Role of Nuclear Receptors in Central Nervous System Development and Associated Diseases

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Supplementary Issue: Molecular and Cellular Mechanisms of Neurodegeneration

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ABSTRACT: The nuclear hormone receptor (NHR) superfamily is composed of a wide range of receptors involved in a myriad of important biological processes, including development, growth, metabolism, and maintenance. Regulation of such wide variety of functions requires a complex system of gene regulation that includes interaction with transcription factors, chromatin-modifying complex, and the proper recognition of ligands. NHRs are able to coordinate the expression of genes in numerous pathways simultaneously. This review focuses on the role of nuclear receptors in the central nervous system and, in particular, their role in regulating the proper development and function of the brain and the eye. In addition, the review highlights the impact of mutations in NHRs on a spectrum of human diseases from autism to retinal degeneration.

KEYWORDS: central nervous system, nuclear hormone receptors, regulation, brain, eye, human disease

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Introduction

The nuclear hormone receptor (NHR) superfamily is a group of transcriptional regulators that play a key role in numerous pathways, including development, growth, metabolism, and maintenance. These receptors belong to a large family of genes that regulate gene expression. NHRs are activated by ligands, such as hormones and vitamins, and a subset of these NHRs fall under the category of orphan receptors with unidentified ligands. NHRs share a common structure characterized by dimeric zinc fingers that can bind to a lipid-soluble hormone and form a complex with other proteins, such as cofactors and histones, to regulate gene expression. NHRs modulate numerous processes, such as central nervous system (CNS) development, homeostasis, reproduction, differentiation, metabolism, circadian functions, steroidogenesis, cell differentiation, and lipid metabolism.[1,2] The goal of this review is to discuss the role of NHRs in the development of the CNS, with an emphasis on their function in the brain and the eye and their impact on human disease.

While being involved in a wide range of functions, NHRs have very conserved structure of functional domains (Fig. 1A). There are two activation function (AF) domains that bind to DNA. The variable NH_2 terminal (A/B) contains an activation function AF-1 domain, and the AF-2 domain is found in the E domain also known as the ligand-binding domain (LBD). Modifying the A/B domain produces different isoforms of the receptors. A conserved DNA-binding domain (C) binds to specific DNA sequences known as the hormone response element (HREs). In addition, the DNA-binding domain is composed of two zinc fingers and is the most conserved region of the NHR. A P-box region is found on the first zinc finger and functions to recognize the *half-site* of a response element. The second zinc finger contains a D-box, which mediates receptor dimerization. The most variable and unique sequence of NHRs is the linker region (D), which aids in the conformational changes of the binding ligands. Finally, there is a conserved region with LBD (E) that contains the activation function AF-2. Some receptors also include a COOH-terminal region (F) that aids in the folding of the receptor into a transcriptionally active form.[3–5]

Regulation

NHRs are involved in a wide spectrum of functions and are key components of a great number of signaling pathways. Nuclear receptors have the ability to enhance or repress the expression of a gene in response to changes in the environment or to endocrine signals. When a ligand binds to its receptor,

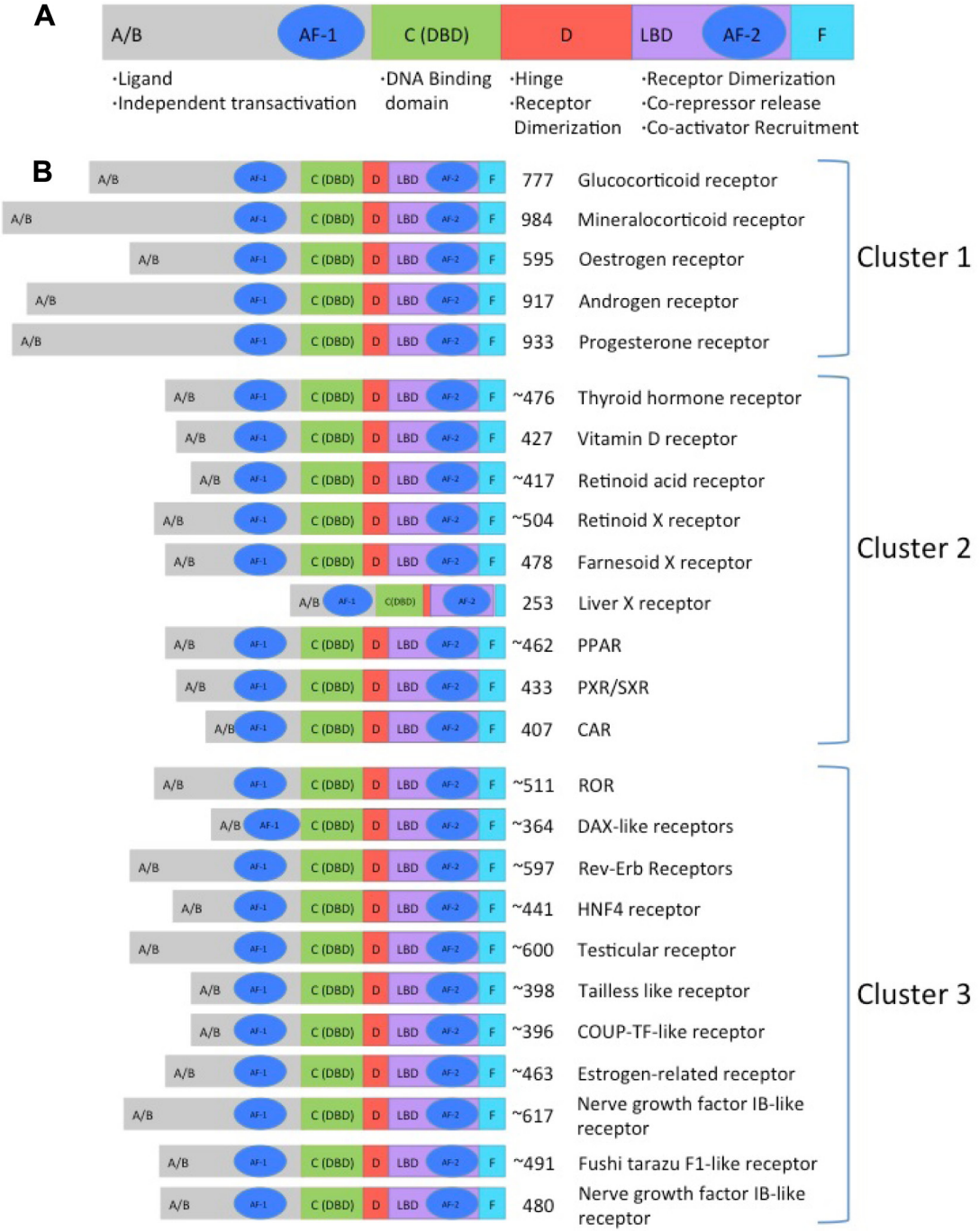

Figure 1. Schematic representation of the functional domains of NHRs in each classification cluster. The A/B domain is the most variable region, and it contains the activation function-1 (AF-1) site. The activation functions AF-1 and -2 are important in the regulation of receptor transcriptional activity. The C domain is one of the most highly conserved regions across the superfamily on nuclear receptors and consists of the DNA-binding region. The D domain, also known as the hinge region, is involved in the conformational changes that occur after ligand binding allowing the coactivators or corepressors to bind. LBD is the second most conserved region and is in charge of the recognition and binding of the ligands. The F region is a carboxyl terminal that is not present in all receptors.[2,4,73]

it alters the receptor activity and thus the expression of entire gene networks. However, ligands are not the only mechanism through which receptors can regulate genes. A set of proteins known as coregulators also interact with the receptors to regulate gene expression. Coregulators facilitate or truncate the receptors' ability to bind to the transcriptional complex as well as the promoter.[6] Receptors use several mechanisms such as interaction with the HREs, coregulators, interaction with the transcription factor complex, and histone modification to finely orchestrate an appropriate gene expression.[6] A collection of HREs and coregulators and corepressors for each nuclear receptor is given in Table 1.

Table 1. Hormone response elements' (HREs) sequences and their coactivators and cosuppressors.

NUCLEAR HORMONE RECEPTOR	HRE SEQUENCE	RESPONSE ELEMENT	CO-ACTIVATORS	CO-SUPPRESORS
Thyroid hormone receptor alpha (NR1A1)	AGGTCA		NCOA1[237]	NCOR1[238]
			NCOA2[239]	NCOR2[240]
			NCOA3[241]	
			MED1[242]	
Thyroid hormone receptor beta (NR1A2)	AGGTCA		NCOA1[237]	NCOR1[240]
			NCOA2[239]	
			NCOA3[241]	
Vitamin D receptor			Not known	Not known
Retinoid acid receptor alpha (NR1B1)	5′-PuG(G/T)TCA-3′	Heterodimer	CREBBP[243]	NCOR1[22,238,240,244]
			EP300[243,245]	NCOR2[246]
			MED1[247]	
			NCOA1[248,249]	
			NCOA2[250]	
			NCOA3[241]	
Retinoid acid receptor beta (NR1B2)	5′-PuG(G/T)TCA	Heterodimer	MED1[22,251–253]	
			NCOA1[248,254,255]	
			NCOA2[250]	
			NCOA3[241,254,256]	
Retinoid acid receptor gamma (NR1B3)	5′-PuG(G/T)TCA-3′	Heterodimer	NCOA1[22,248,255]	NCOR1[22,240,246,254]
			NCOA2[22,250,257]	NCOR2[238]
			NCOA3[241,254,256]	
Retinoid X alpha (NR2B1)	5′-AGGTCA	Homodimer, Heterodimer	CREBBP[258,259]	
			EP300[258]	
			MED1[22,253]	
			NCOA1[22,248]	
			NCOA2[250,257]	
			NCOA3[22,241]	
			PPARGC1A[260]	
			TAF11[261]	
			TAF4[22,262,263]	
			TBP[22,262,263]	
Retinoid X beta (NR2B2)	5′-AGGTCA	Homodimer, Heterodimer	NCOA1[22,248,255]	
			NCOA2[250,255,257]	
			NCOA3[22]	
PNR (NR2E3)	AAGTCA n AAGTCA	Homodimer	CRX[171]	
Retinoid X gamma (NR3B3)	5′-AGGTCA	Homodimer, Heterodimer	NCOA1[22,248,255]	
			NCOA2[250,255,257]	
			NCOA3[22]	
Farnesoid X receptor (NR1H4)	AGTTCAnTGAACT		CARM1[264]	
			MED1[265]	
			NCOA1[266,267]	
			PPARGC1A[268–270]	
			PRMT1[271]	
			TRRAP[272]	
Farnesoid X receptor beta (NR1H5)	AGTTCA N TGAACT	Heterodimer	NCOA1[273]	

(*Continued*)

Table 1. (*Continued*)

NUCLEAR HORMONE RECEPTOR	HRE SEQUENCE	RESPONSE ELEMENT	CO-ACTIVATORS	CO-SUPPRESORS
Liver X receptor alpha (NR1H3)	AGGTCANNNNAGGTCA		EP300[274]	NCOR1[275]
			NCOA1[274]	NCOR2[275]
			NCOA2[276]	
			PPARGC1A[277]	
			PPARGC1B[278]	
			TRRAP[272]	
Liver X receptor beta (NR1H2)	AGGTCANNNNAGGTCA		EP300[274]	
			NCOA1[279]	
			NCOR1[275]	
PPAR alpha (NR1C1)	5′-AACTAGGNCA A AGGTCA-3′	Heterodimer	CITED2[280]	NCOR1[281–283]
			CREBBP[284,285]	NRIP1[286–288]
			HADHA[289]	
			MED1[290]	
			NCOA1[291]	
			NCOA3[292]	
			NCOA6[293,294]	
			PPARGC1A[295]	
			PPARGC1B[295]	
			SMARCA2[296]	
PPAR beta (NR1C2)			NCOA1[297]	NCOR1[298–300]
			NCOA3[292]	NCOR2[298,301]
			NCOA6[293]	
			PPARGC1A[302]	
PPAR gamma (NR1C3)	5′-AACTAGGNCA A AGGTCA-3′	Heterodimer	CITED2[280]	WWTR1[303]
			CREBBP[285,304]	SAFB[305]
			EP300[306]	NRIP1[307]
			MED1[308–310]	NCOR2[298,301]
			NCOA1[285,297,310]	NCOR1[281,300,301]
			NCOA2[311]	
			NCOA3[392]	
			NCOA4[312]	
			NCOA6[294,313]	
			NCOA7[314]	
			PPARGC1A[315–319]	
			PPARGC1B[317–321]	
			PRMT2[322]	
			SCAND1[323]	
			SMARCA1[324,325]	
			TGS1[310]	
PXR/SXR receptor (NR1I2)	AGGTCA	Heterodimer	FOXO1[326]	NCOR2[327,328]
			GRIP1[329]	NR0B2[330]
			NCOA1[331]	
			NRIP1[332]	
			PPARGC1A[333]	
CAR (NR1I3)	AGGTCA	Heterodimer	MED1[334]	
			NCOA1[335]	
			PPARGC1A[336]	

Table 1. (*Continued*)

NUCLEAR HORMONE RECEPTOR	HRE SEQUENCE	RESPONSE ELEMENT	CO-ACTIVATORS	CO-SUPPRESORS
ROR alpha (NR1F1)	T/A A/T T/A C A/T A/GGGTCA	Monomer, Homodimer	EP300[337]	HR[338]
			NCOA2[339]	NCOR1[340]
			MED1[339]	NCOR2[340]
ROR beta (NR1F2)	T/A A/T T/A C A/T A/GGGTCA		NCOR1[341]	NCOR1[342]
				NRIP2[343]
ROR gamma (NR1F3)	AGGTCA nnnnn AGGTCA		NCOA1[344]	HR[342]
DAS-like receptors			Not known	Not known
Rev-Erb alpha (NR1D1)	A/T A A/T N T PuGGTCA		NCOA5[345]	C1D[176]
				HDAC3[346]
				NCOA5[345]
				NCOR1[347]
Rev-Erb beta (NR1D2)	A/T A A/T N T PuGGTCA		NCOA5[345]	NCOA5[345]
				NCOR1[347,348]
HNF4 alpha (NR2A1)			CREBBP[349–351]	NCOR2[352]
			GRIP1[349,350]	
			MED1[353,354]	
			PPARGC1A[355,356]	
			PPARGC1B[356,357]	
HNF4 gamma (NR2A2)	AGGTCA n AGGTCA		Not known	Not known
Testicular receptor 2 (NR2C1)	AGGTCA n AGGTCA	Monomer, Homodimer		HDAC3[358]
				HDAC4[358]
				NRIP1[359]
Testicular receptor 4 (NR2C2)		Monomer, Homodimer, Heterodimer		JAZF1[360]
				NR2C2AP[361]
Tailless like receptor (NR2E1 and NR2E3)	AAGTCA n AAGTCA		Not known	Not known
COUP-TF1 (NR2F1)	AGGTCA n AGGTCA		CREBBP[362]	BCL11A[363]
			NCOA1[364]	BCL11B[363]
				NCOR1[365]
				NCOR2[365]
COUP-TF2 (NR2F2)	A/GGGTCA n AGGGTCA		BCL11B[363]	BCL11A[363]
			SQSTM1[366]	NCOR1[365]
				NCOR2[365]
				ZFPM2[367]
V-erbA-related gene (NR2F6)	AGGTCA n AGGTCA		NCOA1[368]	
Estrogen-related receptor alpha (NR3B1)	TNA AGGTCA		NCOA1[369]	
			NCOA2[369]	
			NCOA3[369]	
			PNRC2[370]	
			PPARGC1A[315,316,371,372]	
Estrogen-related receptor beta (NR3B2)	TNA AGGTCA		NCOA1[373]	
			NCOA2[373]	
			NCOA3[373]	
			PNRC1[374]	
Estrogen-related receptor gamma (NR3B3)	TNA AGGTCA		NCOA1[375]	
			PNRC2[376]	
			PPARGC1A[377]	
			PPARGC1B[377]	
			TLE1[376]	

(*Continued*)

Table 1. (*Continued*)

NUCLEAR HORMONE RECEPTOR	HRE SEQUENCE	RESPONSE ELEMENT	CO-ACTIVATORS	CO-SUPPRESORS
Nerve growth factor IB-like receptor (NR4A1)	AAAGGTCA	Homodimer, Heterodimer	EP300[378]	
			KAT2B[378]	
			NCOA1[378]	
			NCOA2[378]	
			NCOA3[378]	
			MED1[378]	
Nuclear receptor related 1 (NR4A2)	AAAGGTCA		Not known	Not known
Neuron-derived orphan receptor 1 (NR4A3)	AAAGGTCA		SIX3[379,380]	
			MED1[381]	
			EP300[378]	
			NCOA2[378]	
			KAT2B[378]	
Steroidogenic factor 1 (NR5A1)	YCA AGG YCR	Monomer	CREBBP[382]	NCOR2[383]
			EDF1[384]	
			NCOA1[385]	
			NCOA2[383,386]	
			PNRC2[370]	
Liver receptor homolog-1 (NR5A2)	YCA AGG YCR	Monomer	NCOA1[387]	PROX1[388,389]
			NCOA3[390]	
			EP300[391]	
			EID1[392]	
Germ cell nuclear factor (NR6A1)	TCA AGGTCA	Homodimer		NCOR1[393,394]
				NCOR2[393,394]
SHP (NR0B2)				SIN3A[395,396]
				HDAC3[397]
				HDAC1[395,397,398]
				EID1[399]
				NCOR1[395]
				NCOR2[395,400]
Estrogen receptor-α (NR3A1)	GGTCAnnnTGACC	Homodimer	NCOA1[401]	NCOR1[401]
			NCOA2[401]	NRIP1[401]
			NCOA3[401]	
			CREBBP[401]	
			EP300[401]	
			MED1[401]	
			DDX5[401]	
			SRA1[401]	
Estrogen receptor-β (NR3A2)	GGTCAnnnTGACC	Homodimer	NCOA1[401]	NCOR1[401]
			NCOA2[401]	NRIP1[401]
			NCOA3[401]	
			EP300[401]	
			CREBBP[401]	
			MED1[401]	
			DDX5[401]	
			SRA1[401]	

Table 1. (*Continued*)

NUCLEAR HORMONE RECEPTOR	HRE SEQUENCE	RESPONSE ELEMENT	CO-ACTIVATORS	CO-SUPPRESORS
Androgen receptor (NR3C4)	GGTACANNNTGTTCT	Homodimer	CARM1[402]	NCOR1[403,404]
			CCND1[405]	NCOR2[403,404]
			EP300[406]	
			FHL2[407,408]	
			KAT2B[409]	
			KAT5[410]	
			MED1[411]	
			NCOA1[22,412]	
			NCOA2[413–415]	
			NCOA3[22]	
			NCOA4[413–415]	
			RAN[415,416]	
			RNF14[417–419]	
			SMARCD1[420]	
			TGFB1I1[421–423]	
			UBE3A[424]	
Glucocorticoid receptor (NR3C1)	GGTACANNNTGTTCT	Monomer	CREBBP[259]	BAG1[425]
			MED1[426]	NCOR1[427,428]
			NCOA2[250,429,430]	
			NCOA6[431]	
			PTMS[432]	
			SMARCA1[433]	
			SMARCD1[434]	
			TADA2A[435]	
Mineralocorticoid receptor (NR3C2)	ACAAGANNNTGTTCT	Homodimer, Heterodimer	CASP8AP2[436]	DAXX[436]
			ELL[437]	NCOR1[438]
			EP300[439]	NCOR2[438]
			FAF1[436]	NFYC[440]
			MTL5[441]	PIAS1[442]
			NCOA1[248,438,443,444]	
			NCOA2[438,439,445]	
			NRIP1[444]	
			PPARGC1A[439]	
			PPARGC1A[437]	
			PPARGC1A[443,446]	
			TRIM24[444]	
			UBE2I[447]	
Progesterone receptor (NR3C3)	GGTACANNNTGTTCT	Homodimer	NCOA3[130,448]	
			SRA1[449,450]	
			NCOA1[358,451–454]	
			NCOR2[372,455–457]	
			CREBBP[241,458]	
			JDP2[459]	

Regulation by HREs. HREs are small sequences of DNA commonly located near the promoter region of a gene, yet they may also be found up to several hundred kilobases upstream of the promoter and even within the first intron of a gene.[7] Each receptor subfamily has a preferred HRE motif it binds, although significant variation has been observed in the ability of NHRs to bind to particular HRE sequences (Table 1). For example, steroids predominantly bind to the motif AGAACA, while thyroid hormones bind to AGG/TTCA.[8] The motif AGGTCATGACCT is recognized by both the thyroid hormone and the retinoic acid (RA) receptor (RAR). In addition to the motif, the number of nucleotides between motifs and the direction of the motif contribute to binding capacity. For example, the arrangement of direct repeats (DR) AGGTCAnxAGGTCA, inverted repeats AGGTCAnxT GACCT, and reverted repeats (ER) TGACCTnxAGGTCA has anything from 0 to 8 nucleotides as spacers.[9] The different combination of spacing and orientation ensures specificity. Nuclear receptors can bind to more than one half-site configuration, allowing coregulation and cross talk between nuclear receptors.[10] The optimal binding HRE site for the orphan hormone receptor Nr2e3, identified by evaluating a series of synthetic duplex DNA fragments acquired from a library of random segments, is a hexamer core binding site of AG(G/T)TCA.[11] Receptors can bind to the HREs as monomers as in the case of many orphan receptors, as homodimers as in the case of the majority of steroid receptors, or as heterodimers as in the case of several nonsteroid receptors, which usually bind to the promiscuous retinoid X receptor (RXR) (Fig. 2A).[3,12,13] There are nonpermisive heterodimer complexes that are activated only by the partner receptor and not by RXR, and permissive heterodimer complexes that can be activated by either of the receptors.[14,15]

HREs are classified by their ability to repress (negative HREs [nHREs]) or activate (positive HREs) gene expression. HRE sequences have been identified near the 5′ or downstream of the TATA box and even been within the 3′-untranslated region.[6,7] nHREs have been identified in genes that are expressed in the pituitary gland highlighting the importance of the feedback mechanism in hormone regulation.[16] nHREs differ from pHREs in (1) the nucleotide sequence of the half-site, (2) in the orientation of the half-site, and (3) in the number of nucleotides that separates them (Fig. 2B).[17] It is interesting to note that unoccupied nHREs increase the transcription of a gene, while binding to the ligand has the opposite effect of repressing gene expression. Some sequences of the nHREs overlap with the binding site of different activation factors, therefore, creating a physical competition between the receptors and the transcription factors in the regulation gene expression.[18] HREs are one of the several mechanisms by which receptors regulate genes. Another important mechanism is the regulation through coregulators.

Coregulators. Accessory proteins, known as coregulators, can repress (corepressors) or activate (coactivators) the expression of a given gene (Fig. 3 and Table 1). Coactivators have several mechanisms of action. For example, they can directly interact with the nuclear receptor activation domain in the absence of an antagonist and do not directly bind to the promoter, therefore, preventing them from initiating transcription on their own.[19,20] Another way in which coactivators operate is by interacting with components of the transcription machinery and other transcription factors or directly with the promoter changing chromatin conformation via histone acetyltransferase (HAT) proteins (Fig. 3A).[20] Coactivators bind predominantly to the AF-2 and AF-1 domains and interact with transcription factors, such as transcription factor II B

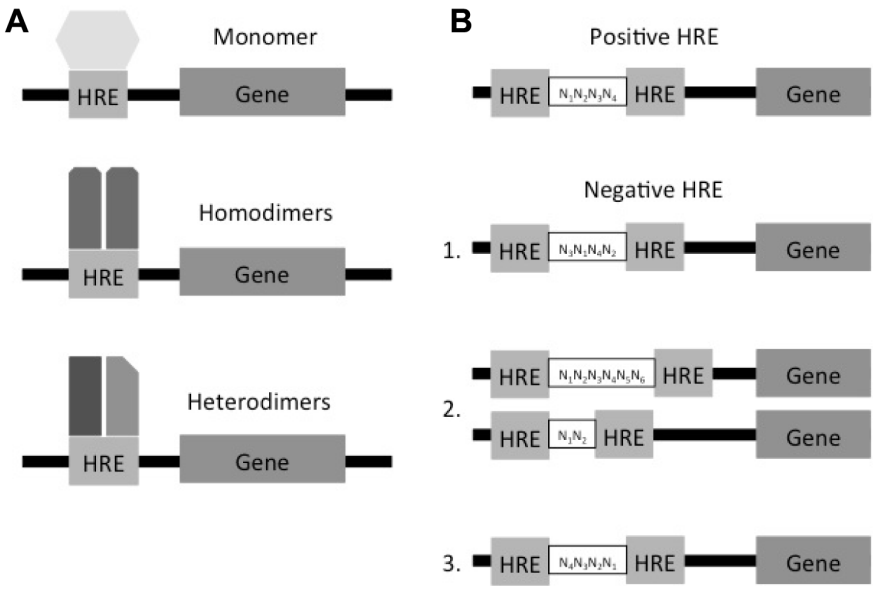

Figure 2. HREs' potential patterns associated with NHRs. Schematic representation of (**A**) NHRs binding to HREs and (**B**) positive HRE and nHRE patterns.

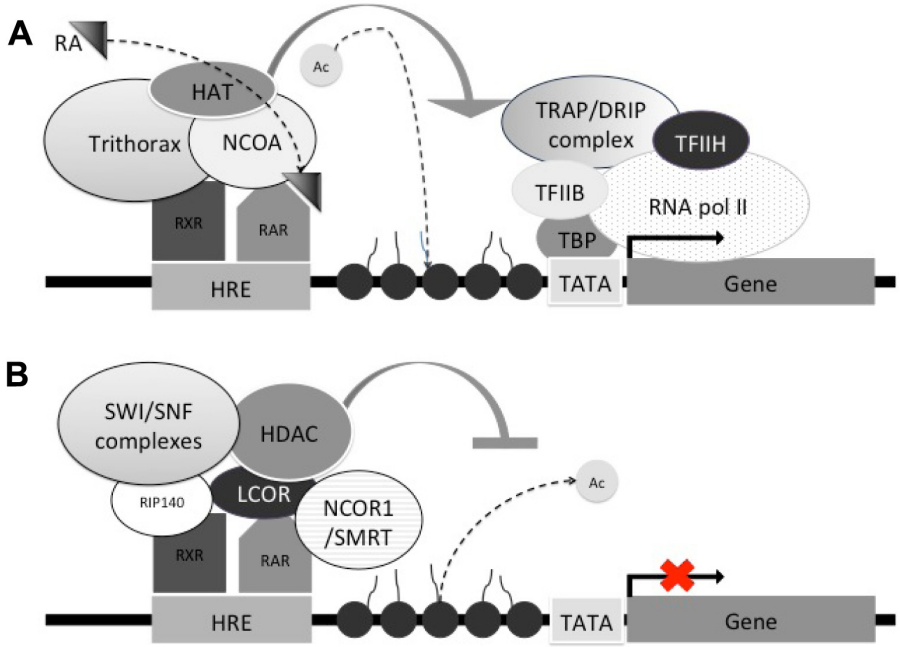

Figure 3. Transcription repression or activation mediated by RAR–RXR nuclear receptors. Coregulator binding can alter chromatin structure, aiding gene transcription or blockage via histone acetylation or deacetylation. (**A**) Transcriptional activation by coactivators NCOA and trithorax and histone acetylation by HAT proteins, in the presence of RA. (**B**) Transcriptional repression by corepressors NCOR, SMRT, LCOR, and RIP140 and histone deacetylation by HDAC proteins, in the absence of RA.

and TATA box-binding protein. A coactivator can contain more than one motif allowing the molecule to interact with receptors found in dimeric form. One of the most common known motifs is the Leucine LXXLL motif; however; not all coactivators have this motif. For example, the coactivator SUG-1, an ATPases of the 26s proteasome, lacks the LXXLL motif and, therefore, does not bind to the AF-2 region.[6,21,22] Several coactivators have been identified, including the steroid hormone receptor coactivator group (SRC-1, -2, and -3), the E3 ubiquitin protein ligase E6-AP, and the RFP-1 coactivator. It is important to highlight that coactivators can also be found in complexes, such as the TRAPs/DRIPs and TRAP220/PBP that also interact with the transcription factors.[23] Expression of genes can be repressed in the presence of an antagonist or in the absence of the ligand.

Corepressors are known for their ability to bind to a receptor as well as to elements of the transcription machinery, thus reducing the promoter activity (Fig. 3B and Table 1).[22] Examples of corepressors includes the nuclear receptor corepressor (NCoR), also known as the silencing mediator for the retinoid and thyroid hormones (SMRT) (Fig. 3B). Steroid hormones, such as glucocorticoid receptor (GR), mineralocorticoid receptor (MR, Nr3c2), and estrogen receptor (ER), do not interact with NCoR; they instead bind to the corepressors in the presence of an antagonist molecules silencing the expression of a gene.[24] The mechanism of action of the coactivators has been defined largely by crystallographic studies that illustrate the molecular conformation changes of NHRs upon ligand binding, thereby releasing the corepressor complex and leaving the site open for the recruitment of a coactivator complex.[25]

Classification

The classification of NHRs has proven to be as complex as the myriad of interactions that they regulate. Another way of grouping the more than 50 members of this group is by focusing on the dimerization and DNA-binding properties of each receptor, grouping the NHRs into four classes. Receptors that belong to Class I bind as homodimers to a palindromic HRE sequence of two half-sites separated by a variable DNA sequence. Class II receptors commonly bind as heterodimers to RXR direct repeats. Class III receptors bind as homodimers to direct repeats. Finally, Class IV receptors bind as monomers to a single half-site.[26,27] This form of grouping does not reflect the great number of functions in which the receptors are involved. Taking into considerations the function they perform, the nuclear receptors are divided into three major clusters. The first cluster contains the families of the glucocorticoid receptors, estrogen receptors, mineralocorticoid receptors, androgen receptors, and progesterone receptors. The second cluster includes the families of the thyroid receptors (THRs), vitamin D receptors (VDRs), retinoic acid receptors (RARs), peroxisome proliferator-activated receptors (PPARs), farnesoid X receptor (FXRs), liver x receptor (LXR), pregnane X receptor/steroid and zenobiotic receptor (PXR/SXR), RXR, and constitutive androstate receptor (CAR). The third cluster is composed of the receptors whose ligands have not yet been discovered and are commonly known as the family of

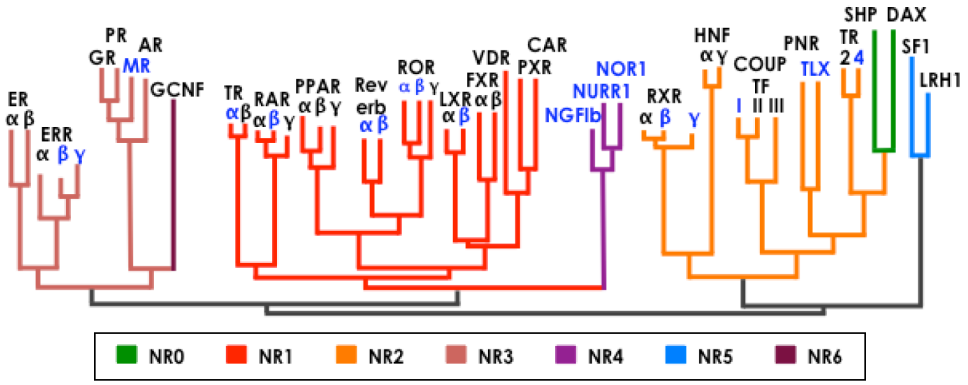

Figure 4. Phylogenetic depiction of the nuclear receptor families. Receptors expressed in the CNS are highlighted in blue.[122]

the orphan nuclear receptors (ONRs).[28–30] Figure 1 illustrates the functional domains of NHRs in each classification cluster. Interestingly, the phylogeny of NHRs depicted in Figure 4 shows the cluster of receptors independent of their expression profile or dimerization and DNA-binding properties, highlighting the importance to put in place another classification system. This classification leads to a different nomenclature where a number from 0 to 6 identifies each clade. In this review, we focus on the major families of NHRs that play important roles in the CNS development. Table 2 describes NHRs expressed in adult mice and in the human brain. It is important to highlight that the receptors involved in the CNS (Fig. 4, blue colored) are common and can be found throughout all the clades.

Nuclear Retinoid Receptors Family and the CNS

There are two families of nuclear retinoid receptors: RARs and RXRs. Both families of receptors can bind to target genes as either heterodimers or homodimers allowing them the capacity to target genes in different pathways.[6] Humans have the following three types of RAR genes: RARα, RARβ, and RARγ; there are the following three types of RXR: RXRα, RXRβ, and RXRγ. Thirteen different proteins can be produced from the six different genes identified thus far as a consequence of alternative splicing and different promoters.[31] An important characteristic that differentiates the two classes of retinoid receptors is the unique amino acid sequence found in LBD conferring each receptor with specific individual characteristics, thereby allowing them to modulate different biological pathways.[32]

The unique LBD sequence establishes varying affinity toward a particular ligand. For example, RARs bind with high affinity to 9-*cis*-RA as well as all-*trans*-RA, while RXR only binds to the 9-*cis*-RA.[33] Along with these differences in the ligand binding, there is also variation in tissue expression. RARα and RARβ are found in the majority of tissues, while RARγ is predominantly expressed in the skin.[32] Similarly, RXRα and RXRβ are widely distributed, while RXRγ is expressed in the muscles and brain and in the differentiation of the cartilage and epithelial cells.[34,35] RXRγ is not only expressed in the CNS, it is also involved in lipid sensing and modulates gene expression accordingly.[36] Retinoic receptors can form heterodimers with both the thyroid hormone nuclear receptors (THRs) and vitamin D receptors (VDRs).

When RXR binds to a THRs or VDR it increases the affinity of DNA biding.[37] Similarly, the interaction of THRs with RARs also increases the affinity of the DNA binding. A study performed in monkey kidneys showed that the interaction of both receptors had a positive effect in the transcriptional rate of the gene whose promoter contains a response element for the thyroid hormone, while it also represses those genes that did not have it. This result suggests that the formation of the heterodimers allows for a better control of the transcription rate, and it also hints to the idea that both RAR and THR control the expression of genes in overlapping networks.[32,38] Retinoid receptors are involved in a wide range of biological processes that include embryonic development, growth, differentiation, apoptosis, and spermatogenesis. Their functions are not only limited to development, but they also play important roles in adults to maintain proper function of the lungs, liver, and neuronal and immune systems.[39] In brain, RARs and RXRs are expressed in multiple stages (Table 2) and play a major role in the development and function of the CNS.

During brain cortex development, RA is synthesized in a tissue-specific manner by the aldehyde dehydrogenase (ALDH) family of enzymes[40–42] that is composed of the following three members: ALDH1A1, ALDH1A2, and ALDH1A3. ALDHs have distinct and specific expression patterns that correlate with RA activity as detected by reporter transgenes.[43] In brain, ALDH1A3 is primarily expressed in the lateral ganglionic eminence, and ALDH1A1 is expressed in the dopamine-containing mesostriatal system and meninges, while ALDH1A2 is present only in the meninges. Consistent with the presence of ALDH1A3 and ALDH1A1 in the lateral ganglionic eminence and its derivative striatum, where high levels of RA and other retinoids are detected in the developing striatum.[40–42] RA is derived from the liposoluble vitamin A and is critical for vision, since its derivative (retinaldehyde) is the light-sensitive molecule, which triggers

Table 2. Nuclear receptors expressed in the different areas of the human or mouse brain.

RECEPTOR	LOCATION
Pparα	BC, C, BS
Pparβ/δ	OA, BC, CP, H, T, HY, AN, CO, C, BS
Pparγ	OA, BC, CO, C
Rxrα	OAM, CP, H, HY, CO, C, BS
Rxrβ	OA, BC, H, T, HY, AN, CO, C, BS
Rxrγ	OA, BC, CP, H, HY, AN, BS
Rorα	OA, BC, CP, H, T, HY, AN, CO, C, BS
Rorβ	OA, BC, CP, H, T, HY, AN, CO, C, BS
Rorγ	BC, H, HY, CO, C, BS
Tr2	OA, BC, CP, H, T, HY, AN, CO, C, BS
Tr4	OA, BC, CP, H, T, HY, AN, CO, C, BS
Tlx	OA, BC, CP, H, T, HY, AN, CO, C, BS
Nurr1	OA, BC, CP, H, T, HY, AN, CO, C, BS
Nor1	OA, BC, CP, H, T, HY, AN, CO, C, BS
Rarα	OA, BC, CP, H, HY, CO, C, BS
Rarβ	OA, BC, CP, H, T, HY, AN, CO, C, BS
Rarγ	OA, BC, H, HY, CO, C, BS
Trα	OA, BC, CO, H, T, HY, CO, C, BS
Trβ	OA, BC, CP, H, HY, AN, CO, C, BS
Mr	OA, BC, CP, H, T, HY, AN, CO, C, BS
Ngf1B	OA, BC, CP, H, T, HY, CO, C, BS
Nr1d1	OA, BC, CP, H, T, HY, CO, C, BS
Nr1d2	BC, CP, H, T, HY, AN, CO, C, BS
Nr2f1	OA, BC, T, HY, C, BS
Nr2f2	BC, H, T, HY, CO, C, BS
Lxrα	OA, BC, H, HY, AN, CO, C, BS
Lxrβ	BC, CP, H, T, HY, AN, CO, C, BS
Lxrγ	OA
Vdr	OA, BS
Gcnf	BC, H, AN, CO, C, BS
Ear2	OA, BC, CP, H, T, HY, AN, CO, C, BS
Errα	OA, BC, H, HY, CO, C, BS
Errβ	BC, H, HY, CO, C, BS
Errγ	OA, BC, CP, H, T, HY, AN, CO, C, BS
Gr	OA, BC, CP, H, T, HY, AN, CO, C, BS
Pr	OA, BC, CP, H, T, HY, AN, CO, C, BS
Car	OA, BC, HY, C, BS
Erα	OA, BC, H, HY, AN, CO, C, BS
Erβ	OA, BC, HY, AN, CO, BS
Ar	OA, BC, H, HY, CO, C, BS
Shp	OA, BC, H, T, HY, AN, CO, C, BS
Fxrα	OA, BC, CP, H, T, HY, AN, CO, C, BS
Trb	T
Dax1	HY, AN
Sf-1	HY
Lrh-1	AN, BS

Abbreviations: BC, brain cortex; C, cerebellum; BS, brain stem; OA, olfactory areas; CP, caudate putamen; H, hyppocamps; T, thalamus; HY, hypothalamus; AN, arcuate nucleus; CO, colliculi.

the phototransduction process in photoreceptor cells in the retina.[44] Vitamin A and RA are essential for eye development and maintenance and serve a similar role in brain cortex development. Young animals raised on a vitamin A-deficient diet grow poorly, become blind, and have a low survival rate.[45,46] The teratogenic effect of RARs was demonstrated in a study using the antagonist of RARs (AGN193109). An- or microphthalmia was observed in 75% of treated mice.[47] Additionally, a recent study revealed mutations in human ALDH1A3 is associated with microphthalmia and anophthalmia.[48–53]

RA biological action is to bind to RARs, switching them from transcription repressive elements to transcription activator elements, while they are bound to RAR elements (RAREs).[54,55] In contrast, RARβ has been involved in brain structure development and maintenance; especially in ventral and dorsal telencephalon development, hippocampal plasticity, and brain barrier development.[56–59] In addition, RARβ is expressed with other RARs and RXRs in adult mice and human brains (Table 2). Other studies revealed that Rarβ expression is inducible by adding external RA at stage E15 to rat brain cortex cultures. Therefore, increases in Rarβ expression by RA in brain cortex may be due to a partial depressive mechanism as *RAR*β is autoregulated by RA through a RARE-dependent mechanism.[60–62] Moreover, in the E15 mouse, *Rarβ* enhances protein tyrosine phosphatase, nonreceptor type 5 (PTPN5) expression, a brain-specific tyrosine phosphatase that has been shown to dephosphorylate several key neuronal signaling proteins in brain cortex.[56,63] Interestingly, Rarβ seems to enhance or repress gene transcription, depending not only on the presence (enhance) or lack (repress) of RA but also on the isoform tissue-specific transcription. Rarβ 1 expression in rats has been shown to upregulate *Ptpn5* gene expression. In contrast, Rarβ 4, an isoform composed of only four amino acids at the N terminus, resulted in a lower transcription of *Ptpn5*.[56] The development and maintenance of the brain demonstrate the complexity of the networks that the hormone receptors regulate, which requires the interaction of the receptors with enzymes. Lack of *Rarβ*, as observed in the Rarb^{tm1Vgi} knockout mouse, presents with memory and spatial learning problems. *Rarβ* deficiency in these mice virtually eliminates hippocampal CA1 long-term potentiation and long-term depression.[64]

RARβ and RA signaling pathway also play an important role in mediating eye development. RA signal depends on the transcription factor Pax-6 to activate the α crystalline β gene, which codes for the formation of the lens in the eye. Inhibition of RA synthesis as a consequence of antagonist results in the inhibition or abnormal morphogenesis of the lens in murine models.[65] RA signaling is detected in the lens placode and lens pit and is also expressed during the differentiation of the primary lens fibers. RA signaling is also active in the surface ectoderm and the corneal epithelium. Finally, during the development of the retina, RA signaling is detected in the optic vesicle and the retinal pigment

ephitelium (RPE).[66] Interestingly, *Rarβ* transcripts were discovered at the onset (E12) of retinal pigment epithelium formation, in the vitreous body, and in the condensed mesenchyme around the eye cup, which forms the choroid layer in mice.[67] Rarβ$^{-/-}$ (Table 3) mice have abnormal retrolenticular mass of pigmented tissue in the vitreous body, which presented a large base adherent to the lens, containing a persistent hyaloid artery and vein.[68] This abnormal structure is found bilaterally in most of the homozygous mice but rarely seen in heterozygosis.[68] By E13.5, mouse fibroblasts of the primary vitreous body expand and thin as the secondary vitreous forms and is found at the optic disk by E15.5, forming Bergmeister's papilla.[68] In E14.5, Rarβ$^{-/-}$ mice, the number of cell nuclei in the secondary vitreous is four to six times higher than the number of nuclei in wild-type animals.[69] These observations indicate that the loss of *Rarβ* results in overproliferation of the fibroblastic neural crest cells of the primary vitreous body in mice.[69] Additional eye defects observed in Rarβ$^{-/-}$-null mice include congenital folds of the retina and cataracts, which are likely to be secondary to mechanical and/or metabolic stresses resulting from the presence of the persistent hyperplastic primary vitreous.[68]

Table 3. Knockout mice models excising that effect the CNS function.

MODEL NAME	BRAIN/EYE DEFECTS
Thrb$^{tm2Df/tm2Df}$	– Lack of M-opsin expressing cones.[106]
	– S cone gradient in the retina disturbed.[106]
TRβ mut	– Impairment in balance and coordination.[95]
	– Reduce cerebellum mass.[95]
	– Decrease in Purkinje cell layer.[95]
Rora^{sg}	– Deficiency of granule cells and Purkinje cells.[460]
	– Cerebellar cortex underdeveloped.[460]
Nr4a2^{tm1Tpe}	– Failure to develop dopaminergic neurons.[218]
Nr2e3^{rd7}/J	– White spots evenly distributed in the retina.[461]
	– Whorls and rossetts can be detected in the retina –Progressive loss of cones and rods.[461]
Rorβ$^{-/-}$	– Loss of rods.[167]
	– Overproduction of primitive S cones.[167]
Nr1d1^{tm1Ven}	– Delay cerebellum development.[462]
	– Abnormal Purkinje ad granule cells.[462]
RAR β^{2} γ$^{2-/-}$	– Marked atrophy and dysplasia of the retina.[463]
	– In the central retina only 2 or 3 rows of nuclei are found.[463]
RXRα$^{-/-}$ and RXR β$^{-/-}$	– Fetus diet at E12.5-16.5.[464]
	– Fetus have conotruncal and ocular defects.[464]
	– Failure to close the neural tube.[464]
TLX KO	– Thickness of the retina is reduces.[465]
	– Increased number of apoptotic cells in the inner nuclear layer of the retina.[465]
	– Decreased proportion of mitotic cells.[465]
Rarb^{tm2Ipc}|Rarg^{tm3Ipc} |Tg (Wnt1-cre)11Rth	– Severe ocular abnormalities.[213]
Rxra^{tm4Ipc}|Tg (Tyrp1-cre)1Ipc	– Decreased number of photoreceptors.[466]
	– Abnormal photoreceptor outer segment morphology.[466]
	– Reduce light response.[466]
Nr1h2$^{tm1.1Gstr}$| Nr1h3$^{tm1.1Gstr}$	– Abnormal astrocyte morphology.[467]
	– Abnormal brain vasculature morphology.[467]

Thyroid Hormone Receptor Family and the CNS

The thyroid hormone receptor (THR) family plays a major role in the development of brain, regulation of metabolic rate, and the development of photoreceptor cells in the vertebrate retina. THRs are involved in a great number of biological activities that are both hormone dependent and independent. Some of the activities in which this receptor is involved include regulation of the *Rous sarcosoma* virus and the human immunodeficiency virus type 1,[27,70] initiation of the metamorphosis in amphibians by controlling the formation of tissues,[71] regulation of body temperature,[72] differentiation of muscle cells by regulating genes of the Ca^{2+} ATPase,[73] and migration of cells in the hippocampus, cerebellum, and cortex.[74] An important characteristic of this family is their ability to also regulate expression in the absence of a hormone.[70] However, when they bind to a hormone, it is either with triiodothyronine (T_3) or with thyroxin (T_4). The nonligand-dependent THR form can regulate transcription of a gene by recruiting corepressors or coactivators to either repress or activate expression by forming protein–protein interactions with members of the transcription initiation machinery, such as the transcription factor IIB.[71,72]

TRs are members of Class II, meaning that they predominantly bind to RXR. However, THRs do not bind exclusively to RXR, and they can also form heterodimers with VDR and PPAR.[73,74] The receptors of this family are coded by two genes, such as thyroid hormone receptor α (*THRα*) and thyroid hormone receptor β (*THRβ*); as a result of splicing differentiation, two isoforms are formed, THRα1 and THRα2, THRβ2 and as a result of different promoter usage, two more isoforms are formed, THRβ1 and THRβ2.[70] THRβ1 and THRβ2 have the exact same LBD, yet the amino-terminal domain is different, therefore making two proteins that have different biological function and are expressed in different tissues. The difference in the amino acid terminal influences the affinity in which the ligand interacts with the initiation complex or, in the case of THRβ2, it has another activation domain.[75] The level of expression of each receptor varies greatly in different tissues according to the respective stage of development. THRβ2 is predominantly found in the hypothalamus, anterior pituitary gland, and cochlea formation. TRα1 is involved in the development of the immune system

as well as signaling of thyroid hormone receptor during postnatal development.[76,77]

Thyroid hormone receptors regulate several developmental events in the CNS, including neuronal differentiation and migration, synaptogenesis, and myelination.[78–80] T3, T4, and TRs are present in the developing cortex, prior to the onset of fetal thyroid gland activity, before week 12 in humans. This suggests that maternal thyroid hormone (TH) concentration is important during brain development.[81,82] Thyroid hormone influence in the CNS is well documented through studies of TH in the cerebellum.[83] Two genes encode at least three high-affinity THRs in mammals, THRβ1 (*Thrb*), THRβ2 (*Thrb*), and THRα1 (*Thra*).[84] Different isoforms of TRs are expressed across the brain, cerebellum, and retina,[85,86] and they continue to be expressed in adult mice and human brains in other brain areas (Table 2). Studies in rats show that THRα1 binds to nearly 80% of T3 and is the main isoform expressed both prenatally and postnatally across the brain, including the developing cerebellum.[87,88] THRβ expression, is not as common, and is confined to a few postnatal neuronal populations in the CNS.[89] In rat cerebellum, both Thrα and Thrβ are expressed; *Thrα* is mostly expressed early in the cerebellar neuroephithelium and granular cell precursors and later in the transient external granular layer, whereas *Thrβ* is predominantly expressed during the later stages.[85,90] Knockout studies of *Thrb* and *Thra* mice (Table 3) depict milder neurological malformations compared to that of hypothyroid animals, demonstrating that T3 has a greater function in the developing CNS than the THR isoforms.[91–94] In contrast, Δ337T Thrb mice, harboring a deletion in LBD that prevents T3 to bind the receptor, presented cerebral deformities similar to the hyt/hyt mouse model affected with congenital hypothyroidism.[95] These mice displayed impairments in balance and coordination and in the Purkinje cell layers and decreases in the number and branching of Purkinje cells, which may account for the decreased cerebellar size observed in these mutant animals.[91,96–98] The role of *THRα1* in brain development has been described recently in humans, since descriptions of patients with mutations in *THRα* gene present cognitive impairment, similar to those observed in congenital hypothyroidism.[99,100] These data suggest that both THRα and THRβ function synergistically to mediate cerebellar development via THs.[101]

Several isoforms of the thyroid nuclear receptors are expressed in the eye. THR form complex with activators, such as SMART and histone deacetylases (HDACs) to regulate the transcription activity of the target genes.[102] The receptor THRα is found in the progenitor layer, while THRβ1 is found in the inner nuclear layer, and THRβ2 is expressed in the photoreceptor layer in particular in the developing cones.[85,102,103] TRs play an important role in the development of the retina by participating in the signaling system by which the progenitor cells are differentiated. It has been determined that the abundance of T3 in the environment can induce the proliferation of cone photoreceptor cells.[104] In general, thyroid hormone receptors act as coactivators in the presence of T3, and in the absence, they repress the expression of their target gene.[105] It has been demonstrated that in *Thrβ2* knockout animals, the S-opsin gene is expressed earlier leading to a failure of the correct expression of the M-opsin gene leading to a failure in the development of the M-cones.[106] The Thrβ2$^{-/-}$ mice have a cell fate switch of their cone photoreceptor cells such that all cones are blue or S cones.

PPARs Family and the CNS

The PPAR family was first discovered for its role in increasing the quantities of peroxisomes in different animal species and increasing the transcription of genes that encode for fatty acids.[107] Since this discovery, several additional roles have been discovered for these receptors, such as lipid metabolism, inflammation, glucose homeostasis, and cell differentiation. It has become clear that PPARs have an important role in body's response toward exogenous ligands.[108] Three different isoforms have been identified for PPAR: α, β/δ, and γ. Each isoform has a unique pattern of expression and has affinity to different ligands. PPARα is an important factor regulating lipid metabolism and is mostly found in the heart, kidney, intestine, and fat tissue.[12] In contrast, PPARβ/δ is found predominantly in different areas of adult brain (Table 2), kidney, and small intestine, is involved in cell survival, and is often present in the formation of tumors in the colon. For this reason, several studies have focused on understanding how PPAR might be an important therapeutic target. It was discovered that the nonsteroidal anti-inflammatory drugs compete with PPARβ/δ for its responsive elements inhibiting the action of PPARβ/δ and eventually reducing tumorigenesis.[109] PPARγ is mostly found in the spleen, intestine, and adipose tissue.[12] PPARs have the ability to bind to different types of fatty acids as well as synthesized compounds. Their ability to bind to different types of molecules is most likely due to the spacious ligand-binding pocket that is observed in the crystallographic structure.[110] While PPARs can be found in different tissues, they are predominantly expressed in tissues that regulate energy homeostasis. The fact that the majority of ligands are fatty acids and other metabolic molecules is evidence that PPARs have an important role in the regulation of metabolism. For example, the signal molecule eicosanoids is a product of fatty acid metabolism and is also known for being an inflammatory agent. This led to the discovery of a second function of PPARs, which is inflammatory signaling regulated in particular by PPARα and PPARγ.[111,112] Since Alzheimer's disease has an inflammatory component to its pathology as a consequence of the neurodegeneration and the extracellular deposition of β-amyloid peptides, recent studies have focused on the protective effects of nonsteroidal anti-inflammatory drugs in delaying or reducing the risk of Alzheimer's disease.[113] PPARs as many other receptors form heterodimers with RXR. Therefore, there is evidence of competition between PPARs and receptors, such as TRs and

vitamin D, which also partner with RXR. As an evidence of this competition, it was observed that the transcription of the genes that are regulated by PPARs was repressed in the presence of T3.[114] The fact that different receptors compete for their heterodimer partners is evidence of the complexity of gene regulation and the dual roles that the nuclear receptors play. The PPARs are an excellent example of previous orphans whose ligands were finally discovered; for all other receptors whose ligands still remain to be discern, they conform the ONR family.[115]

ONRs and the CNS

Orphan receptors are a unique class of NHRs in that they do not have a ligand identified and often lack all of the conserved domains typical of NHRs. Furthermore, a high degree of diversification has been observed in this group of NHRs, as many of them are not evolutionary or functionally related. This is evidenced in a phylogenetic analysis when aligning the DBD and LBD sequences. The resulting evolutionary tree has six major branches with the orphan receptors distributed across all branches.[116,117] The degree of diversification of orphan NHRs is further illustrated by studies revealing that some orphan receptors in invertebrate species such as *Drosophila* and nematodes lack DBD yet have LBD, and other receptors, such as Nr2e3, retain DBD.[118,119]

Another striking difference of orphan NHRs is the size of the A/B region that can range from a minimal eight amino acids in the retinoid orphan receptor (ROR) β to 280 amino acids in the NGFI-B receptor.[30] Some orphan receptors lack the activation function AF-1, while others lack an AF-2 domain. Many orphan receptors form heterodimers with RXR, while the remaining orphan receptors bind to DNA as homodimers.[3] The classification system divides the ONRs into seven different groups starting with group 0. Group I is comprised of seven different families, Group II is comprised of 5 families while group III, IV, V and VI contain one family.[2,12,120]

The NHR Nr2e3 was first identified as photoreceptor-specific nuclear receptor. Unlike most NHRs that exhibit ubiquitous expression, expression of NR2e3 is restricted solely to the outer nuclear layer of the neurosensory retina (cones and rods; Fig. 5).[121–123] During human eye development, Nr2e3 transcription is observed at week 11.7 in the putative immature human rods on the foveal edge.[124] Many studies performed using the Nr2e3$^{rd7/rd7}$ mouse, which lacks a functional Nr2e3 gene, indicate that Nr2e3 has a dual regulation role regulating rod and cone development and function.[60,121,125] Lack of Nr2e3 leads to abnormal proliferation of blue cones (the least populous of the photoreceptors) as a consequence of the loss of Nr2e3 in the mitotic progenitor cell program.[126] In rods, Nr2e3 does not affect rhodopsin expression per se, although it seems that rhodopsin expression needs both Nr1d1 and Nr2e3 potentiated by the orthodenticle-like cone–rod homeobox transcription factor (CRX)- and the neural retina basic motif-leucine zipper transcription factor (NRL)-driven activities.[127] NR2E3 works in conjunction with multiple transcription factors, including CRX, which is detected initially at day E12.5 in retinal progenitor cells and newly postmitotic cells,[128–130] and NRL, which is detected

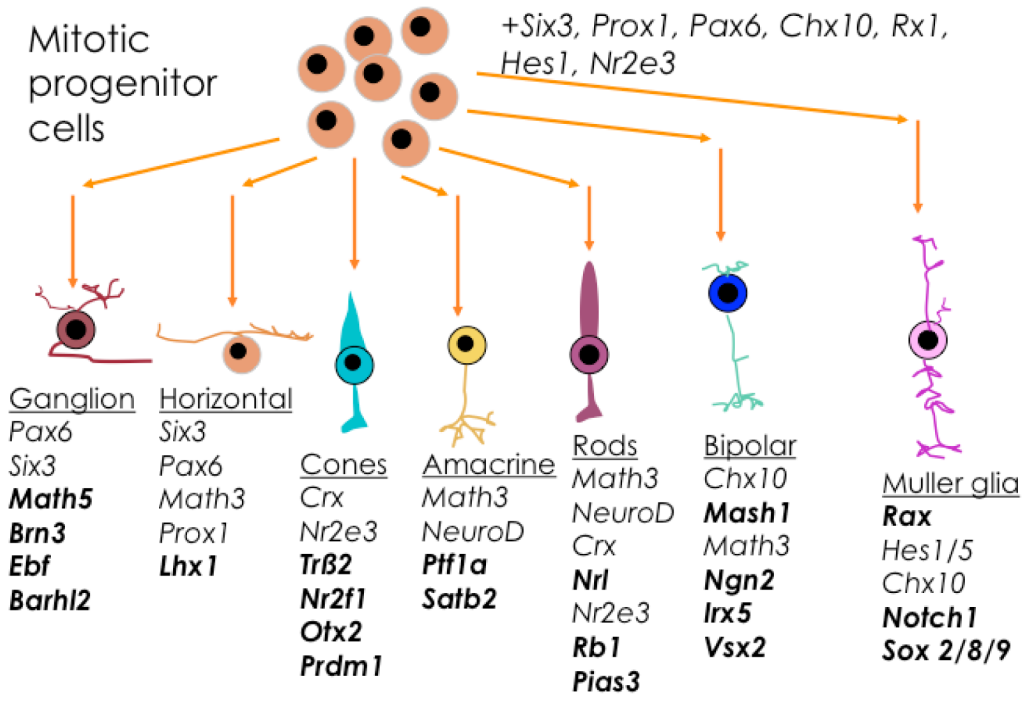

Figure 5. List of NHRs involved in the differentiation of the mitotic progenitor cells and the retinal cell types. Genes marked in bold correspond to NHRs unique for each cell type.

at day E14.5 and directs the generation of rod photoreceptor cells.[131,132] Although previous studies have identified several genes that are differentially expressed between normal and knockout mice, the transcriptional network regulated by Nr2e3 is not fully understood. Some potential genes that are regulated by Nr2e3 include the following cone-specific phototransduction genes: blue opsin (Opn-SW), Gnαt2 and Gnβ3 cone transducing subunits, the rod-specific gene guanine nucleotide-binding protein 1 (*Gnb1*), and the NHR Nr1d1.[121] It is interesting to highlight that, even though in the Nr2e3 regulation network the majority of genes were upregulated, a significant number were also downregulated supporting the hypothesize that Nr2e3 functions as both a suppressor and an enhancer of transcription.[133]

The RORs and the Rev-Erb are two of the receptor families that belong to Group I. The ROR family is made up of the following three members: RORα, RORβ, and RORγ. RORα is ubiquitously expressed and is involved in the development of Purkinje cells (Table 2), bone metabolism, immune response, development of cone photoreceptors of the retina, bone morphogenesis, angiogenesis, and lipid metabolism.[134] RORβ is mostly found in the retina,[135] brain (Table 2),[135–138] and spleen and functions in maintenance of the circadian rhythm.[139–141] RORγ is found in the liver, kidney, thymus, and lungs, and its functions consist of lymph node organogenesis and thymopoiesis.[1,141–145] Each member of the family also has different isoforms that are formed by alternative splicing and alternative promoters.[146] The isoforms differ in the A/B domain: four ROR isoforms have been identified in humans and two have been identified in mice. RORα1 and 4 are localized in the cerebellum.[146] RORβ has two known isoforms; RORβ2 is restricted to the pineal gland and the retina (Fig. 5).[135]

Both RORα and RORβ have an important role in the CNS, as observed by knockout mouse models that have severe cerebral abnormalities.[147,148] Cerebellum development is regulated by RORs and takes a large period during fetal development. The main types of cells in the cerebellum develop at different stages and positions. The Purkinje cells arise from the ventricular zone of the metencephalic alar plates at the fifth or sixth week of development.[149] Granule cells are added from the rhombic lip at the end of the embryonic period, and their migration is facilitated by Bergmann glia cells to their deeper definitive site.[150] During this process, RORα expression is restricted to Purkinje cells and not to the granule cell layer, as observed in mice at age E12.5.[109–116]

The staggerer mouse, which lacks functional RORα (RORα$^{sg/sg}$ or RORα$^{-/-}$), presents with fewer Purkinje cells and a loss of cerebellar granule cells.[147,151–157] RORα heterozygous mice (RORα$^{+/sg}$) with only one functional allele exhibit a milder phenotype and present with an accelerated Purkinje and granule cells loss in aged animals.[154,158–160] RORα regulates genes related to Purkinje cells maturity, in particular its dendritic differentiation. RORα$^{-/-}$-deficient mice show downregulation of several genes involved in signal-dependent calcium release, including the calmodulin inhibitors *Pcp4* and *Pcp2*, the IP3 receptor (ITPr1) and its coreceptor *Cals1*, the calcium-transporting ATPase (Atp2a2) and major intracellular calcium buffer 1 (Calb1), Shh, and solute carrier family 1 (high-affinity aspartate/glutamate transporter), member 6 (Slc1a6).[151,161,162] Moreover, most of the downregulated genes in RORα$^{sg/sg}$ or RORα$^{-/-}$ mice have retinoic orphan receptor elements, a type of HRE recognized by the ROR family of NHRs. The retinoic orphan receptor element pattern sequence consists of the sequence RGGTCA core motif followed by a 6 bp A/T-rich sequence in the regulatory region of RORs' target genes, which explains their downregulation by RORα absence.[135,163,164] As observed by the use of the RORα$^{sg/sg}$, it is clear that animal models are essential for understanding the functions of NHRs and the genes that they regulate.

RORβ plays an important role in retina cell differentiation as studies in murine models have described. Differentiation of cone photoreceptor cells in mice is regulated by the nuclear receptors Rorβ and Rxrγ (Fig. 5), which control the generation of short(S)-opsin-expressing cones (also referred to as blue cones).[165,166] RORβ also stimulates rod photoreceptor differentiation by activating the rod-selective transcription factor neural retina leucine zipper (*Nrl*).[167] The function and survival of rod photoreceptor are also regulated by the estrogen-related receptor β (*Errβ*).[168] Rorβ is expressed in the formative ganglion cell layer, and Rorβ$^{-/-}$ has disorganized cone cell topography and lacks the inner and outer segments, suggesting that RORB exerts an important role in the proper development of cone photoreceptor cells.[165]

NHRs regulate gene expression in a common pool of multipotent retinal progenitor cells found in the neuroephithelium of the optic cup to form all retinal cell types (Fig. 5).[169] Retinal proliferation is a highly conserved dynamic process in vertebrates that occurs in the following two overlapping phases: (1) the first phase begins with the proliferation of ganglion cells followed by horizontal cells, cone photoreceptors, and amacrine cells and (2) the second phase overlaps with the generation of rod photoreceptors, bipolar cells, and Müller glial cells. The differentiation of retinal cells also has overlapping phases.[170] The formation and maintenance of the different types of cells in the retina requires specific gene regulation. The transcription and regulation of NHRs, including Nr2e3, RARβ, RORβ, Nr1d1, RXRγ, and Trβ (Fig. 5), in synergy with several transcription factors, including CRX, NRL, and Chx10, help determine retinal cell fate and pluripotent capacity of retinal progenitors.[171,172]

The Rev-Erb members are characterized for having unique features, such as their transcription from the opposite strand of the T3 receptor gene.[173] They also lack the AF-2 domain and mostly function as repressors of gene expression by associating with the corepressors NCoR.[24,174–176] Rev-Erb has been associated with several functions, such as being a mediator of adiponogenesis,[177] the regulator of myogenesis,[178]

involvement with cell proliferation,[34] the regulator of the circadian clock,[179] and effects on lipid metabolism.[180]

The testicular nuclear receptors (TRs) and tailless (TLX) receptor are two of the five members of Group II of the orphan receptors. There are two members of the testicular nuclear receptors (TR2 and TR4). TR2 is highly expressed in the testes as well as in several other tissues, including brain, retina, kidney, and intestine, with the highest peak of expression during embryonic time points.[181] TR2 can bind as a homodimer or as a heterodimer, and it has the ability to act as a repressor of gene expression.[182] TR4 is expressed in several tissues from the CNS, adrenal gland, spleen, and prostate gland with the highest expression observed in the skeleton and testes, as indicated by the name of the family.[181] TR4 is expressed in a temporal and spatial manner during brain development,[183] and TR4 knockout mice show growth defects, and females exhibited poor maternal behavior skills.[184]

These behavioral traits in TR4 knockout rodent animals seem to be the consequence of a poor cerebellum development. During this process, TR4 expression patterns correlate directly with cerebellum neurogenesis, suggesting a role in this stage.[183,185] During postnatal cerebellum development, several changes occur in the cerebellum laminar construction with engrossing of the external granule layer followed by granule cells migration toward the internal granule layer. Precursors of these cells migrate as well to the internal granule layer guided by Bergmann fibers, which expresses the astrocyte-specific glutamate transporter, GLAST.[150,186,187] This migration process is affected fundamentally by the order of the Bergmann fibers. If these fibers are disorganized or atrophied, migration will not occur. Additionally, migration impairment can also be the consequence of defects in granule cells.[188,189] Mouse models lacking TR4 exhibit abnormal cerebellar development in lobules VI–VII, which correlate with poor granule cell migration and Bergmann glia maturation.[190–195] These alterations are related to a lack of GLAST, causing a long-lasting negative impact on neural connectivity pathways during brain development.[196] As a consequence of TR4 knockout, aberrant neuronal connectivity has been observed due to the delay in granule cell migration and the disarrangement of the cerebellar Purkinje neurons. The result is an abnormal response to environmental changes and also problems with social contact, startle activity, and deficits in prepulse startle inhibition and cerebellar motor learning when no motor coordination seems to be present.[196]

The TLX receptor is the human homolog of the tailless gene in *Drosophila* that is uniquely expressed in the neuroephithelium of *Drosophila* embryonic brain. A unique characteristic of TLX is a highly conserved substitution of a lysine residue in the P-box of DBD.[197,198] TLX is highly conserved in vertebrates and plays a major role in the development of the forebrain and brain function, retinal development, and aggressive behavior[3,199,200] and is expressed in human and mice adult brain areas (Table 2). TLX is a key component necessary to create the superficial cortical layers of the brain in embryos, and it also regulates the timing of neurogenesis in the cortex. TLX knockout mice have reduced cerebral hemispheres and reduced ability to learn. An important function of TLX is the maintenance and self-renewal of neural stem cells in the brain.[201,202] The development of the retina is also influenced by TLX receptors that are expressed in the neuroblastic layer (Fig. 5). Mice that lack the expression of TLX do not respond to light stimuli, suggesting a key role for TLX in the formation of several retinal cell types, such as photoreceptors and bipolar and amacrine cells.[203]

Group IV is composed of one receptor member with three different subtypes, α, β, and γ. This family, also known as Nr4a, is expressed in adult mice and human brain (Table 2). Nr4a receptors play an important role in the retina and cerebellum development and *N*-methyl-D-aspartate (NMDA) receptor-mediated neuroprotection. Barneda-Zahonero et al observed that Nur77 protects hippocampal neurons in culture from staurosporine and growth factor removal-induced toxicity in vitro, and it also protects hippocampal neurons from kainate-induced toxicity in vivo.[204,205] The role of Nr4a subfamily in the survival of cerebral granule cells (CGCs) was studied in cell culture assays and revealed that Nurr1 is involved in the development and differentiation of the midbrain dopaminergic neurons and regulates several of the tyrosine hydroxylase and dopamine transporter gene networks.[66–68] Nurr1 has been shown to regulate genes, such as the vasoactive intestinal peptide (VIP),[206] α-synuclein,[207] and brain-derived neurotrophic factor (BDNF).[208] It was also observed that after silencing Nurr1 expression by shRNA, BDNF transcription levels decreased in CGC cultures treated with the glutamatergic agonist, and NMDA activation promoted Nurr1 binding to promoter IV of BDNF in a specific manner. These studies demonstrated that Nurr1 is involved in the prosurvival of CGC neurons via NMDA receptor activation by enhancing BDNF transcription. Furthermore, CREB shRNA studies revealed a reduction in Nurr1 expression and protein concentration due to a blockage on the NMDA receptor-CREB cascade, leading to lower BDNF transcription levels.[204] These studies provide valuable insight into the biological processes and genes regulated by the NH receptors.

NHRs Associated with Diseases in the Eye and Brain

Animal models provide valuable insight into the biological pathways and roles of the receptors in normal conditions (Table 3). Nuclear receptors have been associated with a wide range of diseases, such as diabetes, obesity, metabolic syndromes, autism, Parkinson's disease, ocular disease, and cancer. In this review, we focus on diseases caused by disrupting the NHR function in the CNS, particularly eye or brain development (Table 4). RARs play an important role in the development of the CNS, and mutations in the RAR networks are associated with complex human diseases. RA is derived from vitamin A (retinoid), which is supplied by mothers to embryos transplacentally.[209] Two classes of

Table 4. Nuclear hormone receptor and associated diseases in humans.

GENE	HUMAN DISEASE	OMIM ID
Nr1b2 (RAR-β)	Syndromic microphthalmia[468]	615524
	Schizophrenia[469]	181500
Nr1c1 (PPAR-α)	Alzheimer's disease[470]	104300
Nr2c2 (Tr4)	Deficit in motor coordination[471]	
Nr2e3 (Pnr)	Enhanced S cone syndrome[472]	268100
	Retinitis pigmentosa[232]	611131
Nr2f1 (Coup-TFI)	Bosch-Boonstra optic atrophy syndrome[473]	615722
Nr3a1 (ER α)	Migraine[474,475]	157300
Nr3a2 (ER-β)	Alzheimer's disease[476]	104300
Nr3c1 (GR)	Depression[477]	608520
Nr3c2	Stress[478]	
Nr3c3 (PR)	Vertigo[479]	193007
Nr4a2	Parkinson disease[480]	300557

enzymes, the cytosolic alcohol dehydrogenases and the microsomal short-chain dehydrogenases/reductases, oxidize retinol into retinaldehyde.[210] Retinaldehyde is then oxidized to RA by the ALDHs (ALDH1A1, ALDH1A2, and ALDH1A3). ALDHs have distinct and specific expression patterns that correlate with RA activity as detected by reporter transgenes.[43] In the CNS, ALDH1A3 is primarily expressed in the lateral ganglionic eminence, while ALDH1A1 is expressed in the dopamine-containing mesostriatal system and meninges, consistent with the presence of ALDH1A3 and ALDH1A1 in the lateral ganglionic eminence and its derivative striatum, where high levels of RA and other retinoid are detected in the developing striatum, eye, and olfactory system.[40–42] ALDH1A3$^{-/-}$ mice present an aberrant development in nasal and ocular systems and die at birth due to respiratory distress.[211] CNS human diseases have been linked to mutations in ALDH1A3, which have been directly associated with microphthalmia and anophthalmia. A recent report has also linked variants in ALDH1A3 with risk for autism.[212] ALDH1A1$^{-/-}$ mice, in contrast, are viable but present minor defects in the dorsal retina.[213,214] As RA regulates genes via RARs, depletion of this metabolite causes a poor gene regulation of RARs, which is the main cause of the diseases exposed, though there are other diseases caused directly by alterations in RARs family.

In the brain, RARs are expressed with different location patterns: RARα is found ubiquitously, and RARβ and RARγ are found in the striated regions that have dopaminergic neurons.[215] Dopamine receptor 2 knockout mouse phenotype resembles the human Parkinson's disease.[216] Parkinson's disease is characterized by the degeneration of the dopaminergic pathway. Both *trans-RA* and *9-cis-RA* induce the expression of dopamine receptor 2. RAR forms a heterodimer with RXR to bind directly to the dopamine receptor gene linking this gene and the nuclear receptors to Parkinson's disease.[217] RXRs also form a heterodimer with the orphan receptor Nurr1 that is expressed in the mesenphalic flexure of the brain, the region that develops the dopamine-producing neurons.[218,219]

The most common disease associated with RARα mutations is acute promyelocytic leukemia (MIM: 612376), caused by gene rearrangements. Often, a gene fusion of promyelocytic leukemia (PML) and RARα occurs due to the translocation t(15,17)(q21;q22).[220] However, though most of the rearrangements involving RARα are associated with different types of leukemia, one individual diagnosed with Smith–Magenis syndrome presented a region translocation of chromosome 17 q11.2–q21.3 that was inserted into the short arm of the same chromosome at region p11.2.[221] Patients with Smith–Magenis syndrome have multiple congenital anomalies, including mental retardation, which are associated with a deletion involving band p11.2 of chromosome 17.[222] Though the report given by Park et al[221] did not expose RARα translocation as causative of Smith–Magenis syndrome, it shows how chromosome 17 q11.2–q21.3 region is a breakage and rearrangement hotspot, same as chromosome 17 p11.2 region, which may cause different related syndromes[221] not directly associated with the CNS.

Unlike RARα, RARβ is important for the proper development of the brain cortex, and variants in this gene have been associated with locomotor disease and ocular disorders. RXRB and RARβ expression have been observed in the striatum.[223] Several polymorphisms in RARβ are associated with microphthalmia in humans (MIM: 615524). Double knockout mutants for RARβ and RXRγ have a 30%–40% reduction in D1 and D2 dopamine receptor expression, though they are the most abundant type of receptors in the striatum,[223] and exhibit reduction in forward locomotion. In the case of D2, its lower expression is possibly explained by the presence of RAREs in its promoter region.[224] This fact permits hypothesize that RARβ and RXRγ are essential in developing the proper locomotion, and it is involved in controlling the dopaminergic system during development and adult stages in CNS.

RORα gene networks appear to play an important role in the neurodegenerative disease spinocerebellar ataxia-1. A microarray analysis from mutant and normal mouse brain showed that genes regulated by RORα were downregulated in the first stages of development of the Purkinje cells. Loss of RORα leads to an increase expression of the ataxia gene ATXN1. A further analysis by coimmunoprecipitation revealed that ATXN1, RORα, and the RORα coactivator Tip60 form a complex to modulate cerebellar development. The RORα1 knockout model lacks the LDB region and is characterized as having abnormal Purkinje cells and abnormal morphology and ataxic.[225,226] The staggerer mouse, which has a deletion in the RORα gene that blocks the translation of LBD, models cerebellar ataxia affecting the development of the Purkinje cells. RORα$^{-/-}$ also shows atrophy and loss of the dendritic cells and synaptic rearrangement of the Purkinje cells.[227] The phenotype of the staggerer mouse

suggests that RORα is involved in the thyroid hormone signaling pathway in charge of the maturation of the Purkinje cells.[227] Different studies have demonstrated that Rorα is also involved in the protection of neurons, suppresses inflammation, and is important in regulating circadian rhythm.[228]

NR2E3 has been associated with several retinal diseases, including enhanced S-cone syndrome (ESCS),[229] Goldmann-Favre syndrome (GFS), and retinitis pigmentosa.[230–232] ESCS and GFS are autosomal recessive diseases characterized by an increase in the sensitivity of the S (blue wavelength)-cone photoreceptor cells accompanied with a decreased in the rods and L/M (red/green) cones.[11,233,234] GFS is a milder form of ESCS. Patients with autosomal dominant retinitis pigmentosa suffer from early onset loss of night vision followed by retinal spots in the peripheral field, and eventually loss of central vision. By analyzing the phenotypes of patients with different diseases caused by mutations in the Nr2e3, it is possible to conclude that the location of the mutation has a major impact on disease outcome. The diseases are viewed as a collection of Nr2e3-associated retinal diseases.[235] NHRs are involved in a myriad of functions that cover more than just the CNS normal functioning. Yet, it is still important to understand how NHRs participate in diseases, as NHRs play a key role in normal CNS development.

Perspectives and Conclusions

This review discusses the important role of NHRs in the development, function, and maintenance of the CNS. There is great variation in the types of isoforms, as well as the abundance and time of expression of NHRs throughout the CNS. Furthermore, it is not uncommon to see members of a particular family with multiple functions as illustrated by the ROR and TR families of NHRs. All members of the THR family, for example, are involved in the development and/or function of the CNS. In contrast, RARβ simply has one member involved in a specific tissue of the CNS, and even more restrictive is the orphan receptor NR2E3 that functions in only one type of retinal cell, the photoreceptor cell. Thus, while most NHRs are ubiquitously expressed, others have family members or isoforms with expression patterns limited to particular in organs or cell types. There is a clear overlap in NHRs signaling of the developing eye and brain, suggesting a common template for CNS development. The majority of NHRs have a dual role as both transcription activators and suppressors. Their function depends on their temporal and spatial expression, cellular context, as well as the interaction with other factors, ligands, and DNA sequences of HREs. Furthermore, NHRs can modulate gene expression, via HRE recognition, by several mechanisms, including ligand binding and cofactor recruitment. A comprehensive reconstruction of the complex, multimodal interacting gene networks and identifying the target genes they regulate will provide greater insight into overall neuronal signaling of the CNS.

It is well established that NHRs regulate numerous biological pathways and processes. NHRs interact with several factors, such as transcription factors, chromatin-modifying complexes, and hormones. NHRs often serve as master regulators simultaneously modulating several signaling pathways in a temporal/spatial/cell type-specific manner. The highly conserved nature of NHRs and their numerous isoforms throughout the CNS suggests functional redundancy and a possible mechanism to avoid disease. This is evidenced in data demonstrating that NHRs can serve as genetic modifiers that alter disease onset, progression, or severity.[236] This new role for NHRs as genetic modifiers of disease is important in understanding normal CNS development and has great therapeutic implications. NHRs that function as master regulators of key biological pathways may have a profound impact on disease treatment as they have the potential to impact multiple mutations and multiple pathways.

Author Contributions

Conceived and designed the experiments: AMO, OAM-R, and NBH. Analyzed the data: AMO, OAM-R. Contributed to the writing of the article: AMO, OAM-R, and NBH. Agreed the manuscript results and conclusions: AMO, OAM-R, and NBH. Jointly developed the structure and arguments for the article: AMO and OAM-R. Made critical revisions and approved the final version: NBH. All authors reviewed and approved the final article.

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