Ludwig Institute for Cancer Research & Department of Cell & Molecular Biology

NR4A ORPHAN NUCLEAR RECEPTORS IN IMMEDIATE EARLY REGULATION OF RETINOID SIGNALING AND NEUROPROTECTION

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ABSTRACT

NR4A receptors show distinct properties that make them unique within the family of nuclear receptors. They lack a ligand-binding cavity and a canonical coactivator-binding site and they are induced both *in vivo* and *in vitro* in an immediate early way by an extremely wide repertoire of substances/conditions. Apart from their specific roles during development, they play crucial, yet not fully charazterized, roles in sensing of and responding to changes in the cellular environment.

In paper I, we provide novel insights into the mechanism of NR4A-mediated transcription by identifying an alternative coactivator-binding surface that is unique to the NR4A family of nuclear receptors. We also report a link between NR4A transcriptional activity and protein turnover and identify protein sequence differences between the NR4A receptor members that may account for their differential transcriptional activity.

In paper II, we provide evidence suggesting that NR4A receptors can influence signaling events of other nuclear receptors via inducing the expression of fatty acid binding protein 5. Specifically, NR4A receptors can enhance retinoic acid-induced signaling of the peroxisome proliferator-activated receptor and docosahexaenoic acid-induced activation of the retinoid X receptor.

In paper III, we demonstrate that NR4A proteins are induced by cyclic AMP response element binding protein (CREB) in neurons exposed to excitotoxic and oxidative insults and that they function as mediators of CREB-induced neuronal survival by inducing the expression of a battery of neuroprotective genes. Moreover, we show that mice with null mutations in three out of six NR4A alleles show increased oxidative damage, blunted induction of neuroprotective genes and increased vulnerability in the hippocampus after treatment with the excitotoxin kainic acid.

In summary, we show that NR4A receptors utilize a distinct surface to bind coactivators, that they can influence signaling by two other nuclear receptors by upregulating a fatty acid binding protein and that they are essential mediators of neuroprotection after exposure to neuropathological stress.

LIST OF PUBLICATIONS

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

I. **Nikolaos Volakakis**, Michal Malewicz, Banafsheh Kadkhodaei, Thomas Perlmann (2006). Characterization of the Nurr1 ligand-binding domain co-activator interaction surface. *Journal of Molecular Endocrinology*. Vol 37: 317-326.

II. **Nikolaos Volakakis**, Eliza Joodmardi, Thomas Perlmann (2009). NR4A orphan nuclear receptors influence retinoic acid and docosahexaenoic signaling via up-regulation of fatty acid binding protein 5. *Biochemical and Biophysical Research Communications*. Vol 390 (4): 1186-91.

III. **Nikolaos Volakakis**, Banafsheh Kadkhodaei, Eliza Joodmardi, Karin Wallis, Lia Panman, Jessica Silvaggi, Bruce M. Spiegelman, Thomas Perlmann (2010). NR4A orphan nuclear receptors trigger a neurorotective pathway induced by elevatated cyclic AMP. *Manuscript submitted for publication*.

Other papers not included in this thesis:

Stina Friling, Elisabet Andersson, Lachlan Thompson, Marie Jönsson, Josephine Hebsgaard, Evanthia Nanou, Zhanna Alekseenko, Ulrika Marklund, Susanna Kjellander, **Nikolaos Volakakis**, Outi Hovatta, Abdeljabbar El Manira, Anders Björklund, Thomas Perlmann, Johan Ericson (2009). Efficient production of mesencephalic dopamine neurons by Lmx1a expression in embryonic stem cells. *Proceedings of the National Academy of Sciences of the Unites States of America.* Vol 106 (18): 7613-18.

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LIST OF ABBREVIATIONS

0-9

3-NP: 3-nitropropionic acid
4E-bp2: eukaryotic translation initiation factor 4E binding protein 2
6-MP: 6-mercaptopurine
6-OHDA: 6-hydroxy-dopamine

A

A: adenine
AA: amino acid
AADC: aromatic L-amino acid decarboxylase
AAV: adeno-associated virus
Abl2: Abelson murine leukemia viral oncogene homolog 2
ACTH: adrenocorticotropic hormone
AcvrIIb: activin A receptor, type IIB
Adcyap1: adenylate cyclase activating peptide 1
Adm: adrenomedullin
AF: activation function
Ala: alanine
AMPK: adenosine monophosphate kinase
AR: androgen receptor
Arg: arginine
ASC-2: anterior suture cataract-2
Asn: asparagine

B

Bcl2: B cell lymphoma 2
BDNF: brain-derived neurotrophic factor
bp: base pairs
Brn3: brain 3

C

C: cytosine
C/EBP: CCAAT/enhancer binding protein
CBP: CREB-binding protein
c-FLAR: CASP8 and FADD-like apoptosis regulator
CAMK: calcium/calmodulin-dependent protein kinase
cAMP: cyclic adenosine monophosphate
CCCP: carbonyl cyanide m-chlorphenyl hydrazone
CDK: cyclin-dependent kinase
CNS: central nervous system
CNTF: ciliary neurotrophic factor
COMT: catechol-O-methyltransferase
COUP-TF: chicken ovalbumin upstream promoter-transcription factor
COX-2: cyclooxygenase-2
CRABP: cellular retinoic acid binding protein
CRE: cAMP response element
CREB: CRE binding protein
CREM: CRE modulator
CRH: corticotropin-releasing hormone
CRIF1: CR6-interacting factor 1
CtBP: C-terminal binding protein
CTCL: cutaneous T cell lymphoma

D

DAP3: death-associated protein 3
DAT: dopamine transporter
DBD: DNA binding domain
DCC: deleted in colorectal carcinoma
Ddx6: DEAD box polypeptide 6
DG: dentate gyrus
DHA: docosahexaenoic acid
DHR38: *Drosophila* hormone receptor 38
DISC: death-inducing signaling complex
Dlk1: delta-like 1 homologue
DMN: dorsal motor nucleus
DN: dominant negative
DNA-PK: DNA-dependent protein kinase
DOPAC: dihydroxy phenylacetic acid
DR: direct repeat
ds: double-stranded
Dyrk1A: dual specificity tyrosine phosphorylation-regulated kinase 1A

E

EBV: Epstein-Barr virus
EcR: ecdysteroid receptor
EcRE: ecdysone response element
EGF: epidermal growth factor
EMC: extraskeletal myxoid chondrosarcoma

En: engrailed
ER: estrogen receptor
ERK: extracellular signal-regulated kinase
ERR: estrogen-related receptor
ES: embryonic stem
EWS: Ewing sarcoma
Ex: embryonic day x

F

FA: fatty acid
FABP: fatty acid binding protein
FAIM: Fas apoptotic inhibitory molecule
Fas: fatty acid synthase
FasL: Fas ligand
FGF: fibroblast growth factor
FLIP: Fas-associated death domain-like interleukin-1-beta-converting enzyme inhibitory protein
Fox: forkhead box protein
Fra-2: fos-related antigen-2
FSH: follicle stimulating hormone

G

G: guanidine
GABA: gamma-amino byturic acid
GFP: green fluorescent protein
GIOT-1: gonadotropin inducible transcription repressor -1
Gja1: gap-junction protein α1
Glu: glutamic acid
GLUT4: glucose transporter 4
GnRH: gonadotropin-releasing hormone
Gpam: glycerol-3 phosphate acyltransferase
GR: glucocorticoid receptor
GSK: glycogen synthase kinase
GST: glutathione S-transferase
GTP: guanidine triphosphate
GTPCH: GTP cyclohydrolase

H

HAT: histone acetyltransferase
HBV: hepatitis B virus
HD: Huntington's disease
HDAC: histone deacetylase
HEK293: human embryonic kidney 293
HIF-1: hypoxia inducible factor-1
HIV-1: human immunodeficiency virus-1
HNF4: hepatocyte nuclear factor 4
HPA: hypothalamus-pituitary-adrenal
HPG: hypothalamus-pituitary-gonadal
HPV: human papilloma virus
HRE: hypoxia response element
HSDx hydroxysteroid dehydrogenase x
Hsp: heat shock protein
HSV: herpes simplex virus
Hx: helix x

I

IAP1: inhibitor of apoptosis protein 1
ICAM: intercellular adhesion molecule
Igf2bp1: insulin-like growth factor 2 mRNA binding protein 1
IFN: interferone
ig: intragastric
IL: interleukin
INSL3: insulin-like 3
ip: intraperitoneal
iv: intravenous

J

JNK: c-Jun N-terminal kinase

K

KA: kainic acid
kb: kilobases
kDa: kilo Dalton
Klhl1: kelch-like protein 1

L

LBD: ligand-binding domain
LBP: ligand-binding pocket
LDL: low-density lipoprotein
Lef-1: lymphoid enhanced binding factor 1
Leu: leucine
LH: luteinizing hormone
LIF: leukemia inhibitory factor
LIMK1: LIM domain kinase 1
LRH1: human liver receptor homolog 1
LSD1: lysine-specific demethylase
LTR: long terminal repeat
LXR: liver X receptor
Lys: lysine

M

mAChRs: muscarinic acetylcholine receptors
MAPK: mitogen-activated protein kinase
MC1R: melanocortin-1 receptor
MCAO: middle cerebral artery occlusion
MCP-1: monocyte chemoattractive protein-1
MEF: myocyte enhancer factor
MEFs: mouse embryonic fibroblasts
MEHP: mono-(2-ethylhexyl) phthalate
MEKK1: mitogen-activated protein kinase kinase kinase 1
MIP-1: macrophage inflammatory protein-1
MMP: matrix metalloproteinase
MMTV: mouse mammary tumor virus
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSH: melanocyte-stimulating hormone
MZF1: myeloid zinc finger 1

N

NAD: Nicotinamide adenine dinucleotide
NBRE: NGFI-B response element
NCAM: neural cell adhesion molecule
NcoR: nuclear receptor corepressor
NFAT: nuclear factor of activated T cells
NFκB: nuclear factor κB
NGF: nerve growth factor
NLK: NEMO-like kinase
NMDA: N-methyl-D-aspartic acid
NMR: nuclear magnetic resonance
NOS: nitric oxide synthase
NR: nuclear receptor
NRF: nuclear respiratory factor
Nrp1: neuropilin1
nt: nucleotide
NuIP: Nurr1-interacting protein

O

O-GlcNAc: O-linked β-N-acetylglucosamine
OGT: O-GlcNAc transferase

P

PACAP: pituitary adenylate cyclase activating polypeptide
Pai-1: plasminogen activator inhibitor-1
PARP-1: poly(ADP-ribose) polymerase I
PC12: pheochromocytoma 12
PCAF: p300/CBP-associated factor
PCP: phencyclidine
PCR: polymerase chain reaction
PD: Parkinson's disease
PDBu: phorbol 12,13 dibutyrate
PDGF: platelet-derived growth factor
PDK-1: phosphoinositide-dependent kinase-1
PELP1: proline-, glutamic acid-, leucine-rich protein 1
PGC-1: PPAR gamma coactivator-1
PGx: prostaglandin x
PHD: prolyl hydroxylase domain
Phe: phenylalanine
PI3K: phosphatidylinositol-3 kinase
PIAS: protein inhibitor of activated STAT
PKx: protein kinase x
PMA: phorbol 12-myristate 13-acetate
PML promyelocytic leukemia protein
PNS: peripheral nervous system
POMC: pro-opiomelanocortin
pp90rsk: 90 kDa ribosomal protein S6 kinase
PPBP: 4-phenyl-1-(4-phenylbutyl) piperidine
PPAR: peroxisome proliferative activated receptor
PR: progesterone receptor
PRMT1: protein arginine methyltransferase 1
PSF: PTB-associated splicing factor
PTEN: phosphatase and tensin homolog
PTH: parathyroid hormone
Ptpru: protein Tyr phosphatase, receptor type, U
pVHL: von Hippel-Lindau protein
PVN: periventricular nucleus
Px: postnatal day x

R

RA: retinoic acid
RAR: retinoic acid receptor
REST: RE1-silencing transcription factor
RNS: reactive nitrogen species
ROR: RAR-related orphan receptor
ROS: reactive oxygen species
RSK: ribosomal protein S6 kinase
RT: reverse transcription
RXR: retinoid X receptor

S

Scd1: stearoyl-coA desaturase-1
SCF: Skp1/collin/F-box
SCN: suprachiasmatic nucleus

SDS-PAGE: sodium dodecyl sulphate polyacrylamide gel electrophoresis
SF-1: steroidogenic factor-1
SHH: sonic hedgehog
shRNA: short hairpin RNA
siRNA: short interfering RNA
SMCs: smooth muscle cells
SMRT: silencing mediator for retinoid and thyroid hormone receptors
SN: substantia nigra
SOCS: suppressor of cytokine signalling
Sod1: Superoxide dismutase 1
SRC: steroid receptor coactivator
SREBP1c : sterol regulatory element-binding protein 1c
StAR: steroidogenic acute regulatory protein
STAT: signal transducer and activator of transcription
SUMO: small ubiquitin-like modifier

T

T: thymidine
TAF: TBP-associated factor
TBP: TATA-binding protein
TCR: T cell receptor
TH: tyrosine hydroxylase
TIF1: translation initiation factor 1
TLE-1: transducin-like enhancer of split-1
Tll1: tolloid-like 1
TLR: toll-like receptor
TNF: tumor necrosis factor
TPA: 12-O-tetradecanoylphorbol-13-acetate
TR: thyroid hormone receptor
TRAP220: thyroid hormone receptor-associated protein complex 220 kDa
Tyr: tyrosine

U

Ucp: uncoupling protein
USP: ultraspiracle
UV: ultraviolet

V

VCAM: vascular cell adhesion molecule
VDR: vitamin D receptor
VEGF: vascular endothelial growth factor
VIP: vasoactive intestinal peptide
Vmat2: vesicular monoamine transporter 2
VSMCs: vascular smooth muscle cells
VTA: ventral tegmental area

W

wt: wild-type

Z

Zbp1: zipcode-binding protein 1

A. INTRODUCTION

1 Nuclear Receptors

1.1 The Nuclear Receptor Superfamily

Intercellular communication is of crucial importance for the development and the maintenance of the functions of multicellular organisms. Steroid hormones and lipophilic signaling molecules such as metabolic intermediates and certain vitamins can either enter or be generated within a target cell and bind to cognate members of a family of transcription factors called nuclear receptors (NRs), which in their turn can regulate gene expression programs (**Figure 1**) that control processes such as differentiation, reproduction, metabolism and homeostasis (Mangelsdorf et al., 1995).

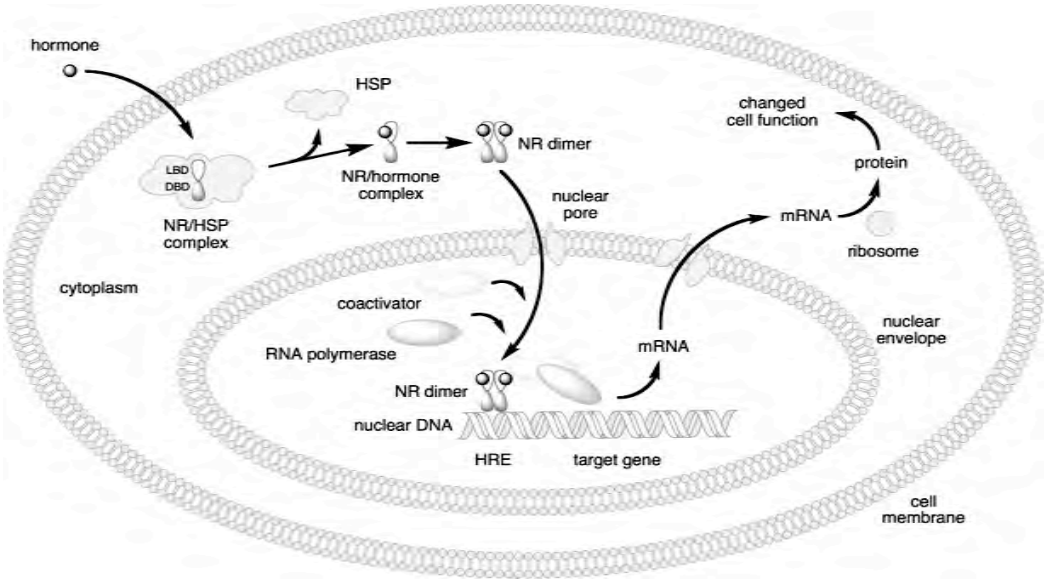

Figure 1 Hormone binding to the steroid NR triggers dissociation of HSPs, dimerization, and translocation to the nucleus where the NR binds to DNA and activates gene transcription (Wikipedia, public domain). Non-steroid NRs are always nuclear.

NRs are specific to metazoans (Escriva et al., 1998). Rats, humans and mice have respectively 47, 48 and 49 NRs each (Zhang et al., 2004). The 48 known human NRs are categorized according to sequence homology to subfamilies that comprise both NRs with known ligands and 'orphan' NRs without or with an unknown ligand (Committee, 1999). Phylogenetic, functional and structural studies support the hypothesis that NRs have evolved from an ancestral orphan receptor through early diversification and only later acquired ligand binding (Escriva et al., 2000)

1.2 Nuclear Receptor Structure

NRs are composed of distinct functional and structural domains (**Figure 2**) that have modular character (Kumar and Thompson, 1999).

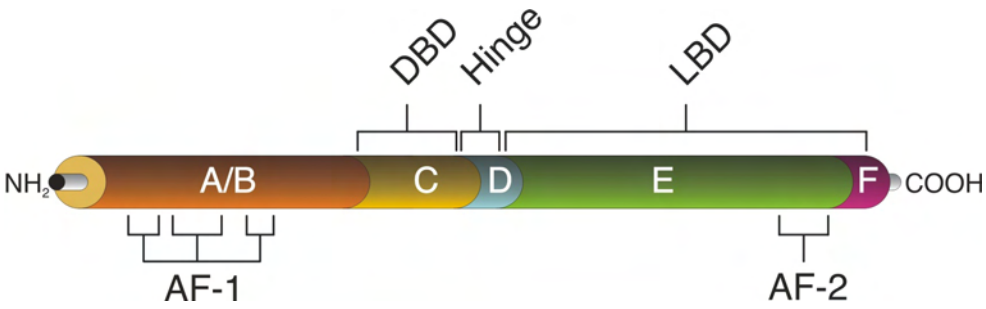

Figure 2 Structural organization of NRs (courtesy of Gérard Benoit).

The N-terminal A/B region contains one or more autonomous transcriptional activation function (AF1) domains that can activate transcription in a constitutive manner and display cell-, DNA-binding domain- and promoter-specificity. It displays the weakest evolutionary conservation, its length differs significantly within different subfamilies and it is subject to alternative splicing and differential promoter usage. Moreover, the A/B region can interact with cofactors or other transcription factors and has been shown to be target for post-translational modifications, especially phosphorylation (Shao and Lazar, 1999).

The DNA-binding domain (DBD) is composed of 2 zinc-finger motifs, in which 4 cystein residues chelate one Zn^{2+} ion. Distinct sequence elements (boxes) have been identified within the DBD that contribute to specific functions (**Figure 3**). The P-box contacts directly the major groove of the DNA molecule and determines sequence specificity. The D-box is involved in dimerization while the T- and A-boxes contact the 5' end of the core recognition site and are important for monomeric DNA binding.(Aranda and Pascual, 2001).

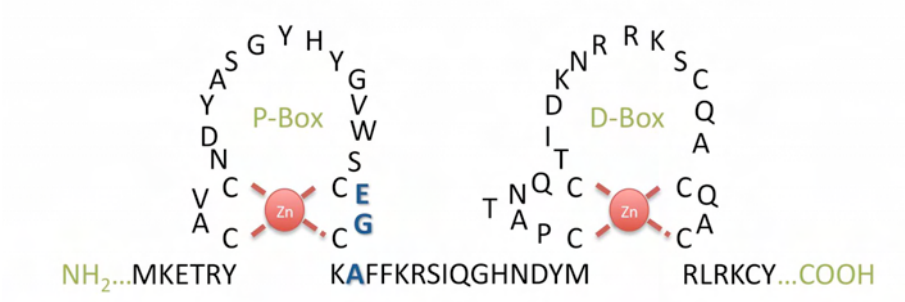

Figure 3 Schematic illustration of the NR DBD (The Nuclear Receptor Resource; nrresource.org).

The ligand-binding domain (LBD) contains the ligand-dependent activation function AF2, a major dimerization interface and sometimes a repression function. The crystal structures of the LBDs of numerous NRs have been solved and they show a rather similar fold,

consisting of a 3-layered antiparallel helical sandwich (Moras and Gronemeyer, 1998). These helices form a cavity, the ligand-binding pocket (LBP), which accommodates the ligand. Thermal denaturation studies, NMR studies and comparison of X-ray crystal structures of liganded vs unliganded NRs have provided a model for ligand-induced transcriptional activation: Upon ligand binding, a series of conformational changes are induced in the LBD, the most important being the repositioning of the helix H12 (**Figure 4**), which in its final position seals the LBP and forms a hydrophobic cleft together with other surface-exposed amino acids from H3, H4 and H5. This cleft can then interact with coactivators resulting in transcription activation (Nolte et al., 1998). Ligand binding can also increase the thermal stability of NRs and directly influence NR dimer affinity and dissociation rates (Greenfield et al., 2001, Tamrazi et al., 2002) while coactivator binding can induce a novel, markedly stabilized receptor conformation (Tamrazi et al., 2005).

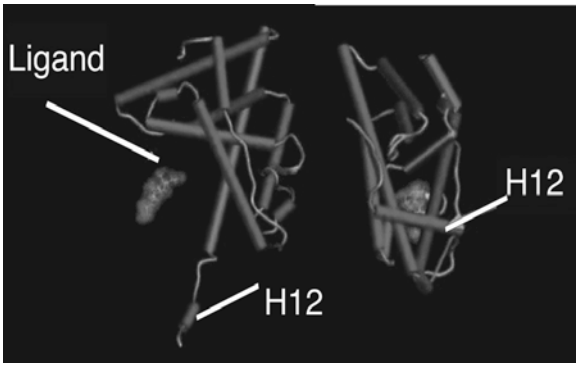

Figure 4 Crystal structure of the ER LBD before and after ligand binding (adopted from the NRRs graphics library; nrr.georgetown.edu/NRR).

Recently, the first crystal structure of an intact NR was solved, that of the PPARγ-RXRα heterodimer. Interestingly, PPARγ and RXRα form a non-symmetric complex with the LBD of PPARγ contacting multiple domains in both proteins. Three interfaces link PPARγ and RXRα and the PPARγ LBD cooperates with both DBDs to enhance response-element binding. Finally, the A/B region was very dynamic, lacking folded substructures despite its gene-activation properties (Chandra et al., 2008).

1.3 Nuclear Receptor Function

The first step of NR action is their binding to DNA at response elements that are normally located in the promoter region of the target gene but can also lie in enhancer regions. These response elements are derivatives of the hexameric consensus motif AorGGGTCA. Mutation, extension, duplication and distinct orientation of this motif generate response elements that are selective for a specific class of NRs (Aranda and Pascual, 2001).

NRs can interact with response elements as monomers, homodimers or heterodimers (**Figure 5**), with monomers binding to a single half-site and dimers to two recognition motifs that can be arranged as palindromes, inverted palindromes or direct repeats (Glass, 1994). Steroid hormone receptors generally bind as homodimers to their response elements

while non-steroid receptors prefer to bind DNA as heterodimers with the promiscuous heterodimerization partner RXR (Kliewer et al., 1992). Some of these heterodimers can respond only to the ligand binding to the RXR partner and not to RXR itself (non-permissive heterodimers) but RXR can also form permissive heterodimers with for example LXR, FXR and Nurr1, where RXR ligands can activate the heterodimer independently of the ligand-binding status of the heterodimerization partner (Blumberg and Evans, 1998).

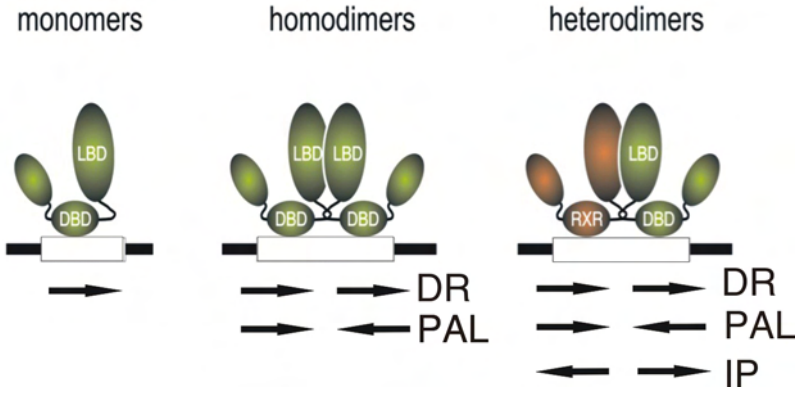

Figure 5 DNA binding to response elements. DR: Direct Repeats, PAL: palindromes, IP: inverted palindromes (courtesy of Gérard Benoit; adopted).

Squelching experiments, yeast two-hybrid and cDNA expression library screening approaches have led to the identification of many NR coactivators that transmit the signal from the NR to its molecular targets.

As already discussed, the conformational changes induced by ligand binding result in the formation of a new hydrophobic surface that is involved in the recruitment of coactivators. The cloning of coactivators has revealed a LxxLL NR box that is necessary and sufficient for their ligand-dependent direct interaction with the newly formed hydrophobic cleft at the NR LBD (Heery et al., 1997). Residues flanking this motif are believed to contact the charged residues at both sides of the hydrophobic surface and contribute to NR selectivity (Darimont et al., 1998). The LxxLL motif is positioned within the groove by a charge-clamp interaction involving a Lys on H3 and a highly conserved Glu on the AF2 helix (Darimont et al., 1998, Nolte et al., 1998).

NR coactivators possess or recruit HAT enzymatic activity that targets the N-terminal tails of different histones, some basal transcription factors and in some cases the coactivators themselves. Histone acetylation contributes to chromatin decondensation, a process that is necessary for subsequent transcription activation (Chen et al., 1999).

The next step in NR-mediated gene activation is the recruitment of the RNA polymerase II holoenzyme that consists of a multisubunit protein complex called the mediator complex and the RNA polymerase II (**Figure 6**). The switch between coactivators and the mediator complex might be regulated by the acetylation of coactivators within the HAT complex

resulting in their dissociation from the NR (Chen et al., 1999). This allows the mediator complex to be recruited to the NR via its TRAP220/DRIP205 subunit that contains a functional LxxLL NR box motif (Freedman, 1999). The recruitment of the RNA polymerase II holoenzyme might also be enhanced by interactions between one of its components, the ATP-dependent chromatin remodeling SWI/SNF complex and NRs (Muchardt and Yaniv, 1993). Finally, factors of the basal transcription machinery, such as TBP and TAFs have also been reported to interact, directly or indirectly with NRs (Laudet and Gronemeyer, 2002).

Coactivators have also been shown to bind to the N-terminal A/B region of some NRs (Benecke et al., 2000), suggesting that the activation functions AF1 and AF2 might not be independent in the context of the NR but even constitute 2 separate docking regions for a single coactivator.

Some NRs such as TR, RAR and VDR can actively repress transcription when unliganded (Glass and Rosenfeld, 2000). These receptors can interact with corepressors that recruit HDAC activity (**Figure 6**), which in turn results in chromatin condensation and silencing (Guenther et al., 2000). The most studied corepressors are the NR corepressor NcoR and SMRT, both of which have a conserved CoRNR box motif that interacts with a surface on the LBD of NRs (Hu and Lazar, 1999).

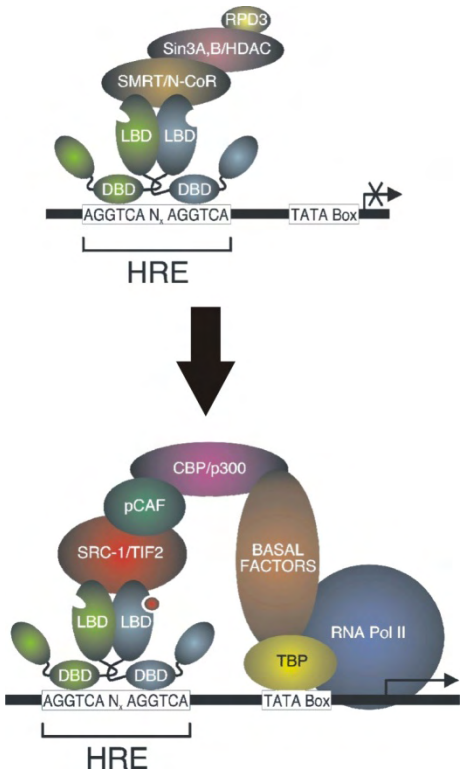

Figure 6 NR-mediated gene transcription: binding of ligand (red dot) induces corepressor dissociation and coactivator recruitment: see text for details (courtesy of Gérard Benoit; adopted).

Another mechanism of NR-mediated transcription is transrepression which does not involve sequence-specific DNA binding but rather tethering of NRs to negatively regulated target genes via protein-protein interactions (Glass and Ogawa, 2006).

1.4 Regulation of Nuclear Receptor activity

Endocrine (steroids, thyroid hormone) and paracrine (retinoids) signaling molecules bind to their respective receptors with high affinity and activate their transcriptional activity. Metabolites of nutrients that are derived from FAs and cholesterol or foreign compounds that are derived from the diet bind to another class of NRs with relatively low affinity and lower specificity and activate metabolic and xenobiotic sensing pathways (Benoit et al., 2004).

The NRs HNF4α and HNF4γ, SF-1 and LRH-1 were shown to bind FAs but in these cases the FAs seem to be integrated components of the LBDs of these NRs and they should be regarded as structural cofactors rather than *bona fide* ligands (Ingraham and Redinbo, 2005).

Ligand-independent regulation

Receptors as the mouse LRH-1, the ERR3 and RORβ have well-formed but empty LBPs, suggesting that they do not have a ligand or that they bind yet unidentified ligands (Benoit et al., 2004).

The NR Nurr1 is the first example of a NR that functions entirely independent of ligand binding. Nurr1 lacks a LBP since bulky hydrophobic amino acids side chains occupy the space that forms the LBP in other NRs (Wang et al., 2003). The related receptors NGFI-B and Nor-1 also seem to lack the capacity for ligand binding since the residues that occupy their LBPs are conserved in them also and the *Drosophila* Nurr1 homolog DHR38 LBD shares similar properties (Baker et al., 2003). Molecular modeling and mutagenesis studies of the Rev-ErbA subfamily of NRs suggest that they might also be ligand-independent lacking a cavity for ligand binding (Renaud et al., 2000).

Ways to regulate the transcriptional activity of NRs apart from ligand binding include the interaction with other proteins (Weigel, 1996) and post-transcriptional modifications.

Post-transcriptional modifications

NR phopshorylation in the A/B region by kinases associated with general TAFs (for example CDK7 within TFIIH) or by kinases activated in response to a variety of signals (for example MAPKs or Akt) can help the recruitment of coactivators and the RNA pol II transcription machinery, while phosphorylation of the AF2 domain can enhance ligand binding, dimerization and/or coactivator recruitment. However, phosphorylation events can also inactivate NRs (Rochette-Egly, 2003). Apart from modulating the NR transcriptional activity *per se*, phosphorylation can also affect the DNA binding, the stability and the localization (nuclear vs cytoplasmatic) of the NR (Weigel and Moore, 2007).

Various NR have been shown to be subject to SUMOylation. This results in most cases in the attenuation of their transcriptional activity. Modification with SUMO promotes or inhibits NR-protein interactions and might also block alternative Lys-targeted modifications such as acetylation or ubiquitination (Verger et al., 2003).

Studies over the past years have revealed that NRs can also serve as direct substrates for HATs, with the most studied acetylated NRs being AR and ER. NR acetylation seems to be a conserved function that can regulate NR activity. NAD-dependent HDACs, the sirtuins, are capable of deacetylating NRs, suggesting that local intracellular NAD concentrations may affect NR physiology (Wang et al., 2008).

NRs can be ubiquitinated and targeted for degradation both in the presence and the absence of ligand. NR-dependent transcription and NR degradation are interdependent processes as, for example, the proteasome can degrade corepressors and relieve NRs from repression and also degrade the NR itself after the completion of transcription leading to NR recycling for a new cycle of transcription (Ismail and Nawaz, 2005).

Finally, methylation of NRs can also regulate their transcriptional activity. A few examples of NRs whose activity is affected by methylation include the ER and HNF4, methylation of which was shown to enhance their ability to bind to their response elements and RARα, that shows enhanced interaction with coactivators after trimethylation on Lys347 (Wu and Zhang, 2009).

1.5 Nuclear Receptors in Disease

Given the important role of NRs in many aspects of animal physiology, it is not unexpected that deregulation of NR function lies behind many pathological conditions.

Just to mention a few examples, the AR is involved in prostate cancer, the ER in breast cancer and osteoporosis, the RXR in acne, psoriasis and obesity, the PPARs in diabetes and inflammation and RAR in acute myeloid leukemia.

A large number of natural and synthetic NR ligands have been identified and are currently in clinical use for therapies of a variety of pathological conditions. Low- and high-throughput screening of compounds, mass-spectrometry and structure analysis by molecular modeling and crystallography are extensively utilized nowadays in an effort to identify novel synthetic NR agonists and/or antagonists that will be used for the prevention and therapy of diseases in which NRs are involved. A lot of focus is laid on the discovery of selective receptor modulators that can affect NR activity in a cell- and tissue context-specific manner (Smith and O'Malley, 2004).

2 The NR4A subfamily of Nuclear Receptors

The NR4A subfamily of NRs consists of 3 receptors in vertebrates and their unique homologue in arthropods and nematodes (**Figure 7**). A pairwise analysis of the human

NR4A and the *Drosophila* DHR38 (NR4A4) sequences shows that DHR38 has the same level of conservation with each human NR4A receptor as the human NR4A receptors have amongst themselves, suggesting that each of these four receptors evolved from a common ancestor (Baker et al., 2003).

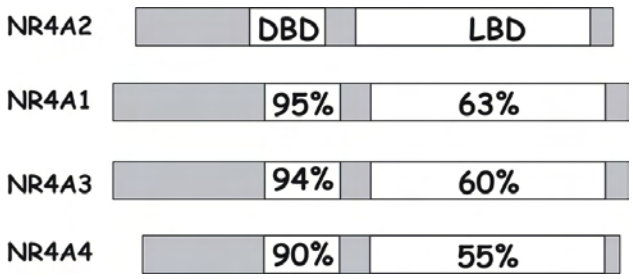

Figure 7: NR4A members and their identity levels.
NR4A1: NGFI-B, NR4A2: Nurr1, NR4A3: Nor-1, NR4A4: DHR38

3 NR4A receptors in disease

Mutations/polymorphisms in NR4A genes have been associated with a number of human disorders. More specifically, Nurr1 has been implicated in schizophrenia, manic depression, mental retardation, Parkinson's disease, alcohol dependence, diffuse Lewy body disease, aortic and coronary calcification, high levels of high-density lipoprotein cholesterol and low systolic blood pressure, NGFI-B in hereditary haemorrhagic telangiectasia and tardive dyskinesia and Nor-1 in increased insulin secretion (Buervenich et al., 2000, Chen et al., 2001, Ishiguro et al., 2002, Xu et al., 2002, Le et al., 2003, Tan et al., 2003, Zheng et al., 2003, Hering et al., 2004, Grimes et al., 2006, Jacobsen et al., 2008, Shoukier et al., 2008, Kardys et al., 2009, Lybaek et al., 2009, Sleiman et al., 2009, Weyrich et al., 2009, Novak et al., 2010).

3.1 Nurr1 in Parkinson's disease

Nurr1 is down-regulated in SN dopaminergic neurons with signs of pathology (Chu et al., 2006) where its reduction is correlated with loss in TH and in peripheral blood lymphocytes from patients with PD (Le et al., 2008). These findings, combined with the data from Nurr1 ablation in mice presented in chapter A4.1 and with the fact that mutations of Nurr1 have been found in cases of familial and sporadic PD suggest that reduction in Nurr1 expression is involved in PD initiation/progression/severity.

3.2 NR4A receptors in vascular disease

NR4A receptors are expressed in human macrophages present in atherosclerotic lesions at areas of plaque activation and progression (Pei et al., 2005, Bonta et al., 2006). In cultured human and mouse macrophages, NR4A receptors are induced in response to atherogenic

stimuli such as LPS, IFNγ, TNFα and oxidized LDL (Barish et al., 2005, Pei et al., 2005, Bonta et al., 2006, Pei et al., 2006a, Shao et al., 2010).

In mouse macrophages, NGFI-B activates inflammatory gene expression by binding to and activating the promoter of inducible IκB kinase in response to LPS (Pei et al., 2006a). However, a resent study shows that NGFI-B is induced in murine macrophages by oxidized LDL via the p38-MAPK pathway and subsequently protects from inflammation by inhibiting the expression of the pro-inflammatory genes COX-2, MCP-1 and TNFα (Shao et al., 2010). In human macrophages, lentiviral over-expression of NR4A receptors results in decreased expression of the inflammatory proteins IL-1β, -6 and -8, MCP-1 and MIP-1, decreased expression of the scavenger receptor SR-A and the FA translocase CD36 (Bonta et al., 2006) and decreased oxidized LDL loading (Bonta et al., 2006, Hu et al., 2008). On the contrary, shRNA-mediated knockdown of NGFI-B or Nor-1 in human macrophages enhances oxidized LDL uptake and increases inflammatory cytokine expression (Bonta et al., 2006). NR4A receptors are thought to mediate their anti-inflammatory role in macrophages via transrepression of NFκB (Pols et al., 2007).

Transgenic mice that express full-length NGFI-B in arterial SMCs show a 5-fold inhibition in neointimal formation after carotid artery ligation while transgenic mice that express the DN variant of NGFI-B show a 3-fold increase in neointimal formation, suggesting that NGFI-B has a protective role in atherogenesis (Arkenbout et al., 2002).

Local perivascular delivery of the antimetabolite 6-MP that enhances NR4A activity inhibits neointima formation in wt mice after cuff-induced vascular injury and enhances protein levels of p27kip1 in the vessel wall. Transgenic mice over-expressing a DN NGFI-B do not respond to 6-MP treatment, while transgenic mice over-expressing full-length NGFI-B show an even stronger inhibition of neointima formation in response to 6-MP (Pires et al., 2007).

NGFI-B is also induced during vascular outward remodeling and inhibits this vascular adaptation in mice. SMC-specific over-expression of NGFI-B in transgenic mice reduces macrophage accumulation and represses MMP-1 and -9 expression (Bonta et al., 2010).

Nor-1 is induced in human SMCs after activation by the growth factors PDGF and EGF (Martinez-Gonzalez et al., 2003, Nomiyama et al., 2006) and is also expressed in human vascular atherosclerotic lesions (Martinez-Gonzalez et al., 2003, Nomiyama et al., 2006). Nor-1 is also transiently expressed in porcine coronary SMCs in response to balloon dilatation (Martinez-Gonzalez et al., 2003). Nor-1 knockout mice show decreased neointima formation after guidewire-induced arterial injury compared with wt mice (Nomiyama et al., 2009) while antisense oligonucleotides against Nor-1 inhibit human coronary SMC proliferation (Martinez-Gonzalez et al., 2003).

3.3 NR4A receptors in diabetes, obesity and insulin resistance

Interestingly, NGFI-B and Nor-1 expression is reduced in skeletal muscle from multiple rodent models of insulin resistance (Fu et al., 2007) and in human skeletal muscle biopsies

from insulin-resistant individuals (Wu et al., 2007). Skeletal muscles from NGFI-B knockout mice show impaired insulin signaling, resulting in greater high-fat diet-induced insulin resistance compared with wt skeletal muscle (Chao et al., 2009). Moreover, skeletal muscles from rats with whole-body insulin resistance have decreased protein levels of NGFI-B and of the NGFI-B target genes Ucp3, CD36 and Ampk-γ3 and show a decreased lipolysis response to β-adrenergic stimulation (Lessard et al., 2009). NGFI-B expression is also reduced in the muscle of obese/insulin-resistant rats after high-fat diet (Kanzleiter et al., 2009). NGFI-B expression in muscle biopsies from obese men is significantly lower than in those from lean men and is closely correlated with body-fat content and insulin sensitivity (Kanzleiter et al., 2010).

Adenovirus-mediated over-expression of NGFI-B in the mouse liver results in modulation of the plasma lipid profile (reduction in plasma HDL-cholesterol, increase in plasma LDL-cholesterol and in plasma LDL-triglyceride) and reduction in hepatic triglyceride (Pols et al., 2008). NGFI-B inhibits the expression of SREBP1c, resulting in decreased expression of its target genes Scd1, mitochondrial Gpam, Fas and the LDL receptor (Pols et al., 2008). The decrease in the expression of the lipogenic enzymes Scd1, Fas and Gpam might explain the reduced hepatic triglyceride levels in response to NGFI-B while the increase in circulating LDL-cholesterol and LDL-triglycerides might be explained by reduced expression of LDL receptor. Enhancing the expression or the activity of liver NGFI-B might be beneficial in patients with type II diabetes since it would result in reduction in triglyceride accumulation in the liver. Hepatic expression of all NR4A receptors is induced by the cAMP axis in response to glucagon and fasting *in vivo* and is increased in diabetic mice that exhibit elevated gluconeogenesis. Adenoviral expression of NGFI-B induces genes involved in gluconeogenesis, raises blood glucose levels and stimulates glucose production *in vivo* and *in vitro* (Pei et al., 2006b). Increased levels of hepatic gluconeogenesis have been shown to cause glucose intolerance and diabetes in animal models (Valera et al., 1994). Expression of a DN NGFI-B antagonizes gluconeogenic gene expression and lowers blood glucose levels in diabetic mice (Pei et al., 2006b). NGFI-B knockout mice exhibit increased susceptibility to high fat diet-induced obesity and insulin resistance in the liver (Chao et al., 2009). The NGFI-B agonist cytosporone B enhances gluconeogenesis and elavates blood glucose levels in fasting wt but not NGFI-B knockout mice (Zhan et al., 2008).

Gene expression of NGFI-B and Nor-1 is reduced in adipose tissue from multiple rodent models of insulin resistance (Fu et al., 2007), suggesting that these 2 receptors might represent novel therapeutic targets for the treatment and prevention of diabetes and other diseases associated with insulin resistance. NGFI-B and Nor-1 expression is induced within 1 h of insulin treatment of 3T3-L1 pre-adipocytes and over-expression of Nor-1 increases the ability of insulin to augment glucose transport activity by promoting the recruitment of GLUT4 to the plasma membrane and to phosphorylate insulin receptor substrate-1 and Akt kinase while inhibition of Nor-1 by siRNA has the opposite effects in insulin action (Fu et al., 2007).

3.4 NR4A receptors in inflammation

NR4A receptors have pro- and anti-inflammatory roles in different contexts.

Synoviocytes

Nurr1 is expressed in human synoviocytes from rheumatoid and psoriatic arthritis explants (Murphy et al., 2001).

Nurr1 expression, its binding to the NBRE within the CRH promoter and CRH expression are induced in primary human synoviocytes treated with TNFα, IL-1β and PGE2 (Murphy et al., 2001, McEvoy et al., 2002b). Ectopic expression of CRH receptor 1α or induction of its expression by histamine in human synoviocytes also induces Nurr1 expression in a CREB-dependent way (Ralph et al., 2007, Zocco et al., 2010) while IL-1 induces Nor-1 expression in human synovial and gingival fibroblasts (Borghaei et al., 1998).

Peripheral CRH is involved in the modulation of immune responses since local production of CRH causes acute inflammation in the rat (Karalis et al., 1991). Transcriptional activation of Nurr1 by TNFα and IL-1β induces NFκB binding to a NFκB DNA-binding motif at the proximal Nurr1 promoter region, while PGE2 induces binding of CREB to a CRE site at the Nurr1 promoter (McEvoy et al., 2002b).

Methotrexate significantly suppresses Nurr1 expression in synoviocytes of patients with active psoriatic arthritis and the reduction in Nurr1 levels correlates with a therapeutic benefit. It also inhibits significantly the TNFα-, IL-1β- and PGE2-mediated induction of Nurr1 in primary synoviocytes via an adenosine receptor A2-mediated mechanism (Ralph et al., 2005).

Over-expression of Nurr1 in the immortalised synoviocyte cell line K41M results to increased gene expression of the pro-inflammatory genes IL-8, amphiregulin and kit ligand (Davies et al., 2005). TNFa treatment of K41M synoviocytes induces Nurr1 and IL-8 expression and the transcriptional activation of the human IL-8 promoter by Nurr1 is enhanced in the presence of TNFα suggesting molecular crosstalk between TNFα signaling and Nurr1. Moreover, coexpression of Nurr1 and the p65 subunit of NFκB leads to synergistic activation of the IL-8 promoter and inhibition of NFκB signaling abrogates TNFα- and Nurr1-induced IL-8 promoter activity (Aherne et al., 2009).

Peripheral blood mononuclear cells

Nurr1 is expressed in infiltrating mononuclear cells from human rheumatoid and psoriatic arthritis explants (Murphy et al., 2001).

Nurr1 expression is down-regulated in peripheral blood mononuclear cells derived from patients with ankylosing spondylitis, a disease characterized by inflammatory arthritis affecting primarily the sacroiliac joints and spine (Duan et al., 2009).

Nurr1 expression is up-regulated in peripheral blood T cells derived from patients with multiple sclerosis, an inflammatory demyelinating disease of the CNS (Satoh et al., 2005).

Nurr1 is also up-regulated in T cells isolated from the CNS of mice with experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (Doi et al., 2008). Retrovirus-mediated over-expression of Nurr1 in primary T cells results in increased production of IL-17 and IFNg, while treatment with siRNA against Nurr1 results in significant reduction of their production and reduces the ability of encephalitogenic T cells to transfer experimental autoimmune encephalomyelitis to recipient mice (Doi et al., 2008). NGFI-B expression in peripheral blood T cells is reduced in the pre-disease state of multiple sclerosis, probably resulting in inhibition of apoptosis of activated T cells (Achiron et al., 2010). NGFI-B also represses IL-2-induced activation of NFkB in Jurkat T cells (Harant and Lindley, 2004).

Transgenic mice over-expressing NGFI-B in the T cell lineage show decreased incidence and severity of collagen type II-induced arthritis. This seems to be the result of increased apoptosis induction in transgenic T cells and decreased production of collagen type II-specific IgG2a antibodies (De Silva et al., 2005).

Endothelial cells

CRH activates Nurr1 expression in primary synovial tissue endothelial cells by inducing CREB-1 and ATF-2 binding to the Nurr1 promoter (McEvoy et al., 2002a). Ectopic expression of CRH receptor 1α or induction of its expression by histamine in human endothelial cells also induces Nurr1 expression in a CREB-dependent way (Ralph et al., 2007, Zocco et al., 2010). Bacterial LPS or staphylococcal enterotoxin B iv injection induces NGFI-B in endothelial and perivascular cells (Serrats and Sawchenko, 2009). NR4A receptors are induced in endothelial cells by TNFα (Gruber et al., 2003, Liu et al., 2003, Rius et al., 2006, Zeng et al., 2006). In endothelial cells, NGFI-B increases the expression of IκBa, attenuates NFκB activation, expression of the adhesion molecules ICAM-1 and VCAM-1 and monocytic adherence to endothelial cells and thus protects from TNFα- and IL-1β-induced endothelial cell activation (You et al., 2009).

TNFα, IL-1β and PGE2 induce Nurr1 expression in human dermal endothelial cells (O'Kane et al., 2008). Nurr1 expression is increased in the nucleus and the cytoplasm of dermal endothelial cells in patients with psoriasis. Nurr1 is also expressed in endothelial cells from human rheumatoid and psoriatic arthritis explants (Murphy et al., 2001). Methotrexate significantly suppresses Nurr1 expression in synovial microvascular endothelial cells of patients with active psoriatic arthritis and the reduction in Nurr1 levels correlates with a therapeutic benefit. It also inhibits significantly the TNFα-, IL-1β- and PGE2-mediated induction of Nurr1 in endothelial cells via an adenosine receptor A2-mediated mechanism (Ralph et al., 2005).

Synovial tissue

Synovial tissue consists of synoviocytes, mononuclear cells and endothelial cells.

Treatment of rheumatoid and psoriatic arthritis explants with CRH induces Nurr1 and NGFI-B expression (Murphy et al., 2001). CREB and NFkB p50 and p65 subunits bind to

the Nurr1 promoter in freshly explanted rheumatoid arthritis synovial tissue (McEvoy et al., 2002b). In patients treated with methotrexate for active inflammatory arthritis, a reduction in Nurr1 synovial tissue levels by methotrexate correlates significantly with reduction in IL-8 expression (Aherne et al., 2009).

Epidermal cells

Nurr1 cytoplasmatic and nuclear expression is increased in involved psoriasis skin compared with uninvolved and normal skin. Following TNFα inhibition with infliximab or etanercept, Nurr1 mRNA and protein levels in involved skin are significantly decreased and cytoplasmatic distribution is restored (O'Kane et al., 2008).

Chondrocytes

Nor-1 is down-regulated in chondrocytes stimulated with supernatant of rheumatoid arthritis synovial fibroblasts that had been treated with antirheumatic drugs (azathioprine, methotrexate or gold sodium thiomalate) compared to chondrocytes stimulated with supernatant of untreated rheumatoid arthritis synovial fibroblasts (Andreas et al., 2009).

Nurr1 is induced by PGE2 in chondrocytes and can repress IL-1β-induced MMP-1,-3 and -9 expression. Nurr1 potently suppresses MMP-1 promoter activity resulting in reduction of MMP-1 mRNA and secreted MMP-1 protein levels (Mix et al., 2007). During the progression of inflammatory joint disease, the secretion of MMPs by chondrocytes leads to degradation of cartilage, bone and tendon.

NGFI-B is up-regulated in mouse primary chondrocytes upon PI3K pharmacological inhibition. Pharmacological inhibition of the PI3K signaling pathway results in reduced endochondral bone growth (Ulici et al., 2010).

CNS

Nurr1 is expressed in primary human and mouse microglia and in the microglia cell line BV2. After LPS treatment, its expression is induced and the protein is translocated from the cytoplasm to the nucleus (Fan et al., 2009, Saijo et al., 2009). Nurr1 is also expressed in human and mouse astrocytes, where its expression is induced by IL-1β and TNFα. Knockdown of Nurr1 in microglia leads to increase in LPS-induced expression of inflammatory mediators including TNFα, iNOS, IL-1α, IL-1β, COX-2, MMP-7, MMP-9, CXCL10 and CCL5 and conditioned medium from microglia or astrocyte cells where Nurr1 expression was knocked down caused increased cell death of *in vitro* differentiated TH positive neurons. Nurr1 inhibits LPS responses by a transrepression mechanism. In particular, Nurr1 in microglia (or astrocytes) is SUMOylated and binds to the p65 subunit of NFκB on inflammatory gene promoters. Nurr1 subsequently recruits the corepressor complex coREST that promotes NFκB clearance from the promoters and repression of the transcription of the inflammatory genes (Saijo et al., 2009).

Nurr1 is also induced in mouse microglia *in vivo* after LPS stereotaxic injection. Knockdown of Nurr1 in microglia and astrocytes by lentivirus-mediated shRNA delivery results in increased loss of dopaminergic neurons in the SN after LPS injection or after over-expression of mutant a-synuclein and in increased expression of inflammatory mediators in response to LPS injection, such as iNOS, TNFα and IL-1β (Saijo et al., 2009).

3.5 NR4A receptors in cancer

Both oncogenic and tumor suppressor properties have been assigned to the members of the NR4A family.

Oncogenic properties

Importantly, Nurr1 was recently shown to interact with the tumor suppressor p53 and suppress its transcriptional activity in non-small cell lung carcinoma H1299 cells. Nurr1 over-expression in neuroblastoma N2a cells and in A549 epithelial cancer cells decreases the expression of the pro-apoptotic protein Bax, while knockdown of Nurr1 expression has the opposite effect. Nurr1 also protects HCT116 colorectal carcinoma cells from doxorubicin-induced apoptosis (Zhang et al., 2009b)

In most cases of extraskeletal myxoid chondrosarcoma (EMC), the chromosomal reciprocal translocation t(9;22)(q22;q12) or t(9;17)(q22;q11) is observed resulting in fusion of Nor-1 with the Ewing sarcoma gene EWS (Labelle et al., 1995, Clark et al., 1996) or with the TATA-binding protein-associated factor 2N TAF2N (Attwooll et al., 1999, Bjerkehagen et al., 1999, Panagopoulos et al., 1999, Sjogren et al., 1999, Harris et al., 2000, Panagopoulos et al., 2002) respectively.

Tumor suppressor properties

Nor-1/NGFI-B double knockout animals develop rapidly lethal acute myeloid leukemia involving abnormal expansion of hematopoietic stem cells and myeloid progenitors, defective FasL and TRAIL (extrinsic apoptosis) signaling and increase in blast myeloid forms in the bone marrow, spleen and peripheral blood (Mullican et al., 2007).

NGFI-B is an important mediator of the effect of different proteins/compounds that have pro-apoptotic action in cancer cells (Li et al., 2007b) (Jeong et al., 2003) (Liu et al., 2002) (Li et al., 2000) (Kang et al., 2000) (Li et al., 2000) (Kolluri et al., 2008) (Jiang et al., 2008) (Chintharlapalli et al., 2005) (Liu et al., 2008a) (Yang et al., 2010) (Maddika et al., 2005) (Wilson et al., 2010). It can promote apoptosis by translocating to the cytoplasm and targeting the mitochondria (Li et al., 2000) or by activating the transcription of pro-apoptotic genes and/or repressing the transcription of anti-apoptotic genes in the nucleus.

4 NR4A receptor knockout mice

4.1 Nurr1 knockout mice

Nurr1 knockout mice die soon after birth because of milk-suckling difficulty (Zetterstrom et al., 1997, Saucedo-Cardenas et al., 1998). They have a disturbed breathing pattern (hypoventilation, apnoeas) and impaired hypoxic response (failure to increase breathing in response to hypoxia) (Nsegbe et al., 2004). Importantly, they lack dopaminergic neurons in the SN and the VTA area of the midbrain at birth (Zetterstrom et al., 1997, Baffi et al., 1999, Le et al., 1999b) and they show a complete dopamine content depletion in the SN and the VTA (Castillo et al., 1998) and decreased dopamine levels in the striatum and the olfactory bulb (Le et al., 1999b). Nurr1 ablation at late stages of dopamine neuron development results in rapid loss of striatal dopamine, loss of mesencephalic dopaminergic neuron markers and dopaminergic neuron degeneration after (Kadkhodaei et al., 2009).

4.2 NGFI-B knockout mice

NGFI-B knockout mice show enhanced spontaneous locomotor activity, dopamine turnover disturbances after acute challenge with the dopamine D2 receptor antagonist haloperidol, increased Nurr1 and TH levels in the SN pars compacta, increased TH activity in the striatum and the frontal cortex, increased levels of the dopamine metabolite DOPAC in the midbrain and the frontal cortex and decreased levels of the COMT enzyme converting DOPAC into another dopamine metabolite (HVA) in the prefrontal cortex, the striatum and the nucleus accumbens (Gilbert et al., 2006).

Moreover, they exhibit reduced expression of a battery of genes involved in skeletal muscle glucose utilization (Chao et al., 2007), greater high-fat diet-induced insulin resistance in skeletal muscle and liver, impaired insulin signaling, increased triglyceride content and accumulation of multiple even-chained acetylcarnitine species in skeletal muscle, hepatic steatosis, enhanced expression of lipogenic genes and reduced oxygen consumption (Chao et al., 2009).

Finally, they show defects in angiogenesis upon VEGF stimulation and in transplanted melanoma tumors (Zeng et al., 2006) and in activation-induced caspase-independent cell death in macrophages (Kim et al., 2003).

4.3 Nor-1 knockout mice

Nor-1 knockout mice show partial bidirectional circling behavior and inner ear defects (Ponnio et al., 2002). They also exhibit defective postnatal hippocampal development exemplified by reduced axon outgrowth of DG granule and mossy cells, disorganization of the pyramidal CA1 and CA3 layers, reduced total number of cells in the CA1 layer and early (between P0 and P7) postnatal death of CA1 pyramidal neurons (Ponnio and Conneely, 2004).

4.4 NGFI-B and Nor-1 double knockout mice

As already mentioned, NGFI-B/Nor-1 double knockout mice have smaller size, ruffled fur, hunched posture and die from rapidly lethal (2-4 weeks after birth) acute myeloid leukemia involving abnormal expansion of hematopoietic stem cells and myeloid progenitors,

decreased expression of the AP-1 transcription factors JunB and c-Jun, defective FasL and TRAIL (extrinsic apoptosis) signaling, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia, increase in blast myeloid forms in the bone marrow, spleen and peripheral blood and severe disruption of the spleen and thymus architecture (Mullican et al., 2007).

5 DNA binding of NR4A receptors

5.1 NR4A monomers

The DBD of NGFI-B and the DNA binding site for NGFI-B were identified by genetic selection in yeast (Wilson et al., 1991, Wilson et al., 1993b). NGFI-B was shown to bind as a monomer to a half-site motif containing a single AAAGGTCA element termed NBRE (Wilson et al., 1991). The A-box of NGFI-B is required for the recognition of the 2 A-T base pairs at the 5' end of the NBRE (Wilson et al., 1992, Wilson et al., 1993a) and the T-box of NGFI-B forms a secondary structure that stabilizes the A-box-DNA interaction (Wilson et al., 1993a). The X-ray crystal structure of the NGFI-B DBD bound to NBRE revealed that the T-box interacts extensively and in a sequence-specific way with the minor groove of the DNA (Meinke and Sigler, 1999). Mutations in the NGFI-B zinc modules, the A-box and the T-box disrupt the *in vitro* binding of NGFI-B to NBRE (Wilson et al., 1993b).

The NR SF-1 can also bind to DNA as a monomer but to a slightly different response element (TCAAGGTCA). The key features that distinguish SF-1 and NGFI-B interactions are an amino group in the minor groove of the SF-1 binding sequence and an Asn in the A-box of SF-1 (Wilson et al., 1993a).

Nurr1, Nor-1 and insect NR4A also bind to the NBRE element as monomers (Fisk and Thummel, 1995, Giguere, 1999). NGFI-B and Nurr1 can even bind as monomers to three variants of the NBRE element (Murphy et al., 1996).

5.2 NR4A homodimers and heterodimers

NGFI-B, Nurr1 and Nor-1 homodimers and NGFI-B/Nurr1 heterodimers can bind to and activate a palindromic NGFI-B response element termed NurRE, containing two everted repeats of the NBRE sequence spaced by 10 bp (Philips et al., 1997a, Maira et al., 1999, Maira et al., 2003b). This element has been found in the promoter of the POMC gene where it is responsible for the NGFI-B-mediated activation of POMC by CRH in pituitary-derived AtT-20 cells (Philips et al., 1997a). TCR activation in T-cell hybridomas induces NGFI-B expression and also induces activation of NurRE (but not NBRE) reporters (Philips et al., 1997a). CRH treatment or over-expression of PKA increases DNA binding activity of NGFI-B homodimers but not monomers and enhances transcription from NurRE but not NBRE elements. Moreover, p160/SRC coactivators are recruited to the AF1 domain of NR4A homodimers but not monomers (Maira et al., 2003b).

NGFI-B homodimers are V-shaped, with the opening angle being significantly larger than that of classical dimers as ER dimers. NGFI-B dimer formation does not occur via the classical NR dimerization interface but instead involves a surface composed of the loop between H3 and H4 and the C-terminal portion of H3 (Calgaro et al., 2007).

NGFI-B and Nurr1 can form heterodimers *in vitro* that synergistically enhance transcription from NurRE reporters (Maira et al., 1999). The naturally occurring NurRE from the POMC promoter preferentially binds NGFI-B homodimers or NGFI-B/Nurr1 heterodimers, while a consensus NurRE sequence does not show this preference, suggesting that specific NurRE sequences might be responsible for the activation of subsets of genes by one of the members of the NR4A subfamily (Maira et al., 1999).

5.3 NR4A-RXR heterodimers

Transfection experiments showed that strong responsiveness to the RXR agonist LG69 was observed when the RXR LBD was coexpressed with a GAL4-Nurr1 chimera, suggesting that the LBDs of Nurr1 and RXR form a complex that is responsive to RXR agonists. Nurr1 and NGFI-B indeed form heterodimers with RXR that can confer LG69-induced activation of a reporter containing three copies of the NBRE response element (Forman et al., 1995). Nurr1/NGFI-B-RXR heterodimers can also specifically bind the direct repeat element DR5 and they efficiently recognize only elements having the NBRE sequence at the 3 half-site (Perlmann and Jansson, 1995). RXR does not bind to DNA when the heterodimer binds to NBRE whereas it binds to the 5' half-site of the DR5 (Perlmann and Jansson, 1995). Nor-1 cannot form heterodimers with RXR (Zetterstrom et al., 1996a).

Substitutions in the Nurr1 I-box in the C-terminus disrupt heterodimerization with RXR but do not affect Nurr1 monomeric activity (Aarnisalo et al., 2002) and a Nurr1 mutant lacking the last 15 C-terminal AAs does not respond to 9-cis-RA in the presence of RXR (Castillo et al., 1998). Nurr1 heterodimerizes with RXRα and RXRγ but not RXRβ (Sacchetti et al., 2002). Another study suggests that NGFI-B/RXR heterodimerization is mediated by dimerization interfaces located in their DBDs (Cao et al., 2004). RXR over-expression results in diminished Nurr1 monomeric activity (Aarnisalo et al., 2002).

NGFI-B and Nurr1 promote efficient activation in response to RXR ligands when forming heterodimers with RXR and therefore shift RXR from a silent (as in the case of RXR-RAR heterodimers) to an active heterodimerization partner (Forman et al., 1995, Perlmann and Jansson, 1995). NGFI-B and Nurr1 can increase the potential of RXR to affect gene expression by allowing it to bind to and activate a distinct class of DRs and taking into consideration that NGFI-B and Nurr1 are rapidly induced by growth factors (chapter A7), NGFI-B and Nurr1 heterodimerization with RXR might constitute a mechanism for convergence between vitamin A/retinoid and growth factor signaling pathways (Perlmann and Jansson, 1995).

The interaction between NR4A receptors and RXR is evolutionary conserved as the insect NR4A from *Drosophila, Aedes* and *Bombyx* heterodimerizes with the RXR homologue USP (Crispi et al., 1998). However, some differences exist. DHR38-USP can bind to DR

elements with varying spacing while Nurr1-RXR specifically binds DRs with 5 nucleotides of spacing (Perlmann and Jansson, 1995), although another study suggests that Nurr1-RXR can form heterodimers on DR10, DR11 and as far as DR27 elements, though not responsive to retinoids (Sacchetti et al., 2002). Moreover, Nurr1/NGFI-B-RXR heterodimers efficiently recognize only elements having the NBRE sequence at the 3' half-site (Perlmann and Jansson, 1995) while the polarity of the EcRE in *Drosophila* that DHR38-USP binds to is inversed with the NBRE sequence at its 5' half-site (Crispi et al., 1998). The USP-NR4A heterodimer can also bind monomeric NBRE sites (Fisk and Thummel, 1995, Sutherland et al., 1995). The DHR38/USP heterodimeric complex is responsive to ecdysteroids but it requires transactivation of both receptor partners for full agonist activity (Baker et al., 2003), while Nurr1 AF2 core is not required for ligand activation of Nurr1/RXR heterodimers (Castro et al., 1999).

6 The transcriptional activity of NR4A receptors

The NR4A receptors are transcriptional activators that have been shown to act in a constitutive active manner in a variety of cell lines such as *Drosophila* S2 cells, PC12 cells, 3T3 fibroblasts, CV1 cells, COS-1 monkey kidney cells, PC-3 human prostate cancer cells, HEK293 cells, MN9D cells, SH-SY5Y cells, C17.2 cells as well as in cultured primary neurons and astrocytes (Davis et al., 1991, Kokontis et al., 1991, Ciani and Paulsen, 1995, Paulsen et al., 1995).

NR4A receptors have also been shown to repress the activity of other transcription factors, namely NFκB (Harant and Lindley, 2004, Hong et al., 2004, Diatchenko et al., 2005), GR (Philips et al., 1997b, Drouin et al., 1998) (Martens et al., 2005) (Bilodeau et al., 2006) and ERR (Lammi et al., 2004, Lammi et al., 2007).

Nurr1 can also be involved in transrepression of pro-inflammatory genes in microglia and astrocytes by tethering to their promoters via docking to NFκB p65 (Saijo et al., 2009).

6.1 AF2 Activity

The AF2 domains of NGFI-B and Nor-1 are inactive in C2C12, Cos-1 and JEG-3 cells and exhibit very low activity in HEK293 cells and COS-1 cells (Castro et al., 1999, Wansa et al., 2002, Wansa et al., 2003, Flaig et al., 2005). Nurr1 AF2 shows different activity depending on cell type, being inactive in JEG-3 cells but constitutively active in HEK293 and COS-1 cells and the neuronal cell lines C17.2, MN9D and SH-SY5Y (Castro et al., 1999, Flaig et al., 2005). Interestingly, an assembly assay (where H1 is fused to GAL4-DBD and the H3-H12 of Nurr1 are fused to the strong activation domain VP16 from HSV) showed that the difference in transcriptional activity of Nurr1 in HEK293 and JEG-3 cells correlates with specific assembly of H1 and H3-H12 LBD fragments in HEK293 cells but not in JEG-3 cells, indicating that Nurr1 LBD is stabilized in HEK293 cells (Wang et al., 2003b).

The X-ray crystallography structures of Nurr1 and NGFI-B superimpose well with the exception of a significantly shifted H12 by 2.8 Å. This differential H12 positioning is caused by conserved AA exchanges in H3 and H12 between Nurr1 and NGFI-B and seems to be responsible for the differential AF2 activity of the two receptors described above. Mutation of these individual residues in H3 and H12 of Nurr1 to the corresponding residues of NGFI-B significantly reduces the activity of Nurr1 LBD. Moreover, swapping of the H11-H12 region of NGFI-B into Nurr1 reduces the AF2 activity of Nurr1 to NGFI-B levels. The reverse swap results in an only slight increase of the activity of the NGFI-B LBD possibly because the LBD body of NGFI-B does not precisely position the swapped H12 of Nurr1 (Flaig et al., 2005). Since the site that Nurr1 utilizes to bind co-regulators is adjacent to H12, it is possible that H12 positioning might regulate the binding of coregulators to Nurr1.

Mutation of Asn589, Phe592 or Leu593 in Nurr1 AF2 completely abolishes its activity, while mutation of Lys590 increases Nurr1 AF2 activity (Castro et al., 1999). Asn589 and Phe592 were later shown to be involved in intramolecular interactions that stabilize Nurr1 AF2 in its active conformation, while Lys590 forms together with Glu422 from H3 the reversed charged clamp in Nurr1 LBD (Wang et al., 2003). Moreover, Phe592 and Leu593 are involved in the formation of the hydrophobic region that Nurr1 uses as a coregulator binding surface (Codina et al., 2004, Flaig et al., 2005).

6.2 Lack of requirement for ligand binding

Nurr1 LBD adopts a canonical protein fold resembling that of agonist-bound transcriptionally active LBDs such as the RARγ or the ERα (Wang et al., 2003b). The AF2 helix folds back towards the body of the LBD and packs against H3, H4, H10, with its hydrophobic residues protruding into the core of the LBD. A salt bridge and hydrophobic interactions between H11 and H12 stabilize the AF2 in this active conformation that can otherwise be achieved by ligand binding in other NRs (Wang et al., 2003b). The AF2 of DHR38 and NGFI-B were also found in the active conformation (Baker et al., 2003).

6.3 Absence of ligand binding space in NR4A LBDs

The LBDs of Nurr1, NGFI-B and DHR38 contain no cavity for ligand binding as a result of the tight packing of side chains from bulky hydrophobic residues that occupy the space where ligands bind in other NRs. The residues that fill the LBP and almost all of the AAs that make up the core of the AF2 are conserved between *Drosophila* and human NR4A receptors (Baker et al., 2003). NMR assignment studies suggest that Nurr1 LBD is flexible despite it being filled with hyfrophobic side chains (Michiels et al., 2010). The Nor-1 LBD X-ray structure has not been solved but UV light absorption and spectroscopy analysis reveal that it has a high α-helical secondary structure content similar to that of Nurr1 LBD (Razzera et al., 2004).

6.4 NR4A coactivator-binding surface

Molecular modeling has shown that the hydrophobic cleft used by other NRs to bind coactivators is replaced with a hydrophilic surface in the LBDs of Nurr1, NGFI-B and Nor-1 (Wansa et al., 2002, Wansa et al., 2003, Codina et al., 2004). X-ray crystallography studies have verified that Nurr1, NGFI-B and DHR38 lack the classical coactivator-binding site that consists of a hydrophobic groove formed by H3, H3, H5 and the AF2 helix (Baker et al., 2003). The hydrophobic cleft seen in other NRs is a completely charged surface in Nurr1, NGFI-B and DHR38. Moreover, Nurr1, NGFI-B, DHR38 (and according to sequence analysis Nor-1) LBDs show a reversed charge clamp with the conserved Glu of the AF2 being an Asn in DHR38 and a Lys in the mammalian NR4As and the conserved Lys on H3 being a Glu in both DHR38 and the mammalian NR4As (Castro et al., 1999, Baker et al., 2003, Wang et al., 2003b, Flaig et al., 2005). In the DHR38 structure, the AF2 helix is shifted by one turn relative to its position in other NR LBD structures, resulting in the positioning of an Asn at the position of the conserved Glu and the loss of the charge clamp (Baker et al., 2003).

The most crucial disruption of the region corresponding to other NRs coactivator-binding site in Nurr1 is that Arg418 folds into the shallow groove and makes van der Waals contacts with Phe439 from H4 at the floor of the groove. Reversal of the reversed charged clamp does not change Nurr1 activity, suggesting that Nurr1 H12 is not a direct interaction surface for coactivators but rather provides stability to the LBD (Wang et al., 2003b).

Calculation of the hydrophobic potential of the Nurr1 LBD has led to the identification of a highly hydrophobic groove between H11 and H12 that Nurr1 utilizes to interact with coregulators (Codina et al., 2004, Flaig et al., 2005). Despite the fact that this novel site lies in the proximity of the surface that Nurr1 uses for dimerization with RXR, Nurr1-RXR heterodimer formation is not totally abolished by mutations (Flaig et al., 2005). Since this novel site is adjacent to H12, it is possible that H12 positioning might regulate the binding of coregulators to Nurr1.

Mutations in this region do not interfere with the structure and the stability of the Nurr1 LBD but severely decrease the AF2 activity of Nurr1 (Flaig et al., 2005) and also decrease the interaction of Nurr1 LBD with a NcoR-derived peptide as shown in pull-down assays and in NMR footprinting experiments, where there is a striking overlap between the signals perturbed by the mutations and those perturbed in the complex of wt Nurr1 LBD with the NcoR peptide (Codina et al., 2004).

Monitoring by fluorescence, spectroscopy and small X-ray scattering have revealed the existence of an intermediate state of the NGFI-B LBD during unfolding induced by guanidine hydrochloride that is partially folded and may resemble an intermediate conformation present transiently upon co-regulator binding or dissociation (Garcia et al., 2008).

6.5 Enhancement of NR4A receptor-mediated transcription

AF1 coactivators

SRC coactivators enhance the AF1 transcriptional activity of all NR4A receptors on NurRE but not NBRE reporters in pituitary, CV-1 cells and HEK293 cells, suggesting that they are recruited only to NR4A dimers but not monomers (Maira et al., 2003b, Castro et al., 1999, Wansa et al., 2002, Wansa et al., 2003). SRC-2 does not increase Nurr1 activity on a NBRE reporter but it increases the dexanethasone-induced activity of GR-Nurr1 complexes on the same promoter (Carpentier et al., 2008).

SRC coactivators enhance NGFI-B activity on the HSD3B2 promoter in Leydig cells (Martin and Tremblay, 2005) and on the POMC promoter in pituitary cells (Maira et al., 2003a). Retinoblastoma protein interacts directly with NGFI-B and the SRC coactivators and potentiates SRC-dependent activity of NGFI-B on the POMC promoter in pituitary cells (Batsche et al., 2005a,b, Martin and Tremblay, 2005). SRC-2 acts synergistically with PRMT1 to enhance NGFI-B transcriptional activity (Lei et al., 2009). In pituitary cells, SRC-2 recruitment to the NurRE is enhanced in response to CRH (Maira et al., 2003b) and in human adrenocortical cells treatment with angiotensin II enhances the interaction between NGFI-B and SRC-1 (Kelly et al., 2005).

The coactivators p300, PCAF and TRAP220 also interact directly with the AF1 domain of NGFI-B and Nor-1 in GST pull-down assays (Wansa et al., 2002, Wansa et al., 2003). TRAP220 potentiates Nor-1-mediated transactivation on a POMC promoter and in a GAL4 assay in C2C12 myoblasts. 6-MP increases the activity of TRAP220 in a dose-dependent manner but via an unknown mechanism (Wansa and Muscat, 2005).

TIF1β binds to NGFI-B AF1 and enhances NGFI-B-mediated POMC transcription in pituitary cells alone or synergistically with SRC coactivators. TIF1β binds also Nurr1 and Nor-1 and enhances the activity of all 3 NR4A receptors on NurRE but not NBRE reporters (Rambaud et al., 2009).

AF2 coactivators

The LBDs of the mammalian NR4A receptors and of DHR38 have been reported to be incapable of binding to classical coactivators (Castro et al., 1999, Baker et al., 2003, Maira et al., 2003b, Wang et al., 2003b, Wansa et al., 2003, Codina et al., 2004). Only a few proteins have been shown to directly bind NR4A LBDs:

SRC-2 interacts with the LBD of NGFI-B and enhances NGFI-B transcriptional activity on a NurRE reporter in HEK293 cells (Lei et al., 2009). When recruited to the RXR LBD, SRC-2 enhances the 9-cis RA-induced RXR-dependent activation of NGFI-B LBD (Wansa et al., 2002).

β-catenin binds to the C-terminus of Nurr1 and activates its transcriptional activity in 293F cells (Kitagawa et al., 2007).

SRC-1, CARM-1, TRAP220 and PGC-1α interact with GAL4-NGFI-B LBD in pancreatic cancer cells treated with DIM-C-pPhCl (Chintharlapalli et al., 2005).

NuIP is a GTPase activating protein-like protein shown to interact with the Nurr1-LBD in a yeast two-hybrid library screening. NuIP interacts with Nurr1-LBD in a mammalian two-hybrid assay and in coimmunoprecipitation experiments in MN9D cells. NuIP enhances the transcriptional activity of Nurr1 on a NBRE reporter and a TH promoter reporter and potentiates the assembly of H1 and H3-H12 domains of the Nurr1-LBD in an assembly assay in HEK293 cells. Suppression of NuIP expression in MN9D cells by siRNA decreases the expression of the Nurr1 target DAT. NuIP is coexpressed with Nurr1 in the cortex, hippocampus and midbrain, but not in dopaminergic neurons of the olfactory bulb and the hypothalamus (Luo et al., 2008, Luo et al., 2009).

The adenovirus E1A protein can enhance AF2-mediated transcriptional activation of Nurr1 and in a lesser extent NGFI-B and Nor-1 in JEG-3 cells but it is not known if it directly interacts with NR4A AF2 (Castro et al., 1999).

Other coactivators

CAMKIV enhances NGFI-B transcriptional activity on NBRE and NurRE reporters in CV-1 cells but whether it phosphorylates NGFI-B or not remains unknown. ASC-2 alone does not affect NGFI-B transcriptional activity in CV-1 cells but when coexpressed with CAMKIV, which stimulates the ASC-2 autonomous activation function, they synergistically enhance NGFI-B transactivation (Sohn et al., 2001).

The coactivator PGC-1α interacts with full-length Nurr1 and enhances Nurr1 activation of a luciferase reporter gene driven by a fragment of the osteocalcin promoter as well as a NBRE reporter in osteoblasts (Nervina et al., 2006).

Compounds as NR4A agonists

The octaketide cytosporone B isolated from the endophytic fungus *Dothiorella sp*. HTF3 binds to the Tyr453 on the surface of the NGFI-B LBD via a hydrogen bond as revealed by fluorescence quenching and molecular modeling and enhances NGFI-B transcriptional activity on a NurRE reporter in gastric cancer cells and *in vivo* in liver lysates of wt but not NGFI-B knockout mice (Zhan et al., 2008).

Isoxazolopyridinone-7e (Hintermann et al., 2007) and 3 benzimidazole compounds (Dubois et al., 2006) activate a NBRE reporter in Nurr1 over-expressing MN9D cells. Their mechanism of action is unknown.

DIM-C-pPhCl activates GAL4-NGFI-B LBD and GAL4-Nurr1 LBD constructs in pancreatic cancer cells and bladder cancer cells respectively (Chintharlapalli et al., 2005, Inamoto et al., 2008).

The compound TEMPO and 4 other small-molecule compounds were identified as Nurr1 LBD-binding molecules by NMR screening. A residue-specific labeling strategy revealed that TEMPO binds to a small space between H4, H11 and H12 of the Nurr1 LBD (Poppe et al., 2007).

PGA1 and PGA2 activate GAL4-NOR-1 constructs in a mammalian two-hybrid assay and bind directly to Nor-1 LBD in a Biacore S51 binding assay (Kagaya et al., 2005).

The antimetabolite 6-MP enhances Nurr1 and Nor-1 transcriptional activity assayed on NBRE and POMC promoter reporters in an AF1-dependent way (Ordentlich et al., 2003, Wansa et al., 2003).

6.6 Repression of NR4A receptor-mediated transcription

AF1 corepressors

CRIF1 interacts with the N-terminus of NGFI-B in a yeast two-hybrid system and coimmunoprecipitates with NGFI-B in foreskin fiboblasts. It represses basal, SRC-2-mediated and PKA-mediated transactivation of NGFI-B in C2C12 cells and the NGFI-B-induced expression of its target E2F1 in HEK293 cells. Silencing of CRIF1 by siRNA relieves repression but its repressor activity is not affected by the HDAC inhibitor trichostatin suggesting that it possesses intrinsic repressor activity (Park et al., 2005).

PARP-1 interarcts with the N-terminal domain of Nor-1 in HEK293 cells and acts as a transcriptional repressor for Nor-1 and Nurr1 (but not NGFI-B) on NurRE but not NBRE reporters. The poly(ADP-ribosyl)ation enzymatic activity of PELP1 is not required for the repression of Nurr1 and Nor-1 activity (Ohkura et al., 2008).

The atypical NR SHP that lacks a DBD interacts with NGFI-B *in vitro* and *in vivo* on the CYP17 promoter and inhibits AF1-mediated transactivation on NBRE and CYP17 promoter reporters in CV-1 cells and hepatoma cells by competing with NGFI-B for binding to CBP. Over-expression of SHP in the hepatoma cell line SNU354 renders it resistant to anti-Fas antibody/IFNγ-induced apoptosis probably via inhibition of the pro-apoptotic action of NGFI-B. SHP can also repress the activity of Nurr1 and Nor-1 in CV-1 cells (Yeo et al., 2005).

GR has been shown to repress NR4A transcriptional activity at the POMC promoter in adrenocortical cells and the StAR promoter in Leydig cells as well as on NurRE reporters (REF). However, in PC12 cells, GR was shown to interact directly with the N-terminus of Nurr1 and to potentiate Nurr1-induced transcription from NurRE and NBRE reporters (Carpentier et al., 2008). Interestingly, Nurr1 and GR colocalize in the SN and the hippocampus (Carpentier et al., 2008) and GR has been shown to be involved, like Nurr1, in memory consolifation in the hippocampus (Oitzl and de Kloet, 1992), in the regulation of dopamine neuron physiology by facilitating dopamine release (Piazza et al., 1996) and in dopamine neuron protection from MPTP- or LPS-induced toxicity (Castano et al., 2002).

AF2 corepressors

The LBD of the atypical NR DAX-1 that lacks the classical DBD domain interacts with the AF2 of NGFI-B and inhibits NGFI-B transactivation on NBRE and P450c17 promoter

reporters in CV-1 cells and Leydig cells respectively by competing with NGFI-B for binding to SRC-1 and thus titrating away SRC-1 from NGFI-B AF-1. DAX-1 can also repress the activity of Nurr1 and Nor-1 in CV-1 cells (Song et al., 2004).

The p65 subunit of NFκB interacts with the AF2 of NGFI-B in Leydig cells *in vitro* and *in vivo* on the promoter of P450c17. p65 represses NGFI-B transactivation on P450c17, StAR and HSD3B promoter reporters in Leydig cells and exerts its effect by competing with NGFI-B for the AF1 coactivator SRC-1 (Hong et al., 2004).

SMRT interacts *in vitro* with NGFI-B LBD in Leydig cells (Song et al., 2002) and in a yeast two-hybrid screen (Sohn et al., 2001). It represses NGFI-B activity on a NurRE reporter in CV-1 cells (Sohn et al., 2001). SMRT does not decrease Nurr1 activity on a NBRE reporter but it decreases the dexanethasone-induced activity of GR-Nurr1 complexes on the same promoter (Carpentier et al., 2008). NGFI-B also interacts with the corepressor SMRT upon treatment with forskolin as shown by immunoprecipitation experiments (Kelly et al., 2005). Nurr1 LBD interacts with peptides derived from SMRT and NcoR in pull-down, fluorescence quenching and NMR binding assays (Codina et al., 2004). A weak interaction between the N-terminal of the Nurr1 LBD and SMRT and NcoR has been reported in HEK293 cells. In Nurr1-RXR heterodimers, RXR is mainly the partner that interacts with SMRT and NcoR and releases them in response to RXR ligand (Lammi et al., 2008).

In E14.5 mouse midbrain dopaminergic neurons, Nurr1 interacts with the corepressors PSF, Sin3a and SMRT that recruit HDACs and repress Nurr1 transcriptional activity. Pitx3 decreases the interaction of Nurr1 with SMRT since the Nurr1-SMRT interaction is increased in E14.5 midbrain dopaminergic neurons derived from Pitx3 knockout mice. Treatment of E14.5 midbrain dopaminergic neurons with the HDAC inhibitor sodium butyrate restores the expression of Nurr1 target genes in Pitx3 knockout embryos, bypassing the necessity for Pitx3-mediated release of Nurr1 from SMRT-mediated repression (Jacobs et al., 2009b).

Other corepressors

Nurr1 associates with corepressors complexes consisting of Lef-1, CtBP, TLE-1, HDAC-1, HDAC-3 and PIASγ in the absence of β-catenin in 293F cells (Kitagawa et al., 2007).

The corepressor PELP1 interacts with NGFI-B in NIH 3T3 cells and represses its transcriptional activity. The N-terminal Leu-rich domain of PELP1 interacts with HDAC2 while its C-terminal Glu-rich domain binds hypo-acetylated histones 3 and 4 and prevents them from becoming substrates of HAT (Choi et al., 2004).

Neurogenins 1 and 2 and NeuroD repress Nurr1 transcriptional activity on a NBRE and a TH promoter reporter and Nurr1-induced expression of TH, VMAT, AADC and DAT in rat neuronal precursor cells (Park et al., 2006b).

NR4A and NR3B (ERR) receptors mutually repress each others' transcriptional activity as shown in osteosarcoma and cervical cancer cells. This repression was seen on reporters with NR4A or NR3B binding sites and on the osteopontin promoter and does not involve competition for DNA binding. The AFs of NR4A and NR3B receptors are dispensable for the cross-talk while their DBDs and heterodimerization interfaces must be intact (Lammi et al., 2004, Lammi et al., 2007).

Nurr1 docked to NFκB p65 on the promoters of pro-inflammatory genes in microglia and astrocyte cells interacts with the corepressor coREST directly via its DBD to mediate transrepression of pro-inflammatory gene expression. The histone methyltransferase G9a, LSD1 and HDAC1 were also shown to be required for Nurr1-coREST-mediated repression (Saijo et al., 2009). Knockdown of NLK, a kinase that phosphorylates Nurr1 *in vitro* reduces the interaction between Nurr1 and coREST and abolishes Nurr1 repression of iNOS in BV2 microglia cells (Saijo et al., 2009).

A constitutively active derivative of Ret significantly represses AF2-mediated Nurr1 activity on a NBRE reporter in HEK293 cells. Ret signaling results in the destabilization of the active conformation of Nurr1 LBD as shown by an assembly assay and the inhibitory effect of Ret is dependent on MAPK activation (Wang et al., 2003b).

6.7 Other ways to modulate NR4A receptor activity

Phosphorylation

Two-dimensional gel electrophoresis reveals that Nurr1 is likely a phosphoprotein (Nordzell et al., 2004). A Consensus site for MAPK exists in Nurr1 AF1 and is also conserved in NGFI-B and Nor-1. Mutation of the site or MAPK inhibition dramatically decreases the activity of a GAL4-AF1 Nurr1 construct in JEG-3 cells (Nordzell et al., 2004).

Dopamine D2 receptor activation in mesencephalic neuronal cell cultures results in ERK-mediated increase of Nurr1 expression and transcriptional activity (Kim et al., 2006a). A Nurr1 mutant that cannot be phosphorylated by ERK2 at Ser126 and Ser132 cannot increase rat TH promoter activity in response to ERK2 activation (Zhang et al., 2007, Jacobsen et al., 2008). ERK2 and ERK5 have been shown to interact with Nurr1 in CDM14.1 cells of mesencephalic origin and to increase its transcriptional activity in PC12 cells. ERK5 seems to activate Nurr1 via phosphorylation at Thr168 and/or Ser177 (Sacchetti et al., 2006).

LIMK1 has been shown to interact with Nurr1 in CDM14.1 cells of mesencephalic origin and to decrease its transcriptional activity in PC12 cells. However, it has not been shown if Nurr1 is a phosphorylation substrate for LIMK1 (Sacchetti et al., 2006).

NGFI-B is rapidly phosphorylated in PC12 cells and migrates on SDS-PAGE gels as multiple bands that coalesce into a single band when treated with alkaline phosphatase. EGF, TPA and A31287 stimulate the synthesis of under-phosphorylated, predominantly

nuclear NGFI-B, while FGF2 and NGF stimulate the synthesis of highly phosphorylated NGFI-B, present in the cytoplasm and the nucleus in equal amounts (Fahrner et al., 1990). NGFI-B is phosphorylated, primarily in the N-terminal domain (Davis et al., 1993).

SUMOylation

The SYMO-E3 ubiquitin protein isopeptide ligase PIASγ was found to interact with Nurr1 LBD in a yeast two-hybrid screen and in coimmunoprecipitation and GST pull-down assays in COS-7 cells. PIASγ represses Nurr1 transcriptional activity on a NBRE reporter in HEK293 cells and on a TH promoter reporter in PC12 cells and this repression does not require 2 of the SUMO sites (Lys91 and Lys577) found in Nurr1. PIASγ and Nurr1 colocalize in transfected COS-7 cells in vitro and in neurons in the SN and forebrain areas *in vivo* (Galleguillos et al., 2004). Recently, it was shown that Nurr1 can be SUMOylated with SUMO2 and SUMO3 using PIASγ as an E3 ligase (Saijo et al., 2009). The substitution of Lys91 by Arg enhances the transcriptional activity of Nurr1 in HEK293 cells, whereas the substitution of Lys577 by Arg decreases the transcriptional activity of Nurr1 (Galleguillos et al., 2004). 2 other SUMO sites have been identified (Lys558 and Lys576) and were shown to be essential for transrepression of inflammatory genes in microglia by Nurr1 (Saijo et al., 2009). Knockdown of Ubc9, an essential E2 enzyme for SUMOylation reverses Nurr1-mediated transrepression of iNOS in microglia (Saijo et al., 2009).

Protein levels

Proteins/events affecting the stability of NR4A proteins have an indirect effect on their transcriptional activity.

JNK phosphorylation of NGFI-B at Ser95 induces degradation of the protein in gastric cancer cells and HEK293 cells (Liu et al., 2007).

Akt activity was recently shown to be required for NGFI-B ubiquitination and degradation. FAIM knockout thymocytes exhibit defective TCR-induced activation of Akt, reduced ubiquitination and degradation of NGFI-B protein and enhanced NGFI-B protein levels (Huo et al., 2010).

The catalytic domain of the Arg methyltransferase PRMT1 interacts with NGFI-B LBD and delays NGFI-B degradation thus enhancing its transactivation activity (Lei et al., 2009). NGFI-B binding in its turn inhibits the PRMT1 methyltransferase activity *in vitro* in HEK293 cells and *in vivo* since NGFI-B knockout mice show increased PRMT1 methyltransferase activity assayed by asymmetric dimethylation of Arg3 on histone 4. The NGFI-B agonist cytosporone B enhances NGFI-B-PRMT1 interaction and inhibits PRMT enzymatic activity (Lei et al., 2009).

Nurr1 degradation in neural precursor cells is mediated via the ubiquitine/proteasome and is activated by Nurr1 phosphorylation via Akt at Ser347 and repressed by FGF treatment (Jo et al., 2009).

Cellular localization

The shuttling of NR4A receptors between the nucleus and the cytoplasm controls their relative concentration in the nucleus and thus their transcriptional activity.

DNA binding regulation

The DNA-binding activity of NR4A receptors is mainly modulated by phosphorylation and has a direct impact on their transcriptional activity.

7 The immediate early aspect of NR4A receptors

The NR4A subfamily is the only one within the NR family that is encoded by immediate early genes, whose expression is activated rapidly and transiently. An extremely wide repertoire of substances/conditions induces the expression of the NR4A receptors in an immediate early way in a variety of contexts, both *in vivo* and *in vitro*.

Table 1: Factors inducing NR4A expression.

Factors inducing NR4A expression	**Example References**
Stress conditions	
Ischemia	(Tang et al., 2002) (Roth et al., 2003) (Lu et al., 2004) (Johansson et al., 2000) (Kury et al., 2004) (Lin et al., 1996) (Honkaniemi et al., 1997) (Gubits et al., 1993) (Kim et al., 2006b) (Neumann-Haefelin et al., 1994) (Ohkubo et al., 2002)
Hypoxia	(Choi et al., 2004a, Yoo et al., 2004, Huang et al., 2008) (Martorell et al., 2009)
Seizures	(French et al., 2001) (Jung et al., 1998) (Crispino et al., 1998) (Honkaniemi and Sharp, 1999) (Lemberger et al., 2008) (Pena de Ortiz and Jamieson, 1996) (Watson and Milbrandt, 1989) (Ponnio and Conneely, 2004)
Trauma	(Honkaniemi et al., 1995) (Giza et al., 2002) (Jacobs et al., 1994) (Giza et al., 2002) (Dragunow et al., 1996) (Nathans et al., 1988, Scearce et al., 1993) (Landesberg et al., 2001) (Chan et al., 1993, Brown and Sawchenko, 1997)
Endogenous substances	
Inflammatory cytokines	Chapter A3.4
Neurotransmitters	(Arenander et al., 1989) (Gervais et al., 1999) (Dragunow et al., 1996, von der Kammer et al., 1999, von der Kammer et al., 2001)

Prostaglandins	(Moldovan et al., 2009) (Murphy et al., 2001, McEvoy et al., 2002b) (O'Kane et al., 2008) (Holla et al., 2006) (Liang et al., 2004) (Stocco et al., 2000, Stocco et al., 2002)
Calcium	(Enslen and Soderling, 1994, Klopotowska et al., 2005) (Uemura and Chang, 1998, Li et al., 2000) (Watanabe et al., 2001) (Garcia et al., 1994, Liu et al., 1994, Ivanov and Nikolic-Zugic, 1997) (Fahrner et al., 1990) (Okabe et al., 1995) (Torii et al., 1999) (Ohkubo et al., 2000)
Growth factors	(Kendall et al., 1994) (Fahrner et al., 1990, Yoon and Lau, 1993, Bandoh et al., 1995, Katagiri et al., 1997, Cosgaya et al., 1998b, Swanson et al., 1999, Maruoka et al., 2010) (Lammi and Aarnisalo, 2008) (Ryseck et al., 1989, Williams and Lau, 1993) (Lim et al., 1995) (Fahrner et al., 1990) (McEvoy et al., 2002b) (O'Kane et al., 2008)
Fatty Acids	(Roche et al., 1999) (Garcia et al., 1994) (Navarro et al., 2010)
Peptide hormones	(Day et al., 1994, Tetradis et al., 2001a, Tetradis et al., 2001b, Pirih et al., 2003, Pirih et al., 2005, Zierold et al., 2007, Catania et al., 2010)
cAMP	(Bondy, 1991) (Martin and Tremblay, 2005, Inaoka et al., 2008, Martin et al., 2008, Martin et al., 2009) (Kiss et al., 2006) (Chao et al., 2008) (Kovalovsky et al., 2002) (Klopotowska et al., 2005) (Davis and Lau, 1994, Kelly et al., 2004, 2005) (Satoh and Kuroda, 2002) (Pei et al., 2006b)
Exogenous substances	
Addictive substances	(Torres et al., 1996) (Werme et al., 2000a) (Ichino et al., 2002) (Schochet et al., 2005, Schiltz et al., 2007) (Schochet et al., 2005) (Akiyama et al., 2008) (Backman and Morales, 2002, Gonzalez-Nicolini and McGinty, 2002) (Raatesalmi et al., 2002) (Rivier and Lee, 1996, Rivier et al., 1996, Ogilvie et al., 1997, Ogilvie et al., 1998)
Serum	(Yu et al., 1993) (Cosgaya et al., 1998a) (Ryseck et al., 1989, Nakai et al., 1990) (Bondy, 1991) (Kolluri et al., 2003) (Martinez-Gonzalez et al., 2003)
Antipsychotics	(Werme et al., 2000b, Maheux et al., 2005, Bruins Slot et al., 2009)
Phtalate esters	(Ohno et al., 2009) (Noda et al., 2007)
Phorbol esters	(Williams and Lau, 1993) (Bandoh et al., 1995) (Fernandez et al., 2000) (Bondy, 1991) (Liu et al., 2002, Wu et al., 2002)

Toxins	(Kinser et al., 2004) (Kiss et al., 2006)
Viral proteins	(Chen et al., 1997b, Chen et al., 1998, Liu et al., 1999, Lee et al., 2001)
Physical stimuli	
Electrical stimulation	(Sheng et al., 1993) (Kawasaki et al., 2009) (Rivest and Rivier, 1994, Lee and Rivier, 1998)
Magnetic fields	(Miyakoshi et al., 1998)
Mechanical agitation	(Bandoh et al., 1997b)
Cold exposure	(Kanzleiter et al., 2005, Au et al., 2008)
Osmotic stimulation	(Luckman, 1995) (Luckman, 1997) (Kawasaki et al., 2005) (Chan et al., 1993)
Membrane depolarization	(Volpicelli et al., 2004, Volpicelli et al., 2007) (Pena de Ortiz and Jamieson, 1996) (Yoon and Lau, 1993, Katagiri et al., 1997, Lam et al., 2010) (Tian et al., 2010)

8 NR4A receptors in the CNS

As revealed by a number of studies, NR4A receptors show a complex expression pattern in the mammalian CNS (Watson and Milbrandt, 1990, Saucedo-Cardenas and Conneely, 1996, Xiao et al., 1996, Zetterstrom et al., 1996a, Zetterstrom et al., 1996b, Bandoh et al., 1997a, Maruyama et al., 1997, Li et al., 2009b, Luo et al., 2009).

8.1 Nurr1 in the dopaminergic system

Dopamine-mediated neurotransmission is important for the control of motor and reward behaviour, learning, cognition and hormone production. Clinical evidence suggests that dopaminergic pathways are involved in neurological and psychiatric disorders. For example, degeneration of neurons in the SN and subsequent depletion of striatal dopamine results in Parkinson's disease (PD), a disease characterized by rigidity, bradykinesia, tremurs and postural instability (Bernheimer et al., 1973).

In the adult mouse brain, the majority of TH+ neurons in the SN, the VTA, the retrorubral field, the olfactory bulb, the linear nucleus raphe and the central grey express Nurr1. Only a few of the dopaminergic cells of the PVN are double positive for Nurr1 and TH, while TH+ neurons in the arcuate nucleus zona incerta do not express Nurr1 (Backman et al., 1999). In the rat ventral mesencephalon, Nurr1 shows a sharp peak between E13 and E15 when most dopaminergic neurons differentiate (Volpicelli et al., 2004). Nurr1 expression in human SN decreases with age and this decrease correlates with a decrease in TH expression (Chu et al., 2002). Nurr1 is also expressed in TH+ neurons intrinsic to the human striatum (Cossette et al., 2004).

8.2 Nurr1 and dopamine neuron differentiation

In the midbrain of Nurr1 heterozygote mice, the range of TH+ neurons is normal (Le et al., 1999a). However, the absence of dopaminergic neurons in the SN and the VTA area of the midbrain in Nurr1 knockout mice revealed the importance for Nurr1 in the differentiation of midbrain dopaminergic cells (Zetterstrom et al., 1997, Baffi et al., 1999, Le et al., 1999b).

The normal early dopamine neuron differentiation and normal expression of genes detected in developing dopamine cells, such as En-1 and Pitx3 suggest that Nurr1 in involved in the differentiation of midbrain dopaminergic cell progenitors that degenerate in its absence (Saucedo-Cardenas et al., 1998, Wallen et al., 1999, Witta et al., 2000). In the dopaminergic cell line MN9D, Nurr1 induces cell cycle arrest and morphological differentiation (Castro et al., 2001).

The over-expression of Nurr1, alone or with other transcription factors, in the presence of the absence of extrinsic signals, has been used as a tool to drive stem cell/precursor cells towards a dopaminergic fate. These attempts are of therapeutic interest since dopaminergic cells generated *in vitro* could be grafted to Parkinson's patients to relieve/reverse the symptoms of the disease.

8.3 Nurr1 and dopamine neuron maintenance

Ablation of Nurr1 at late stages of midbrain dopamine neuron development by crossing with mice carrying Cre under control of the DAT locus or in the adult brain by transduction of AAV encoding Cre results in loss of midbrain dopamine neuron markers, neurodegeneration and loss of striatal dopamine, suggesting that Nurr1 is required for the maintenance of maturing and adult midbrain dopamine neurons (Kadkhodaei et al., 2009).

Moreover, a decreased number of dopaminergic neurons has been reported in the striatum of old (older than 15 months) Nurr1 heterozygote mice (Jiang et al., 2005a).

8.4 Nurr1 and dopamine neuron protection

Findings in Nurr1 heterozygote mice suggest that Nurr1 might have a neuroprotective role in dopamine cells. Mesencephalic dopamine neurons from Nurr1 heterozygote mice show increased vulnerability to the selective dopaminergic neurotoxin MPTP *in vivo* (Le et al., 1999a) and to the proteasome inhibitor lactacystin *in vivo* (Pan et al., 2008). Human neuroblastoma cells where Nurr1 expression is silenced by siRNA show increased death in response to lactacystin *in vitro* (Pan et al., 2008). Moreover, striatal dopaminergic neurons from Nurr1 heterozygote mice show increased expression of NOS and α-synuclein, increased protein nitrosylation and increased apoptosis (Imam et al., 2005). However, adenovirus-mediated ectopic expression of Nurr1 in rats does not protect nigrostriatal dopamine cells from 6-OHDA-induced neurodegeneration (Hurtado-Lorenzo et al., 2004).

Moreover, dopaminergic neurons derived from stem cells over-expressing a degradation-resistant variant of Nurr1 show increased survival after hydrogen peroxide or 6-OHDA treatment and after transplantation (Jo et al., 2009).

Importantly, it has been shown that RXR ligands increase the number of surviving rat primary dopaminergic neurons and mouse ES cell-derived dopaminergic neurons by a process mediated by Nurr1-RXR heterodimers and also protect them from hypoxia- and 6-OHDA-induced cell death (Wallen-Mackenzie et al., 2003, Friling et al., 2009).

Finally, Nurr1 is part of an anti-inflammatory pathway in astrocytes and microglia that has been shown to protect dopaminergic neurons from inflammation-induced death (chapter A3.4).

8.5 NR4A receptors and neuronal plasticity, spatial discrimination and memory

Plasticity occurs at the synapse where it takes the form of activity-dependent changes in the efficacy of synaptic transmission. It is an important property of neuronal cells that underlies learning and memory processes (Shatz, 1990, Hevroni et al., 1998).

Nurr1 expression is elevated in the CA1 and the CA3 region of the hippocampus during spatial discrimination learning (food search task) in rats, suggesting that Nurr1 might be involved in long-term information storage in the hippocampus (Pena de Ortiz et al., 2000). Decrease in Nurr1 expression in the rat hippocampus induced by chronic lithium treatment or by infusion of antisense oligodeoxynucleotides impairs spatial discrimination (Al Banchaabouchi et al., 2004, Colon-Cesario et al., 2006). Antisense-mediated knockdown of Nurr1 results in long-lasting cognitive dysfunction, since antisense-treated rats subjected to reversal training 3 days after the initial training are fixated with the previously learned pattern and are impaired in the extinction of acquired spatial preferences and in future learning (Colon-Cesario et al., 2006).

NGFI-B is induced in the CA1 area of the hippocampus during consolidation but not reconsolidation of contextual fear conditioning. Consolidation is the process of stabilization of a memory for long-term storage while reconsolidation is a second consolidation process induced by memory reactivation (von Hertzen and Giese, 2005).

NGFI-B and Nurr1 are expressed in granule cell and glomerular layers of the olfactory bulb. Down-regulation of their expression by olfactory odor deprivation suggests that they might play a role in neuronal plasticity in the olfactory system (Liu and Baker, 1999).

NGFI-B is down-regulated in monkey primary visual cortex by monocular enucleation during the visual critical period, suggesting that it might be involved in activity-dependent visual cortical neuroplasticity (Lachance and Chaudhuri, 2004).

NGFI-B is induced via mAChRs, which are involved in higher cognitive functions including synaptic plasticity and memory (Dragunow et al., 1996, von der Kammer et al., 1999, von der Kammer et al., 2001).

Enhanced synaptic activity is the hallmark of neuronal plasticity. Treatment of cortical and hippocampal primary neurons with the GABA receptor antagonists bicucculine or gabazine that cause excitatory neurons to fire synchronous bursts of action potential and thus enhance synaptic activity induces NR4A expression (Xiang et al., 2007, Zhang et al., 2009a, Pegoraro et al., 2010). NGFI-B is also induced in hippocampal neurons *in vivo* after activation of NMDA receptors (Dragunow et al., 1996).

8.6 Retina differentiation

NGFI-B might play a role during the postmitotic differentiation of neuronal cells in the retina (Li et al., 2009b), while Nurr1 plays an essential role in the specification of a subset of GABAergic amacrine cells in the retina. More specifically, Nurr1 is expressed in a subset of postmitotic GABAergic amacrine cells and their precursors during mouse retinogenesis. Its targeted inactivation results in the loss of a subpopulation of GABAergic amacrine cells while its over-expression promotes GABAergic amacrine cell differentiation. Finally, Nurr1 expression is positively regulated by Foxn4 and negatively by Brn3b, two retinogenic factors previously shown to promote and suppress GABAergic amacrine cell differentiation respectively (Jiang and Xiang, 2009).

8.7 Forebrain

Nor-1 might be involved in molecular mechanisms blocking neural differentiation of forebrain cells, since delivery of Nor-1 antisense oligonucleotides to cultured forebrain cells induces migration and neurite extension (Ohkura et al., 1996).

Nurr1 plays a role in the establishment and maintenance of normal corticortical circuitry and function in the rat since it is expressed in developing and mature glutamatergic-excitatory neurons that contribute to long-range intra-hemispheric corticortical projections (Arimatsu et al., 2003).

Nurr1 over-expression can promote differentiation of rat cortical neuronal precursors towards neurons at the expense of astrocytic differentiation. Coculture experiments reveal that Nurr1 exerts its neurogenic role via an extrinsic paracrine mechanism. Nurr1-transduced neuronal precursor cells show increased mRNA levels of the neurotrophic factors BDNF, GDNF and neurotrophins-3 and -4/5 and decreased mRNA levels of the astrocyte differentiation factors LIF and CNTF (Bae et al., 2009). NGFI-B has been shown to bind to a NBRE at the fifth intron of the CNTFα receptor and induce the enhancer activity of this element (Mu et al., 1998).

8.8 NR4A receptors in other areas of the brain

NGFI-B in the striatum is expressed in pre-proenkephalin- and prodynorphin-positive neurons, suggesting that it might play a role in the function of striatal opiate-peptide neurons (Backman et al., 2001).

Nurr1 is induced in lateral amygdala after establishment of conditioned taste aversion in rats, suggesting that it might be implicated in the acquisition of associative aversive experiences (Ge et al., 2003).

Nurr1 might be involved in axon guidance in the DMN by controlling the expression of the semaphoring coreceptor Nrp1 in this region (Hermanson et al., 2006). A subtle disorganization of the fibers derived from the DMN and reduced Ret expression at the DMN have been observed in E13.5 and E16.5 Nurr1 knockout animals (Wallen et al., 2001).

Nurr1 is implicated in the development of habenula, a dorsal diencephalic structure that forms a link between the limbic forebrain and the ventral midbrain. It is coexpressed with Brn3a in the developing habenula, it is downstream Brn3a and it mediates the expression of a subset of Brn3-regulated transcripts (Etv1, Plch2, Kcnma1, Gpr151), which are down-regulated in the habenula of Nurr1 knockout mice (Quina et al., 2009).

In the pituitary, CRH induces NGFI-B and Nurr1 expression and binding to the NurRE site in the POMC promoter and subsequent POMC transcription (Murphy and Conneely, 1997, Philips et al., 1997a, Maira et al., 1999, Kovalovsky et al., 2002, Maira et al., 2003b).

9 NR4A receptors in neuroprotection

NR4A receptors are induced under conditions of neuronal stress, such as seizures, ischemia, trauma and hypoxia (chapter A7). It is tempting to consider the possibility that they are mediating survival or, on the contrary, cell death pathways in neurons under stressful conditions. *In vitro* and *in vivo* data suggest that NR4A receptor expression/induction is neuroprotective.

NGFI-B protects hippocampal neurons in culture from staurosporine- and growth factor removal-induced toxicity and inhibits significantly the NMDA-induced break-down of their mitochondrial membrane potential NGFI-B also protects hippocampal neurons from KA-induced toxicity *in vivo* (Zhang et al., 2009a).

Moreover, the NR4A receptors are induced during ischemic preconditioning (Honkaniemi et al., 1995, Carmel et al., 2004, Kawahara et al., 2004, Yakubov et al., 2004, Kamphuis et al., 2007), a protective mechanism whereby the application of a potentially harmful insult below the threshold for producing permanent neuronal injury can render neurons less vulnerable to subsequent ischemic injury (Pignataro et al., 2009).

Furthermore, the fact that reduction in Nurr1 expression is involved in PD initiation/progression/severity (chapter A8) and that Nurr1 expression is down-regulated in SN neurons with neurofibrillary tangles in patients with AD (Chu et al., 2006) suggests that the expression of Nurr1 might be neuroprotective since its loss is associated with neurodegenerative diseases.

9.1 Neuronal activity-dependent neuroprotection

Synaptic activity induces NR4A expression, probably via CREB. Treatment of cortical and hippocampal primary neurons in culture with the GABA receptor antagonists bicucculine or gabazine that cause excitatory neurons to fire synchronous bursts of action potential and thus enhance synaptic activity induces NR4A expression (Xiang et al., 2007, Zhang et al., 2009a, Pegoraro et al., 2010). NGFI-B is also induced *in vivo* by survival-promoting enhanced synaptic activity caused by exposure of rats to enriched environment (Dahlqvist et al., 2003) or by pharmacological activation of NMDA receptors (Dragunow et al., 1996).

Synaptic NMDA receptor activation results in calcium influx that mediates prosurvival events (Chuang et al., 1992, Damschroder-Williams et al., 1995, Mabuchi et al., 2001, Jiang et al., 2005b, Soriano et al., 2006, Valera et al., 2008). Stimulating synaptic activity *in vivo* by exposing rats to an enriched environment reduces spontaneous apoptotic cell death in the hippocampus and protects against neurotoxic injuries (Young et al., 1999). On the contrary, blockade of NMDA receptors *in vivo* causes widespread apoptosis in the developing and the adult CNS (Ikonomidou et al., 2000, Olney et al., 2002, Adams et al., 2004).

B. RESULTS AND DISCUSSION

1 Paper I: The coactivator-binding site of Nurr1

1.1 Identification of the Nurr1 coactivator-binding site

As discussed in detail in chapter A6, NR4A receptors do not recruit coactivators using the classical coactivator-interacting surface. In order to identify the novel coactivator-binding site utilized by Nurr1, we (Paper I) and others have used electrostatic and hydrophobic mapping of the Nurr1 LBD (Flaig et al., 2005) or NMR footprinting (Codina et al., 2004) to search for a non-polar groove suitable for protein-protein interactions. These attempts have led to the identification of a highly hydrophobic groove between H11 and H12 (**Table 2**) that Nurr1 uses to interact with coregulators. The 3 studies have identified almost the same residues (AAs) forming this surface:

Table 2 : Residues forming the Nurr1 coactivator-binding site.

Residues identified	**Residues mutated**	**Reference**
570, 574, 592, 593, 596, 598	592, 593, 598	(Codina et al., 2004)
567, 571, 574, 577, 578, 592, 593, 596, 598	571, 574, 578, 592, 598	(Flaig et al., 2005)
570, 574, 577, 592, 593, 596, 597, 598	570, 574, 577, 596, 597, 598	Paper I

1.2 Dissection of the novel coactivator-binding site by mutagenesis and NMR

Importantly, AAs 592 and 593 that were identified in all 3 studies are crucial for AF2 activity, since their substitution abolishes Nurr1 AF2 activity (Castro et al., 1999).

Ala substitutions of the AAs identified in our study (Paper I) resulted in abolishment of the activity of GAL4-Nurr1 LBD constructs in HEK293 cells, with the exception of Leu570Ala mutant that showed only reduced activity and the Lys577Ala mutant that showed increased activity. The same effects but in a much smaller scale, are seen in the context of the full-length Nurr1, because of the background AF1 activity.

Substitution of AAs 571, 574 or 592 results in dramatic reduction of GAL4-Nurr1 LBD activity in COS-1 cells, while mutation of Leu578 almost halvates activity and mutation of Phe598 reduces activity only slightly (Flaig et al., 2005).

Substitution of AAs 592, 593 or 598 decreases the interaction of Nurr1 LBD with a NcoR-derived peptide as shown in pull-down assays and in NMR footprinting experiments (Codina et al., 2004).

1.3 Coactivator binding and RXR heterodimerization

This novel coactivator-binding site lies in the proximity of the surface that Nurr1 uses for dimerization with RXR (Aarnisalo et al., 2002, Sacchetti et al., 2002) suggesting that mutations affecting Nurr1 monomer activity might affect the ability of Nurr1 to heterodimerize with RXR. Indeed, all GAL4-Nurr1 derivatives with reduced activity show a significantly reduced transcriptional activity after treatment with the RXR ligand SR11237 in HEK293 cells but RXR over-expression partially rescues the reduced RXR ligand-induced activation suggesting that the mutations reduce but not totally abolish RXR dimerization capacity (Paper I). Reduced, but not abolished Nurr1-RXR heterodimer formation upon mutation in the coactivator binding site was also observed by (Flaig et al., 2005) in COS-1 cells upon treatment with the RXR ligand BMS649 and over-expression of VP16-RXR.

Mutations in the C-terminus can disrupt heterodimerization with RXR without affecting Nurr1 monomeric activity but some of them increase the ability of Nurr1 to activate as a monomer (Aarnisalo et al., 2002). This observation, together with our findings that mutations affecting Nurr1 monomeric activity destabilize Nurr1-RXR heterodimerization suggest that RXR and a Nurr1-specific cofactor interact with distinct but overlapping surfaces on Nurr1. This could explain why RXR over-expression results in diminished Nurr1 monomeric activity (Aarnisalo et al., 2002) and why Nurr1 monomeric activity is very low in JEG-3 cells. JEG-3 cells presumably express high levels of RXR since they show very efficient Nurr1-RXR activation in response to RXR ligand (own data).

1.4 Identification of a hyperactive Nurr1 mutant

Substitution of Lys577 with an Ala dramatically increased Nurr1 AF2 activity, both in HEK293 cells and in JEG-3 cells, where Nurr1 LBD is normally almost inactive (Castro et al., 1999), while substitution with an Arg resulted in decreased activity (Paper I). The increased transcriptional activity might be explained by abolishement of interaction with a corepressor but we were unable to show direct interaction of the corepressors NcoR or SMRT with Nurr1 LBD in pull-down assays. However, Nurr1 LBD was shown to interact with SMRT-derived short peptides (Codina et al., 2004) and SMRT and Nurr1 were found to interact in primary midbrain dopaminergic neurons (Jacobs et al., 2009). Moreover, a weak interaction between Nurr1 LBD and SMRT and NcoR has been reported in HEK293 cells (Lammi et al., 2008). It is still possible that another corepressor interacts with wt Nurr1 but not the Lys577Ala mutant, or even that wt Nurr1 cannot strongly interact with a coactivator that is recruited more efficiniently by the Lys577Ala mutant. Finally, Lys577 may be post-translationally modificated in a way that influences Nurr1 activity. Interestingly, it has been shown that Nurr1 can interact with be the SYMO-E3 ubiquitin protein isopeptide ligase PIASγ (Galleguillos et al., 2004) and that it can be SUMOylated with SUMO2 and SUMO3 using PIASγ as an E3 ligase (Saijo et al., 2009). Lys577 is part of a SUMO site and its substitution by Arg, which cannot be SUMOylated decreases the transcriptional activity of Nurr1 (Galleguillos et al., 2004). However, since mutation of Lys577 to Ala, which also cannot be SUMOylated strongly increases activity (Paper I), the SUMO state of this residue cannot simply determine Nurr1 transcriptional activity.

1.5 A link between Nurr1 transcriptional activity and Nurr1 protein turnover

We observed that the steady state protein levels of the Lys577Ala mutant were decreased compared to those of wt Nurr1 and by use of a proteasome inhibitor we could show that this decrease seems to be associated with increased proteasome turnover (Paper I). Thus, the increased transcriptional activity of this mutant is associated with increased turnover of its protein. Introduction into the Lys577Ala mutant of a second mutation (Phe598Ala), that we showed before abolishes Nurr1 AF2 activity, also abolishes the activity of the previously hyperactive Lys577Ala mutant and increases its steady state protein levels (Paper I).

Links between increased NR transcriptional activity and increased turnover by the proteasome have been described before for RAR, ER and PR, which after ligand-induced activation are rapidly degraded via the ubiquitin-proteasome pathway (Lonard et al., 2000, Shen et al., 2001, Callige and Richard-Foy, 2006). The targeted degradation of RAR, RXR, ER, TR and VDR is mediated via the ligand-dependent recruitment of Sug-1, a protein belonging to the regulatory subunit of the 26S proteasome (vom Baur et al., 1996) but Sug-1 over-expression did not affect the protein levels or the transcriptional activity of Nurr1 (Paper I: data not shown) suggesting that there must exist an alternative mechanism for degradation of active Nurr1 protein.

1.6 A link between H11-H12 sequence and differential transcriptional activity of NR4A receptors

Finally, we investigated if the 5 AAs in H11 and H12 that are different between NGFI-B and Nor-1 could be responsible for the differential AF2 activity between NGFI-B and Nurr1 (described in chapter A7.2.1). Swapping of the H11-H12 region of Nurr1 into GAL4-NGFIB increases the AF2 activity of NGFI-B by 4-fold in HEK293 cells (Paper I) while the same experiment performed in COS-1 cells results in an only slight increase of the activity of the NGFI-B LBD (Flaig et al., 2005). This slight increase and the fact that we did not see increase of NGFI-B AF2 activity to the levels shown by wt Nurr1 (Paper I) suggest that the LBD body of NGFI-B does not precisely position the swapped H12 of Nurr1 and/or that additional regions outside H11/H12 could play critical roles in AF2 transcriptional activity. Swapping of the H11-H12 region of NGFI-B into Nurr1 reduces the AF2 activity of Nurr1 to NGFI-B levels (Flaig et al., 2005). Residues within H3 have been implicated in the differential H12 positioning of NGFI-B compared to Nurr1 and their subsitution significantly reduces the activity of Nurr1 AF2 (Flaig et al., 2005).

2 Paper II: FABP5 as a NR4A target gene

2.1 FABPs

FABPs are cytoplasmic proteins that bind amphiphilic ligands such as long-chain FAs, bile acids, retinoids and eicosanoids (Glatz and van der Vusse, 1996). 9 different FABP types have been identified, named after the tissue of first isolation (Veerkamp and Maatman, 1995, Glatz and van der Vusse, 1996). They are divided in 3 groups on the basis of their AA sequence identity and their binding abilities. Group I proteins bind FAs and bulky

ligands such as bile salts, cholesterol and haem, group II proteins bind FAs and retinoids and eicosanoids and group III bind solely FAs (Chmurzynska, 2006). FABPs show a highly conserved folding motif consisting of a twisted barrel surrounding a hydrophobic core. The ligand is non-covalently bound inside the cavity and its conformation in the cavity differs among the different FABP types (Banaszak et al., 1994, Thompson et al., 1997).

Functions of FABPs include facilitation of FA influx across the plasma membrane and modulation of the activity of enzymes involved in FA metabolism (Hertzel and Bernlohr, 2000), solubilization and protection of their ligands in aqueous spaces and facilitation of their transport across the cytosol among cellular organelles where FAs exert various functions (Coe and Bernlohr, 1998, Storch and Thumser, 2000). Moreover, FABPs neutralize cytosolic FAs to minimize their toxic effects in the cells by sequestering them to their interior and thus making them unavailable for deleterious interactions with cellular components (Bernlohr et al., 1997). Interestingly, FABPs can indirectly regulate gene expression via delivery of FAs to the nucleus, where they can modify a transcription factor or affect its expression or mRNA stability (Duplus et al., 2000) or bind to a NR and activate it. For example CRABP-II binds RA, translocates to the nucleus and associates directly with RAR and directly delivers RA to it (Dong et al., 1999). FABP4 and FABP5 translocate to the nucleus in response to PPARγ and PPARβ/δ selective ligand respectively, interact with PPARγ or PPARβ/δ respectively and enhance its transcriptional activity (Tan et al., 2002). FABP1 delivers phytanic acid and eicosatetraynoic acid and the hypolipidemic drugs bezafibrate, Wy14 and 643 to PPARα and activates its transcriptional activity (Wolfrum et al., 2001). Finally, FABP5 can bind RA, translocate to the nucleus in response to it and deliver it to PPARβ/δ (Schug et al., 2007).

2.2 Nurr1 modulates FABP5 expression

Over-expression of each of the 3 NR4A receptors in HEK293 cells increases FABP5 mRNA and protein levels (Paper II). However, it is unlikely that NR4A receptors are critical for FABP5 *in vivo*. Firstly, tissues with high levels of FABP5 (Chmurzynska, 2006) and NR4A mRNAs do not correlate and NR4A and FABP5 immunoreactivity in the mouse brain do not colocalize (own data). Moreover, FABP5 expression is not affected in Nurr1 knockout brain (own data). Finally, at the murine FABP5 promoter, binding sites for many different transcription factors (MyoD, E47, AP1, C/EBP, HNF1, MZF1, GATA1), have been found suggesting that factors other than NR4As can control mouse FABP5 expression (Bleck et al., 1998).

We propose instead, that FABP5 could be a downstream NR4A target not during development but in an immediate early context.

2.3 Links between FABP5 and NR4A receptors

NR4A receptors could be inducing FABP5 expression in stress response pathways initiated by brain injury, seizure or inflammation.

Both NR4A receptors (chapter A7) and FABP5 (Owada et al., 1996) are induced in the hippocampus by KA-induced seizures. Moreover, NR4A receptors are induced by brain injury (chapter A7) and FABP5 is up-regulated upon peripheral nerve injury (De Leon et al., 1996, Owada et al., 1997). Finally, NR4A receptors have been shown to be induced by ischemia (chapter A7) and FABP5 was recently shown to be induced in CA1 neurons (Ma et al., 2009) and in the subgranular zone (Boneva et al., 2009) of the hippocampus after ischemia in monkeys.

In the context of inflammation, treatment with LPS induces NR4A (chapter A3.4) and FABP5 (Thomas et al., 2001) expression in macrophages. Moreover, Nurr1 is expressed in high levels in endothelial and epidermal cells of psoriatic skin (chapter A3.4) and FABP5 is dramatically up-regulated in psoriatic tissue (Siegenthaler et al., 1994, Masouye et al., 1996, Coe and Bernlohr, 1998, Thomas et al., 2001). Furthemore, FABP5 knockout mice show protection from development of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, with reduced levels of IFNγ and IL-17 in the CNS tissue (Reynolds et al., 2007, Li et al., 2009a). Interestingly, Nurr1 also has a pro-inflammatory role in multiple sclerosis (chapter A3.4).

Furthermore, NGFI-B and FABP5 are both induced 12 h after FSH treatment in Leydig cells (Abel et al., 2009). NR4A receptors (chapter A7) and FABP5 are induced in PC12 cells after NGF treatment (Liu et al., 2008b). Nurr1 and FABP5 increase neurite extension in MN9D and PC12 cells respectively (Allen et al., 2000, Castro et al., 2001, Liu et al., 2008b) and NGFI-B was recently shown to mediate cAMP-induced neurite outgrowth in PC12 cells (Maruoka et al., 2010). Finally, TPA treatment, known to induce NR4A expression (chapter A7) also induces FABP5 expression in mouse epidermis (Krieg et al., 1988).

2.4 Nurr1 can regulate the human FABP5 promoter

Nurr1 can bind to a NBRE at the human FABP5 promoter and enhance its activity (Paper II). However, the activation of the human FABP5 promoter reporter construct is rather weak (2-fold) since the FABP5 promoter already has a strong basal activity as indicated by the detection of basal FABP5 mRNA and protein levels. Alternatively, additional regulatory regions not included in the cloned promoter may contribute to activation or sequences not included in the fragment may negatively influence basal, but not induced, expression thus decreasing the fold activation by Nurr1. Of course, one should not forget that transiently transfected plasmids are not integrated into the intact genome and are not in a natural chromatin context.

2.5 Nurr1 enhances RA-induced PPARβ/δ signaling

Apart from RAR, RA serves as a ligand for PPARβ/δ (Shaw et al., 2003, Schug et al., 2007). RA is delivered to RAR and PPARβ/δ by CRABP-II and FABP5 respectively and functions through RAR and to trigger apoptosis, differentiatiation or cell cycle arrest in cells with high CRABP-II/FABP5 ratio but it functions through PPARβ/δ in cells with high levels of FABP5 (Schug et al., 2007). Decreasing the ratio of FABP5/CRABP-II in

mammary tissue diverts RA from PPARβ/δ to RAR and suppresses tumor growth, suggesting that the inhibition of FABP5 might be a therapeutic strategy for overcoming tumor RA resistance (Schug et al., 2008).

FABP5 can bind RA, translocate to the nucleus in response to it and enhance RA-induced activation of PPARβ/δ in skin cells, cancer cells and adipocytes (Schug et al., 2007, Schug et al., 2008, Berry and Noy, 2009).

Nurr1 could further enhance the RA-induced activation of PPARβ/δ on a reporter containing PPAR binding sites via the induction of FABP5 expression (Paper II).

Nurr1 could play an indirect pro-survival role since RA activation of PPARβ/δ activates cellular pro-survival pathways in skin or cancer cells (Schug et al., 2007, Schug et al., 2008) and could potentiate the RA-induced suppression of obesity and insulin resistance mediated by FABP5-PPARβ/δ in adipose tissue (Berry and Noy, 2009).

2.6 FABP5 enhances DHA-induced RXR signaling

FABP5 has been shown to bind the polyunsaturated FA DHA (Kingma et al., 1998, Liu et al., 2008b) that is an endogenous ligand for RXR (de Urquiza et al., 2000, Lengqvist et al., 2004).

DHA is highly enriched in the CNS during late gestation and early postnatal development and is essential for neural development and function (Neuringer et al., 1988, Makrides et al., 1995, Salem et al., 2001). DHA deficiency results in impaired spatial learning (Gamoh et al., 1999) and has been associated with depression (Liperoti et al., 2009) and childhood ADHD, dyslexia and autism (Richardson, 2004). It can promote adult hippocampal neurogenesis (Coti Bertrand et al., 2006, Kawakita et al., 2006, Beltz et al., 2007) and it also has effects on metabolism and energy homeostasis and beneficial effects on blood cholesterol levels (Storlien et al., 1998).

As we show in Paper II, over-expression of FABP5 leads to increased DHA activation of GAL4-Nurr1/RXR heterodimers, suggesting that FABP5 can promote DHA-induced RXR signaling. In contrast, FABP5 could not promote RXR signaling induced by LG268, a synthetic RXR ligand that has different structure from the FAs that can bind to FABP5. Treatment of JEG-3 cells with DHA resulted in translocation of over-expressed FABP5 from the cytoplasm to the nucleus, suggesting that FABP5 delivers DHA from the cytoplasm to the nucleus where it can affect transcription as an RXR ligand. FABP5 can also translocate to the nucleus in response to the PPARβ/δ ligands RA (Schug et al., 2007) and L165041 (Tan et al., 2002).

2.7 Nurr1 enhances DHA-induced RXR signaling

Enhanced DHA-induced RXR signaling is also observed when a RXR-dimerization mutant of Nurr1, but not a DNA binding-deficient mutant of Nurr1 is over-expressed. The RXR dimerization mutant of Nurr1 can induce the expression of FABP5 but cannot compete

with GAL4-Nurr1 for interaction with RXR. In cells over-expressing siRNA against FABP5, the enhancement of the reporter activation by Nurr1 was blunted, suggesting that the induction of FABP5 by Nurr1 mediates the enhancement of DHA-induced activation of RXR. In summary, we have shown that the Nurr1 induction of FABP5 can serve to deliver DHA to Nurr1/RXR heterodimers and further potentiate DHA-mediated RXR activation, indicating the existence of a positive loop. In that way, Nurr1 could potentially modulate the activity of permissive RXR heterodimers PPAR/RXR, LXR/RXR, FXR/RXR and Nurr1-NGFI-B/RXR.

2.8 Stress-induced survival by Nurr1 and FABP5

Nurr1-induced FABP5 expression upon neuronal stress could positively influence cellular survival in two ways (**Figure 8**): Firstly, FABP5 could bind free FAs and reduce the toxic effects of FA accumulation under stress. Secondly, FABP5 could deliver the endogenous RXR ligand DHA to Nurr1/RXR heterodimers and activate their transcriptional activity. Nurr1/RXR heterodimers have been shown to mediate survival signaling in neurons as described in chapter A9.

DHA has been shown to be neuroprotective (Glozman et al., 1998, Kim et al., 2000, Lauritzen et al., 2000, Tsukada et al., 2000, Politi et al., 2001, Wallen-Mackenzie et al., 2003, Choi-Kwon et al., 2004, Akbar et al., 2005, Belayev et al., 2005, Bas et al., 2007) and can be released from membrane phospholipids upon ischemia (Neuringer et al., 1988, Baker and Chang, 1992) and brain injury (Homayoun et al., 2000). Nurr1 is also induced upon ischemia and brain injury (chapter A7) suggesting that both Nurr1 and DHA could be made available under stressful conditions.

2.9 Cross-talk

We have shown that Nurr1 can indirectly influence PPARβ/δ and RXR signaling. It becomes more and more evident that NR action is not confined to the regulation of cognate target genes but it also involves the modification of other transcription factors, including other NRs. Well known examples of such a signal cross-talk is the mutual repression of NR and AP1 activities, initially documented for the GR and confirmed for other NRs (Jonat et al., 1990, Yang-Yen et al., 1990, Schule and Evans, 1991) and the repression of NFκB by GR (Heck et al., 1997). NR4A receptors have been described to repress the activity of other transcription factors (chapter A6).

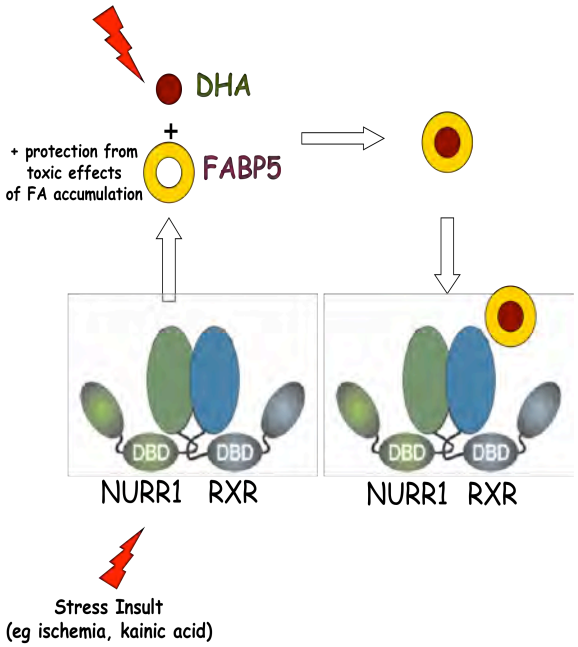

Figure 8: Nurr1 and FABP5 in neuronal stress (see text for details).

3 Paper III: NR4A receptor-mediated neuroprotection

3.1 Neuronal stress: excitotoxicity, ichemia and oxidative stress

Excitotoxicity is the pathological process by which neurons are damaged and killed due to the over-activation of receptors for the excitatory neurotransmitter glutamate by NMDA, KA and pathologically high levels of glutamate. This results in excessive calcium influx into the cells, which in turn activates a number of enzymes, including phospholipases, endonucleases, and proteases such as calpain that damage cell structures and DNA. Excessive calcium also induces opening of the mitochondrial permeability transition pore resulting in swelling of the mitochondria and release of pro-apoptotic proteins (Luetjens et al., 2000). Excitotoxicity is an important cause of neuronal damage in epilepsy, neurodegenerative diseases and ischemia. (Doble, 1999).

Ischemia is a restriction in blood supply that results in decrease in oxygen and glucose in the brain and subsequently damage of brain tissue (**Figure 9**). Neurons starved of oxygen and glucose release excessive amounts of glutamate (Rossi et al., 2000) from their synaptic bulbs that then binds to glutamate receptors and causes excitotoxicity. Before glutamate-poisoned neurons die, they release excessive amounts of glutamate inducing a toxic glutamate cascade (Choi and Rothman, 1990).

The formation of ROS occurs when unpaired electrons escape the electron transport chain and react with molecular oxygen and also as a result of second message signaling and metal ion redox chemistry. ROS can directly damage proteins, lipids, DNA and RNA and can also react with nitric oxide, generating toxic RNS (Brown and Borutaite, 2001). Oxidative

stress plays a central role in aging and in the slow progression of neurodegenerative disorders such as AD and PD and the relatively rapid neuronal degeneration resulting from seizure activity and ischemic insults (Love, 1999, Patel, 2004, Halliwell, 2006).

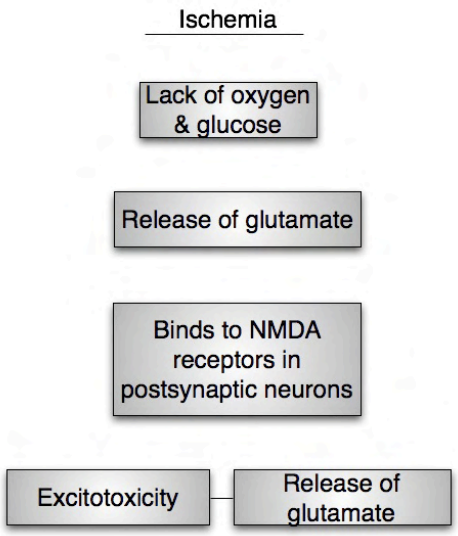

Figure 9: Involvement of glutamate in schemia.

3.2. CREB and neuronal survival

3.2.1 Data from *in vivo* experiments

Abundant evidence derived from *in vivo* experiments indicates that CREB plays an important role in neuronal survival:

CREB phosphorylation is correlated with the *in vivo* differentiation of cerebellar and hippocampal granule cells (Bender et al., 2001, Pons et al., 2001).

CREB knockout mice show apoptosis, axonal growth defects, degeneration of peripheral neurons (Lonze et al., 2002) and defects in axonal projections within the corpus callosum and the anterior commissure (Rudolph et al., 1998).

CREB/CREM conditional knockout in neuronal and glial precursors during embryonic development results in generalized cell death in the CNS (Mantamadiotis et al., 2002) while CREB/CREM postnatal conditional knockout results in progressive neurodegeneration in dorsolateral striatum and CA1/DG of the hippocampus (Mantamadiotis et al., 2002). CREB conditional knockout in the forebrain results in deregulation of cholesterol metabolism and pathological accumulation of cholesterol, which might play a crucial role in neurodegeneration and also in up-regulation of genes associated with inflammation and cell death (Lemberger et al., 2008). CREB conditional

knockout in dopaminergic neurons results in partial (20-25%) loss of dopaminergic neurons (Parlato et al., 2006).

A DN form of CREB abolishes the counteraction of the inhibitory effects of myelin on axonal axonal regeneration induced by cAMP and neurotrophins *in vivo*, suggesting the implication of CREB in neuronal regeneration after trauma (Gao et al., 2004).

Over-expression of DN CREB in the forebrain induces neuronal degeneration (Ao et al., 2006, Jancic et al., 2009). Other studies where DN CREB was over-expressed in mice did not observe loss of neurons, probably because the time window or the level of CREB inhibition achieved were different (Rammes et al., 2000, Kida et al., 2002, Pittenger et al., 2002, Lee et al., 2009a). In DN CREB transgenic mice, there is an increase in neurodegeneration and in Tyr nitration (a ROS marker) after pilocarpine-induced seizures and the induction of the antioxidant PGC-1α after status epilepticus is diminished (Lee et al., 2009a).

3.2.2 Data from *in vitro* experiments

In vitro experiments have also shown that CREB is essential for neuronal protection against an array of pathophysiological effectors such as NMDA (Lee et al., 2005a), glutamate (Mabuchi et al., 2001), the excitotoxin MPTP (Yang et al., 2008), okadaic acid (Walton et al., 1999b), staurosporine and C2 ceramide (Papadia et al., 2005), ROS (St-Pierre et al., 2006), HIV-1 gp120 (Chun et al., 2009) and nutrient deprivation (Yang et al., 2009, Patel et al., 2010).

Neuronal progenitors from CREB knockout mice mice show defects in expansion and survival (Dworkin et al., 2009), while DN CREB attenuates outgrowth of cortical neuron dendrites *in vitro* (Redmond et al., 2002). Activated CREB mediates the differentiation of cultured hippocampal H19-7 cells induced by forskolin and KCl, FGF2 treatment, or Dyrk1A kinase activation (Son et al., 2001, Sung et al., 2001, Yang et al., 2001).

CREB is also present in the mitochondrial matrix of neurons and it binds directly to CREs found within the mitochondrial genome. Disruption of CREB activity in the mitochondria increases susceptibility to 3-NP, a mitochondrial toxin that induces a clinical and pathological phenotype similar to HD (Lee et al., 2005b). Depletion of mitochondrial DNA or treatment with the mitochondrial poison CCCP initiates mitochondrial stress signaling which involves CREB up-regulation and results in increased resistance to etoposide-induced apoptosis (Biswas et al., 2005).

3.2.3 Pharmacological activation of CREB: *in vitro* and *in vivo* data

Lithium, that has been shown to activate CREB, protects from KA, glutamate and MPTP excitotoxicity in a variety of *in vitro* and *in vivo* models (Chuang et al., 2002).

The phosphodiesterase inhibitor rolipram that increases cAMP levels, PKA activity and activates CREB protects dopaminergic neurons from MPTP excitotoxicity (Yang et al.,

2008), hippocampal neurons from toxic NMDA concentration-induced cell death (Valera et al., 2008) and cortical neurons from hypoxia/hypoglycemia, glutamate, staurosporine (a general kinase inhibitor) and the sodium channel activator veratridine (Chen et al., 2007). Rolipram can suppress the glutamate-induced up-regulation of cyclin D1 and of pro-apoptotic caspase-3 activity (Chen et al., 2007). Rolipram also increases CREB DNA binding and reduces glutamate- and hydrogen peroxide-induced toxicity (Zou and Crews, 2006). Importantly, rolipram promotes the survival of newborn hippocampal neurons after ischemia (Sasaki et al., 2007), induces proliferation and differentiation of DG neurons via CREB activation (Nakagawa et al., 2002) and reduces neuronal damage after cerebral ischemia (Kato et al., 1995, Block et al., 1997). Rolipram can also inverse the inhibition of LTP induced by amyloid β peptide or by sleep deprivation and enhance synaptic plasticity and spatial memory (Vitolo et al., 2002, Vecsey et al., 2009).

Another phosphodiesterase inhibitor, cilostazol, prevents TNFα-induced cell death by suppression of PTEN phosphorylation and activation of Akt/CREB phosphorylation (Hong et al., 2003, Kim et al., 2004), protects from ischemia (Lee et al., 2004b, Lee et al., 2006, Watanabe et al., 2006, Lee et al., 2007, Lee et al., 2009c) and promotes survival of axotomized retinal ganglion cells in adult rats (Kashimoto et al., 2008).

NS-7, a blocker of voltage-sensitive Ca2+ and Na+ channels results in persistent CREB phosphorylation and significant reduction of the infarct size after focal cerebral ischemia (Tanaka et al., 2000).

Other compounds shown to activate CREB and induce neuroprotection include estradiol-17β, simvastatin and rapamycin that protect against cerebral ischemia (Watters and Dorsa, 1998, Choi et al., 2004b, Carloni et al., 2009, Raval et al., 2009, Carloni et al., 2010), cyclosporin A, whose neuroprotective effects are mediated by pCREB-induced BDNF expression (Miyata et al., 2001) and the σ1-receptor ligand PPBP that protects primarycortical neuronal cultures drom glucose deprivation (Yang et al., 2009).

3.2.4 CREB as a downstream target of survival factors

CREB has also been shown to be activated by and mediate the effect of factors promoting neuronal growth and survival, such as NGF (Riccio et al., 1999, Du et al., 2000, Bedogni et al., 2003, Cox et al., 2008, Zhang et al., 2010), RSKs (Bonni et al., 1999), Akt kinase (Du and Montminy, 1998), BDNF (Finkbeiner et al., 1997, Pizzorusso et al., 2000, Gao et al., 2004, Lee et al., 2009a), insulin-like growth factor 1 (Kulik et al., 1997, Pugazhenthi et al., 1999), Adcyap1 (Tanaka et al., 1997a, Tanaka et al., 1997b, Villalba et al., 1997, Lioudyno et al., 1998, Takei et al., 1998), valproic acid (Lasseck et al., 2009), VEGF-A (Lee et al., 2009b), NCAM (Azizeh et al., 1998, Schmid et al., 1999) and vitamin E (Aiguo et al., 2010).

3.2.5 Stress-induced CREB activation

Interestingly, CREB is activated in response to not only the prosurvival factors described above but also to stressful stimuli such as hypoxia, oxidative stress, excitotoxicity and

ischemia (Beitner-Johnson and Millhorn, 1998, Hu et al., 1999, Tanaka et al., 1999, Irving et al., 2000, Tanaka et al., 2000, Jin et al., 2001, Mabuchi et al., 2001, Lonze and Ginty, 2002, Sugiura et al., 2004, St-Pierre et al., 2006, Barlow et al., 2008, Raval et al., 2009), suggesting that stress-induced CREB activation might represent a cellular defense mechanism.

Indeed, *in vivo* experiments have revealed a neuroprotective role for CREB in ischemia. The DNA binding activity of CREB was found to be increased in ishaemic hippocampus and cortex (Yoneda et al., 1994). Later, it was shown that the DG and cortical cells that are resistant to ischemia show increased levels of activated CREB (Walton et al., 1996) and that activation of CREB protects from ischemia (Kato et al., 1995, Block et al., 1997, Tanaka et al., 2000, Choi et al., 2004b, Liu et al., 2004, Lee et al., 2006, Peng et al., 2006, Watanabe et al., 2006, Lee et al., 2007, Carloni et al., 2009, Raval et al., 2009, Carloni et al., 2010) and stimulates neurogenesis after ischemia as well as survival of the newborn neurons (Zhu et al., 2004, Sasaki et al., 2007, Lee et al., 2009c) Moreover, CREB is required for acquisition of ischemic tolerance**,** an endogenous neuroprotective mechanism whereby prior exposure to brief ischemia produces resilience to subsequent normally injurious ischemia (Nakajima et al., 2002, Hara et al., 2003, Lee et al., 2004a, Meller et al., 2005, Lee et al., 2009b, Lin et al., 2009, Terasaki et al., 2010).

Furtermore, CREB is activated in glial and endothelial cells of the hippocampus that replace the degenerating CA fields 1-4 weeks after KA injection, possibly in order to promote cell proliferation and survival (Ong et al., 2000). Rats exposed to an enriched environment have reduced spontaneous apoptotic cell death in the hippocampus and are protected against KA-induced seizures. Some of the resistant cell populations in the hippocampus show increased CREB phosphorylation, which might account for their increased resistance to damage after environmental stimulation (Young et al., 1999).

In vitro, CREB induction after glutamate preconditioning results in bcl-2 induction and reduces oxygen-glucose deprivation in cultured cortical neurons (Mabuchi et al., 2001, Lin et al., 2008). Finally, oxidative stress has been shown to activate CREB and induce CREB-mediated PGC-1α expression. PGC-1α activates a ROS defense mechanism (St-Pierre et al., 2006).

3.2.6 CREB targets in the context of neuroprotection

Despite the fact that the neuroprotective effect of CREB is well documented, only a few target genes of CREB that could be mediating this effect have been identified. These include the neurotrophic factor BDNF (Ghosh et al., 1994, Shieh et al., 1998, Tao et al., 1998, Bonni et al., 1999, Walton et al., 1999a, Miyata et al., 2001, Tabuchi et al., 2002) and the anti-apoptotic gene bcl-2 (Chen et al., 1997a, Mabuchi et al., 2001, Chuang et al., 2002, Meller et al., 2005, Watanabe et al., 2006, Barlow et al., 2008, Lin et al., 2008, Chun et al., 2009, Lin et al., 2009). CREB is also a direct regulator of the antioxidants Mn-superoxide dismutase (Bedogni et al., 2003) and oxygenase-1 (Kronke et al., 2003) and induces the expression of PGC-1α, a key effector in ROS-detoxifying enzyme expression (St-Pierre et al., 2006).

3.3 Rolipram-induced CREB-mediated neuroprotection

To study CREB-dependent neuroprotection, we assayed neuronal survival after pharmacological up-regulation of CREB with rolipram, which has been shown to confer neuroprotection from various types of stress *in vivo* and *in vitro* (chapter B3.2.3). Rolipram preconditioning of stem cell-derived forebrain neuron cultures resulted in enhanced resistance to hydrogen peroxide-, ionomycin- and glutamate-induced toxicity (Paper III).

To verify that the effect of rolipram is CREB-mediated, we blocked CREB-mediated transcription by phosphorothioate oligonucleotides, containing the CRE element where CREB binds, which we annealed in order to generate duplex/hairpin oligos that bind CREB and can titrate it away from the natural CREs occuring within the promoters of its target genes. The decoy oligonucleotides blocking CREB-mediated transcription were first described by (Park et al., 1999) and have been successfully used since then both *in vitro* (Mabuchi et al., 2001, Meller et al., 2005) and *in vivo* (Hara et al., 2003, Tischkau et al., 2003, Lee et al., 2004a). Similarly, in other experiments, oligos containing the NBRE site were used to inhibit NR4A-mediated transcription (**Figure 10).**

Rolipram-induced neuroprotection was indeed dependent on CREB activation since the effect was abolished when neurons were pretreated with CRE decoy (Paper III).

3.4 Stress-induced CREB-mediated NR4A receptor induction

In response to increased intracellular cAMP levels, Nurr1 induction in our *in vitro* system was CREB-dependent. Rolipram and the cAMP analogue 8CPT-cAMP increased mRNA expression of all 3 NR4A receptors. phosphoCREB and Nurr1 became coexpressed after rolipram treatment but the fraction of Nurr1/phosphoCREB double-positive nuclei after rolipram treatment decreased dramatically in cells pre-treated with CRE decoy (Paper III).

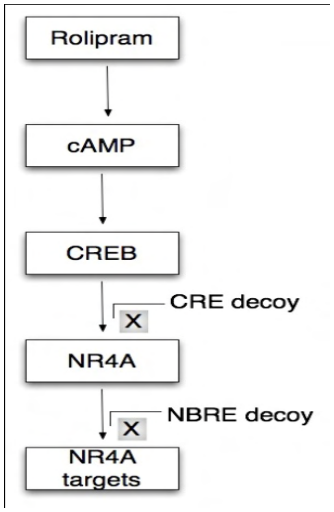

Figure 10: The use of decoy oligonucleotides to block CREB- and/or NR4A-mediated transcription.

Neuronal stress has been shown to induce NR4A receptors *in vivo* (chapter A7). Moreover, oxidative stress induced by hydrogen peroxide treatment has been shown to induce NGFI-B expression in VSMCs (Watanabe et al., 2001) and in HEK293 and SH-SY5Y cells (No et al., 2010). We used ionomycin and hydrogen peroxide to induce excitotoxic and oxidative stress respectively and we noted that both stressors induced NR4A mRNA and protein in a CREB-dependent way. CREB, shown before to be activated under conditions of neuropathological stress (chapter B3.2.5) could bind to the endogenous Nurr1 promoter and also activate a fragment of the Nurr1 promoter in C17.2 cells. In contrast, glutamate did not induce the expression of NR4A receptors, consistent with its ability to trigger a CREB inhibitory pathway (Hardingham et al., 2002).

3.4.1 CREB as an upstream factor controlling NR4A receptor expression

Recently, using genome-wide expression profiling in mice lacking CREB in the forebrain, Nurr1 and NGFI-B were identified as 2 of the few genes that require CREB for their induction in the hippocampus after KA administration (Lemberger et al., 2008), suggesting that CREB might also play a role in NR4A induction in neuronal cells. Later, it was shown that NGFI-B induction following depolarization in PC12 cells and neurons is CREB-dependent and is modulated by MEF2 transcription factors (Lam et al., 2009). cAMP also activates PKA that in turns activates CREB and turns on NR4A expression in neuronal cells (chapter A9.2.9). The dependence on the PKA-CREB pathway has been shown for example in ST14A neuronal cells where down-regulation of CREB/CREM interfered with the induction of Nurr1 by forskolin (Lemberger et al., 2008) and in N2A neuroblastoma cells where the PKA inhibitor H89 blocked forskolin-induced Nurr1 expression (Lee and Nikodem, 2004).

Binding site for CREB have been found in the promoters of Nurr1 (Castillo et al., 1997, Saucedo-Cardenas et al., 1997), NGFI-B (Uemura et al., 1995) and Nor-1 (Maltais and Labelle, 2000). The induction of NR4A receptor expression by different stimuli has also been shown to be CREB-mediated in a variety of non-neuronal contexts.

More specifically, CREB is mediating the NR4A induction:

- by LH in mouse Leydig tumor cells (Inaoka et al., 2008, Martin et al., 2009).

- by LDLs (Rius et al., 2004, Crespo et al., 2005), VEGF (Rius et al., 2006), PDGF (Nomiyama et al., 2006) and thrombin (Martorell et al., 2007) in VSMCs.

- by PGE2 and CRH in rheumatoid arthritis synovial tissue and human endothelial cells (McEvoy et al., 2002a, McEvoy et al., 2002b, Ralph et al., 2007, Zocco et al., 2010).

- by ischemia-reperfusion injury in the rat liver (Ohkubo et al., 2002).

- by thromoboxane A2 receptor agonist in human lung cancer (Li and Tai, 2009).

- by PMA, EGF, TNF and anisomycin in in Hela cells (Darragh et al., 2005).

- by the MECT1-MAML2 fusion oncoprotein (Coxon et al., 2005, Wu et al., 2005).

- by cAMP (chapter A7) since cAMP activates PKA that in turns activates CREB.

- by rolipram in N2A neuroblastoma cells (Lee and Nikodem, 2004) and in B and T cells (Meyers et al., 2009).

3.5 NR4A receptor-mediated neuroprotection *in vitro*

We found that the neuroprotective effect of rolipram was significantly reduced in neurons been transfected with NBRE decoy, suggesting that the NR4A receptors are mediating a significant portion of the rolipram-induced neuroprotection. Moreover, neurons transduced with NR4A-expressing lentiviruses showed increased survival from ionomycin-, glutamate- and hydrogen peroxide-induced toxicity (Paper III).

3.6 Nurr1 activates neuroprotective gene expression

Several of the genes induced by Nurr1 over-expression in neurons (Paper III) were previously shown to promote neuronal survival after stressful insults. These genes were also induced in neurons treated with 8CPT-cAMP, suggesting that NR4A receptors play a role in the CREB-mediated gene activation of these protective gene products, whose expression is reduced after treatment of neurons with CRE decoy or NBRE decoy (Paper III). Since expression was not completely abolished by NBRE decoy we conclude that the decoy is unable to completely block NR4A function or, alternatively, additional factors are also contributing to CREB-induction of these genes. Interestingly, a gene list enrichment analysis that identifies gene sets associated with common functions or pathways revealed that additional pathways linked to neuroprotection are up-regulated in mRNA samples from Nurr1 lentivirus-transduced neurons (Paper III). Notably, mTOR (Koh et al., 2008), adrenergic (Weber et al., 2007), insulin receptor (Gonzalez et al., 2008) and VEGF signaling pathways (Vezzani, 2008) have been linked to neuroprotection and are significantly enriched in Nurr1-expressing neurons.

3.7 CREB-induced PGC-1α-mediated neuroprotection

Rolipram, 8CPT-cAMP and hydrogen peroxide treatment of neurons resulted in induction of PGC-1α mRNA. Increased steady-state PGC-1α protein levels were also observed and the increase was partially blocked in the presence of CRE decoy. Notably, PGC-1a is only induced by the stress it protects from, oxidative stress. PGC-1α is neuroprotective after exposure to oxidative stress but not ionomycin or glutamate. PGC-1α shRNA reduced survival and infection of neurons with a PGC-1α lentivirus conferred neuroprotection, but only against hydrogen peroxide-induced oxidative stress (Paper III). PGC-1α has been shown to be induced by calcium (ionomycin or caffeine) before but in muscle cells (Ojuka et al., 2003, Ojuka, 2004).

3.7.1 Links between PGC-1α and CREB

CREB has been shown to control PGC-1α expression induced by both stress and physiological stimuli (**Figure 11**).

Exercise and physical activity elevate PGC-1α levels by activating CAMKIV which induces CREB binding to the PGC-1α promoter in C2C12 muscle cells and transcription of PGC-1α (Baar et al., 2002, Handschin et al., 2003, Pilegaard et al., 2003).

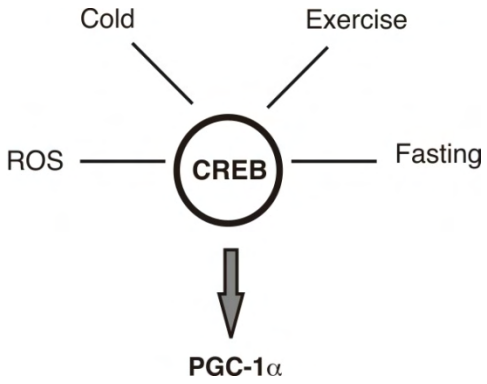

Figure 11: CREB-mediated PGC-1α expression.

PGC-1α is induced by CREB in response to the glucagon-cAMP axis and promotes hepatic gluconeogenesis (Herzig et al., 2001, Pei et al., 2006b).

Disrurption of the CREB-mediated trascription of PGC-1α by mutant huntingtin protein is believed to contribute to the pathology of HD (chapter B3.7.2).

The PGC-1α promoter is bound by and activated by CREB in fibroblasts in the presence of oxidative stress. A DN CREB almost completely suppresses CREB induction by hydrogen peroxide (St-Pierre et al., 2003).

Cold induces PGC-1α via the adrenergic-cAMP pathway in brown adipose tissue (Puigserver et al., 1998).

3.7.2 PGC-1α-mediated neuroprotection

PGC-1α has been shown to bind OGT and target the enzyme to FoxO transcription factors, resulting in their increased GlcNAcylation and increased transcriptional activity (Housley et al., 2009). Since, GlcNAcylation is rapidly elevated upon different types of stress (hydrogen peroxide, hypoxia, UV light, sodium arsenite or thermal stress) in COS-1 cells (Zachara et al., 2004) and upon glucose deprivation in neuronal cells (Cheung and Hart, 2008) and protects myocardium cells from ischemia (Fulop et al., 2007), it would be tempting to consider the possibility that PGC-1α could target OGT to transcription factors mediating survival.

Loss of PGC-1α leads to degeneration, most prominently in the striatum, accompanied by hyperactivity (in one of the 2 PGC-1α knockout lines generated) reminiscent of HD, an autosomal dominant disorder caused by CAG repeats in the huntingtin protein (Browne and Beal, 2004), and signs of increased anxiety (in the other knockout lines generated). In PGC-1α knockout mice, large vacuolar lesions associated with gliosis are present in the striatum. Much smaller and less abundant lesions are also found in the cortex, nucleus accumbens, thalamus, SN, hippocampus and the mammalliary body (Lin et al., 2004, Leone et al., 2005). Striata from postmortem HD patient brains and from a HD knock-in mouse model that over-expresses mutant huntingtin as well as a cultured HD striatal line show markedly reduced PGC-1α and mitochondrial PGC-1α target gene expression (Cui et al., 2006), Similarly, microrarray data analysis has shown reduced PGC-1α target gene expression in HD postmortem brain tissue (Weydt et al., 2006). A lentivirus over-expressing PGC-1α in the striatum of a HD mouse model induces an increase in mean neuronal volume suggesting that PGC-1α is neuroprotective. Morever, down-regulation of PGC-1α worsens behavioral and neuropathological abnormalities in a HD knock-in mouse that otherwise has a mild phenotype and increases its susceptibility to 3-NP (Cui et al., 2006). Finally, a HD mouse model shows hypothermia at baseline temperatures and following cold exposure, decreased Ucp1 expression in brown adipose tissue following cold exposure and dysregulation of other targets of PGC-1α in primary brown adipocytes and in pre-adipocytes, suggesting disability of PGC-1α to induce its target (Weydt et al., 2006). Mutant huntingtin protein could interfere with the formation of the CREB/TAF4 complex that regulates PGC-1α transcription (Cui et al., 2006) and/or bind to PGC-1α impairing its ability to activate transcription (Weydt et al., 2006).

Under conditions of oxidative stress in neurons, CDC4, a component of the SCF E3 ubiquitin ligase that targets PGC-1α for ubiquitin-mediated proteolysis is down-regulated, leading to an increase of PGC-1α protein and PGC-1α-mediated transcription (Olson et al., 2008).

PGC-1α was recently shown to be a potent suppressor of ROS both *in vitro* in fibroblasts, endothelial cells and in neurons but also *in vivo* (Valle et al., 2005, Kukidome et al., 2006, St-Pierre et al., 2006). In fibroblasts exposed to hydrogen peroxide, PGC-1α expression is induced in a CREB-mediated way and induces the expression of ROS defense enzymes such as Sod1, Sod2, catalase, glutathione peroxidase and Ucps (St-Pierre et al., 2003). Ucps shorten the half-life of the electron transport chain reactions by decreasing the electrochemical potential across the inner mitochondrial membrane and thus limit ROS production (Arsenijevic et al., 2000). Ucp2 has been shown to have a neuroprotective effect in cerebral ichemia (Mehta and Li, 2009). Brown fat fibroblasts derived from PGC-1α knockout mice show a blunted disruption of the ROS defense system genes, increased ROS levels and are more susceptible to oxidative stress-induced cell death. Over-expression of PGC-1α in murine neuronal progenitors from the striatum or SH-SY5Y neuroblastoma cells also induces ROS defense genes expression and protects them from oxidative stress (St-Pierre et al., 2003).

PGC-1α knockout mice exhibit considerably lower Sod1, Sod2 and catalase basal levels in the heart and the brain and show increased oxidative stress and neurodegeneration in the CA1 region of the hippocampus and the SN, in response to the neurotoxins KA and MPTP respectively (St-Pierre et al., 2003). The abrogation of PGC-1α induction in DN CREB transgenic mice after pilocarpine-induced oxidative stress is associated with increased degeneration and ROS levels (Lee et al., 2009a).

Primary striatal neurons isolated from PGC-1α knockout mice display a severe impairment in neurite growth (Lin et al., 2004).

3.8 Links between NR4A receptors and PGC-1α

PGC-1α and NR4A have been linked to each other in previous studies.

NR4A receptors and PGC-1α are induced in human skeletal muscle during recovery from endurance exercise (Mahoney et al., 2005) and in rat skeletal muscle after dietary restriction (Oita et al., 2009). In addition, they both promote glucose uptake in the muscle and their expression is reduced in skeletal muscle and adipose tissue of insulin-resistant mice (chapter A3.3) Moreover, transfection of siRNA against Nor-1 in C2C12 myocytes results in reduced PGC-1α expression (Pearen et al., 2008), suggesting that PGC-1α might be a direct or indirect target gene of Nor-1.

Moreover, both PGC-1α and NR4A receptors are induced by cold in adipose tissue and promote adaptive thermogenesis (Puigserver et al., 1998, Kanzleiter et al., 2005, Au et al., 2008). PGC-1α (Puigserver et al., 1998, Miura et al., 2007) and NR4A (Myers et al., 2009) are both induced upon adrenergic stimulation in muscle and adipose tissue.

Furthermore, PGC-1α interacts with GAL4-NGFI-B LBD in pancreatic cancer cells treated with DIM-C-pPhCl (Chintharlapalli et al., 2005) and with full-length Nurr1 in osteoblasts, where it is induced by PTH and enhances Nurr1 activation of a luciferase reporter gene driven by a fragment of the osteocalcin promoter as well as a NBRE reporter in osteoblasts (Nervina et al., 2006).

Finally, NR4A receptors and PGC-1α have been shown before to cooperate in the transcriptional regulation of hepatic glucose metabolism (Pei et al., 2006b). They are both induced in the liver by CREB in response to the glucagon-cAMP axis and fasting and they exert distinct but complementary effects on hepatic glucose metabolism. The ability of NR4A receptors to regulate gene expression controlling hepatic glucose metabolism does not require PGC-1α nor does PGC-1α act as coactivator for NR4A in this context. A few glucose metabolism genes are additively induced by NR4A and PGC-1α but most of them are preferentially regulated by one of them (Pei et al., 2006b).

Similar to the glucagon-cAMP axis in the liver, NR4A receptors and PGC-1α appear to represent two independent but complementary CREB-dependent regulatory ‘legs’ in adaptation to neuronal stress (**Figure 12**) since:

- Nurr1 and PGC-1α activate almost completely independent sets of target genes (Paper III)
- Coexpression of PGC-1α together with Nurr1 does not enhance the expression of tested NR4A targets (Paper III, data not shown).
- Coexpression of both PGC-1α and Nurr1 results in additive rather than synergistic protection of neurons from oxidative stress (Paper III).

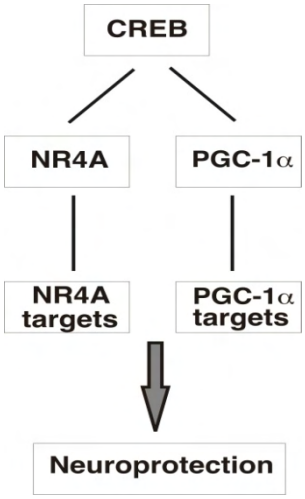

Figure 12 : NR4A receptors and PGC-1α in CREB-mediated neuroprotection

3.9 NR4A receptor-mediated neuroprotection *in vivo*

To assess the role of NR4A receptors in neuroprotection *in vivo* we used the KA model of neurodegeneration (**Figure 13**). KA is a non-degradable, extremely potent glutamate analogue (Bleakman and Lodge, 1998) isolated from the alga *Digenea* (Coyle, 1987) that activates glutamate receptors and induces excitotoxicity and oxidative damage (Wang et al., 2005) and subsequently neuronal cell death, consistently within the olfactory system, amygdaloid complex, hippocampus, thalamus and neocortex (Schwob et al., 1980, Sperk, 1994). KA has been shown to induce NR4A expression *in vivo* (Ponnio and Conneely, 2004) (Crispino et al., 1998) (Honkaniemi and Sharp, 1999) (Lemberger et al., 2008) and this induction is CREB-mediated as shown in a CREB konditional knockout in the forebrain (Lemberger et al., 2008), suggesting that the KA model is a relevant system to try to recapitulate the *in vitro* results pointing towards a role of NR4A receptors in CREB-induced neuroprotection. The role of PGC-1α in protection from KA-induced toxicity has been assayed before (chapter B3.7.2).

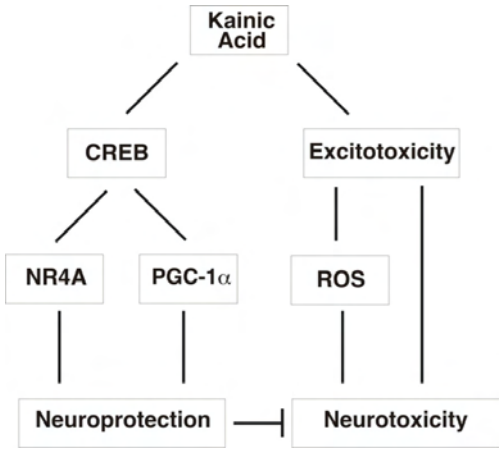

Figure 13: The KA model used in the study: KA induces toxicity but KA-stressed neurons respond by activating survival-promoting CREB signaling.

We injected wt mice or NR4Amut mice lacking 3 out of 6 NR4A alleles (Nurr1+/-; Nor-1-/-) with 25 mg/kg KA or saline. 3 days following status epilepticus the histology of mice was analyzed within the hippocampus. Saline treated NR4Amut mice showed decreased cell density within the CA1 hippocampal field (Paper III). This observation is consistent with previous analysis showing a developmental decrease in neuron density within the hippocampus of Nor-1 knockout mice (Ponnio and Conneely, 2004). NR4mut mice showed a significant decrease in the number of remaining cells within the CA1 region of the hippocampus following KA treatment and a strong increase in oxidative stress and in the number of degenerating neurons within the CA3 region (Paper III). The DG was not affected in either wt or NR4Amut mice, consistently with the observation that it it extremely resistant to KA-induced damage (Grooms et al., 2000). CA3 neurons have been shown before to be particularly sensitive to KA-induced damage, probably due because they contain a large number of KA receptors (Malva et al., 1998)

The increased sensitivity to degeneration of NR4Amut mice could be the result of decreased induction of a NR4A-dependent neuroprotective gene program. As expected, all 3 NR4A genes were up-regulated by KA in wt mice hippocampus, but loss of Nurr1 and Nor-1 alleles resulted in a corresponding decreased expression of these genes (Paper III). Importantly, several NR4A target genes were induced by KA (Adcyap1, Prkaa2, Adm, 4E-bp2, C-flar and Adm) but the levels of all of them apart from 4E-bp2 were lower in NR4Amut mice.

3.10 Therapeutic implications

It is tempting to consider the possibility of increasing NR4A activity in neurons to promote neuronal survival in neurodegenerative diseases such as AD and PD or in situations of a more acute neuronal loss, such as after ischemia/stroke or brain injury. That could be achieved by compounds that activate NR4A trancription (chapter A6.5) or by increasing NR4A expression either by gene delivery or by activation of pathways inducing NR4A expression.

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