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Review

Nuclear receptors in neurodegenerative diseases

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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.

Contents

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Introduction

Nuclear receptors are ligand activated transcription factors that act globally to regulate a diverse array of homeostatic processes (Castrillo and Tontonoz, 2004; Chawla et al., 2001). 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 (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 (Fig. 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 (Fig. 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., 2013). 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 (Núñez et al., 2010) have been genetically inactivated exhibit reduced phagocytosis

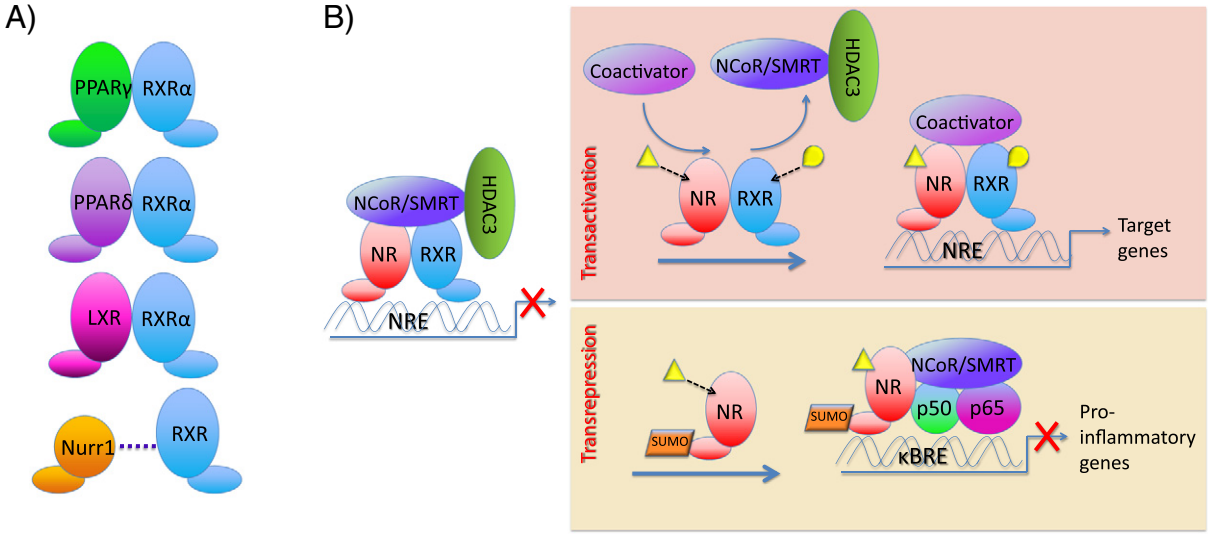

Fig. 1. Nuclear receptors are ligand-activated transcription factors. Nuclear receptors (type II) form obligate heterodimers with RXR and comprise the functional transcription factor. The nuclear receptor complex transactivates its target genes by binding to sequence specific elements in their promoters. 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.