraperitoneal; i.c.v.: intracerebroventricular; s.c: subcutaneous; sol Aβ: soluble amyloid β; insol Aβ: insoluble amyloid β; n.c: no change; ISF: interstitial fluid; TH: tyrosine hydroxylase; DA: dopamine; MWM: Morris water maze; CFC: contextual fear conditioning; NOR: novel object recognition; RWM: radial arm water maze