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The role of Nurr1 in the development of dopaminergic neurons and Parkinson's disease

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Abstract

Nurr1, a transcription factor belonging to the orphan nuclear receptor superfamily, is critical in the development and maintenance of the dopaminergic system and as such it may have role in the pathogenesis of Parkinson' disease (PD). Human Nurr1 gene has been mapped to chromosome 2q22-23 and Nurr1 protein is predominantly expressed in central dopaminergic neurons. Nurr1 interacts with other factors critical for the survival of mensencephalic dopaminergic neurons and it appears to regulate the expression of tyrosine hydroxylase (TH), dopamine transporter (DAT), vesicular monoamine transporter 2 (VMAT2), and L-aromatic amino acid decarboxylase (AADC), all of which are important in the synthesis and storage of dopamine. Experimental studies in Nurr1 knock-out mice indicate that Nurr1 deficiency results in impaired dopaminergic function and increased vulnerability of those midbrain dopaminergic neurons that degenerate in PD. Decreased Nurr1 expression is found in the autopsied PD midbrains, particularly in neurons containing Lewy bodies, as well as in peripheral lymphocytes of patients with parkinsonian disorders. Several variants in Nurr1 gene have been reported in association with PD. All these studies suggest that Nurr1 is not only essential in the development of mensencephalic dopaminergic neurons and maintenance of their functions, but it may also play a role in the pathogenesis of PD.

Keywords: Nurr1; Transcriptional factor; Dopaminergic neuron; Parkinson's disease; Polymorphisms

Contents

Abbreviations: AADC, L-aromatic amino acid decarboxylase; ADH2, retinoid acid converting enzyme; AF1, N-terminal region; BDNF, brain-derived neurotrophic factor; CRE, cAMP-response element; CNS, central nervous system; CRF, corticotrophic releasing factor; DAT, dopamine transporter; DBD, DNA binding domain; ES, embryonic stem cells; FGF, fibroblast growth factor; GDNF, glial—cell-derived neurotrophic factor; LBD, ligand-binding domain; MARK, mitogen-activated protein kinase; NBRE, NGFI-B response element; PD, Parkinson's disease; PTH, parathyroid hormone; RARγ, retinoic acid receptor; SN, substantial nigra; TGF-α, transforming growth factor-α; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2; VTA, ventral tegmental area

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1. Introduction

Nuclear receptor superfamily includes a variety of transcription factors, such as receptors for steroid and thyroid hormones, and Vitamins A and D. Nurr1 (also called NR4A2/NOT/TINUR/RNR-1/HZF-3) is a member of this nuclear receptor superfamily of transcription factors, first identified from mouse brain cDNA library in 1992 (Law et al., 1992) and localized to human chromosome 2q22-q23 in 1994 (Mages et al., 1994). The DNA sequence, of Nurr1 overlaps, especially in the CyS2-CyS2, with that of Nurr77 (NGFI-B/TR3/NAK-1/N10/ST59/T1S1) and NOR-1 (MI-NOR/TEC/CHN/NOR-2) (Saucedo-Cardenas et al., 1997; Wang et al., 2003). Nurr1/Nur77 subfamily plays an important neuroendocrine regulatory role at all levels of the hypothalamic/pituitary/adrenal axis (Murphy and Conneely, 1997). Since the ligands for these transcription factors have not yet been found, they are referred to as "orphan" nuclear receptor family (Saucedo-Cardenas et al., 1997; Wang et al., 2003). These transcription factors are products of immediate-early genes whose expression and activity are regulated in cell-specific manner by a variety of extracellular mitogenic, apoptotic and differentiation stimuli (Mages et al., 1994; Martinez-Gonzalez and Badimon, 2005).

Nurr1 is expressed predominantly in the central nervous system, especially in substantia nigra (SN), ventral tegmental area (VTA), and midbrain and limbic areas (Zetterstrom et al., 1996; Backman et al., 1999). In addition, it is expressed highly in olfactory bulb, hippocampus, temporal cortex, subiculum, cerebellum, posterior hypothalamus and habenuclear nuclei (Saucedo-Cardenas and Conneely, 1996). Nurr1 is exclusively distributed within the neuronal nucleus (Chu et al., 2002). Several lines of evidence have indicated that Nurr1 is essential for the development, migration and survival of dopaminergic neurons (Zetterstrom et al., 1997; Saucedo-Cardenas et al., 1998). Defects in Nurr1 gene or altered expression of the gene in SN have been found in association with PD and certain psychiatric disorders, such as schizophrenia, manic behavior, and predisposition to cocaine addiction (Buervenich et al., 2000; Bannon et al., 2002; Xu et al., 2002; Le et al., 2003; Zheng et al., 2003; Grimes et al., 2004).

Central dopaminergic system plays a role in motor as well as other behaviors, including learning and the reward mechanisms (Albanese et al., 1986; Wise, 2004). There are three important dopaminergic pathways in the central nervous system, the most important of which originates in the SN and innervates the caudate and putamen, the nigrostriatal pathway. This pathway participates in the regulation of movement. The second dopaminergic pathway, the mesolimbic pathway, connects the VTA of midbrain with the amygdala, septal nuclei and cingulate gyrus, and it modulates perception, cognition and emotion. The third dopaminergic pathway, the mesocortical pathway, connects the VTA with the cerebral cortex of the temporal lobe. Degeneration of dopaminergic neurons in SN is typically found in PD (Fearly, 1994) and dysfunction of the dopaminergic limbic system of midbrain may lead to schizophrenia (Gibb and Lees, 1991).

The mechanism of the development and differentiation of dopaminergic neurons is very complex and is regulated by various genes and factors, including Nurr1, Lmx1b-Pitx3, SHH, Engrailed 1, Engrailed 2, Wnt-1, Wnt-3, and Wnt-5 (Smidt et al., 2000, 2003; Castelo-Branco et al., 2003; Smits et al., 2003). Some neurotrophic factors also participate in this process, including brain-derived neurotrophic factor (BDNF), glial-cell-derived neurotrophic factor (GDNF), and transforming growth factor (TGF-2) (Lin et al., 1993; Yurek et al., 1996). While all these factors interact with each other to a variable degree, Nurr1 is essential for both development and final differentiation of ventral mesencephalic late dopaminergic precursor cells and promotes the development of these precursor cells into a complete dopaminergic phenotype (Saucedo-Cardenas et al., 1998; Joseph et al., 2003).

2. The structure of Nurr1 gene

Using PCR primer extension analysis the DNA sequence of human Nurr1 gene has been identified (Ichinose et al., 1999; Torii et al., 1999). Mapped to chromosome 2q22-23, the human Nurr1 gene includes eight exons and seven introns; the total length is 9.822 kb (Fig. 1A). The open reading frame of Nurr1 gene contains 1794 bases that encode for 598 amino acids (Fig. 1B). The initiation site of translation (initiation codon) is

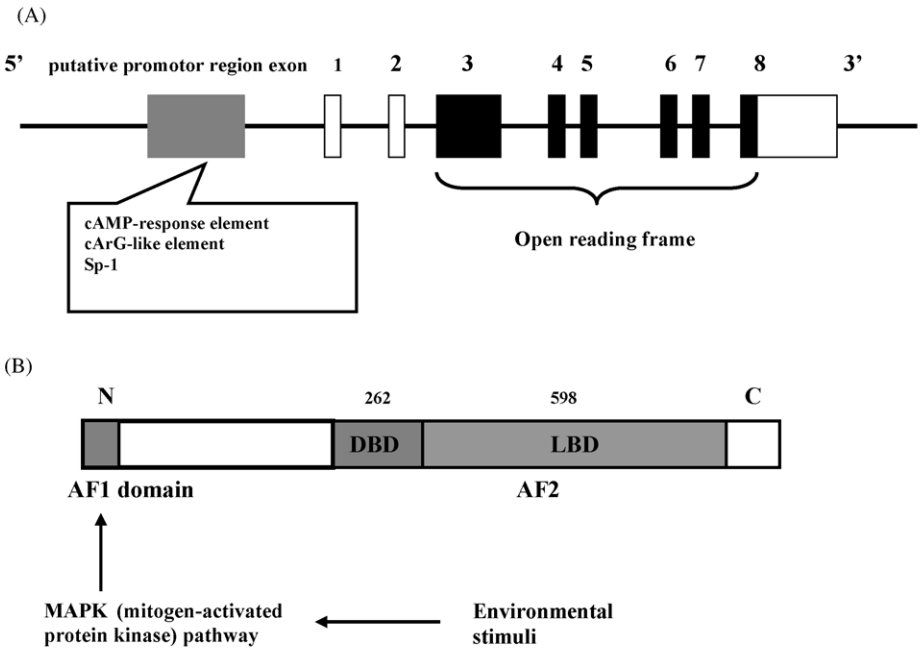

Fig. 1. The structure of Nurr1 gene. (A) Nurr1 gene includes eight exons. The open reading frame initiates in the third exon and terminates at the upstream region of the eighth exon that encode for 598 amino acids. Promotor region contains three elements: CRE, cArG and SP-1. (B) Nurr1 contains DBD (DNA-binding domain) and LBD (ligand-binding domain) AF1 domain is in N terminal region that can be activated by MAPK pathway due to the environmental stimuli.

in the third exon and the termination of translation (stop code) is at the upstream region of the eighth exon (Ichinose et al., 1999; Torii et al., 1999). There is a 3′-untranslated region (NTR) that contains ATTTA repetitive sequence at the downstream region of the eighth exon and the total length is about 1.3 kb. NTR is important for the stabilization of mRNA transcription. This feature of Nurr1 gene as an immediate early gene facilitates rapid transcription in response to stimulation by any of several of factors involved in the regulation of the gene expression (Fig. 1A).

2.1. Promoter and transcription regulatory element

Nurr1 gene has promoter and transcription regulatory element (cAMP-response element, CRE; CArG-like element; SP-1 element) at the upstream region of transcription initiation site (Maruyama et al., 1998; Torii et al., 1999). The sequence of CArG-like element, CC (A/T) 7GG, is similar to the c-fos promoter. Sp-1, with the GGGCGG sequence, takes part in the transcription regulation and probably participates in the delayed early response (Maruyama et al., 1998; Torii et al., 1999). CRE plays an important role in the signal transduction mediated by cAMP. The sequence of human Nurr1 gene is highly conserved compared with the Nurr1 gene of mice.

The expression of Nurr1 gene is regulated by many transcription regulators. Nurr1 and Nur77 can be rapidly induced by corticotrophin releasing factor (CRF) in primary pituitary cells and this induction is mimicked by forskolin in an anterior pituitary cell line (Murphy and Conneely, 1997). Further, both Nurr1- and forskolin-dependent induction of a POMC-chloramphenicol acetyltransferase reporter gene are inhibited by mutation of the Nurr1-binding site within the POMC promoter; and this site alone can confer cAMP responsiveness to a heterologous promoter (Murphy and Conneely, 1997). Parathyroid hormone (PTH) can induce expression of the nuclear orphan receptor Nurr1 in bone cells, which is mediated primarily through the cAMP/PKA pathway (Tetradis et al., 2001). PTH also stimulates Nurr1 protein production in MOB cells and Nurr1 mRNA expression in calvarial organ cultures. Thus, Nurr1 induction represents a potential cross-talk mechanism between PTH and steroid hormone signaling at the transcription factor levels (Tetradis et al., 2001).

2.2. DNA binding domain, ligand binding domain and N-terminal region

Nurr1 includes three major parts: DNA binding domain (DBD) in the central region of Nurr1, ligand-binding domain (LBD), and variable region (Ichinose et al., 1999; Wang et al., 2003) (Fig. 1B). Nurr1 LBD adopts a canonical protein fold resembling that of agonist-bound and transcriptionally active LBDs in nuclear receptor (Wang et al., 2003). Nurr1 LBD is most similar to the LBD of holo retinoic acid receptor γ(RARγ) (Renaud et al., 1995). The structure of Nurr1 has two distinctive features (Wang et al., 2003). The first feature is that Nurr1 LBD has no cavity that is normally occupied by ligands because of the tight packing chains from several bulky hydrophobic residues (Fig. 2). The second feature is that Nurr1 LBD lacks the binding site for co-activators. Nurr1 regulates the transcription probably through its binding to NGFI-B response element (NBRE:AAAGGTCA) of DNA or binding to Nurr77

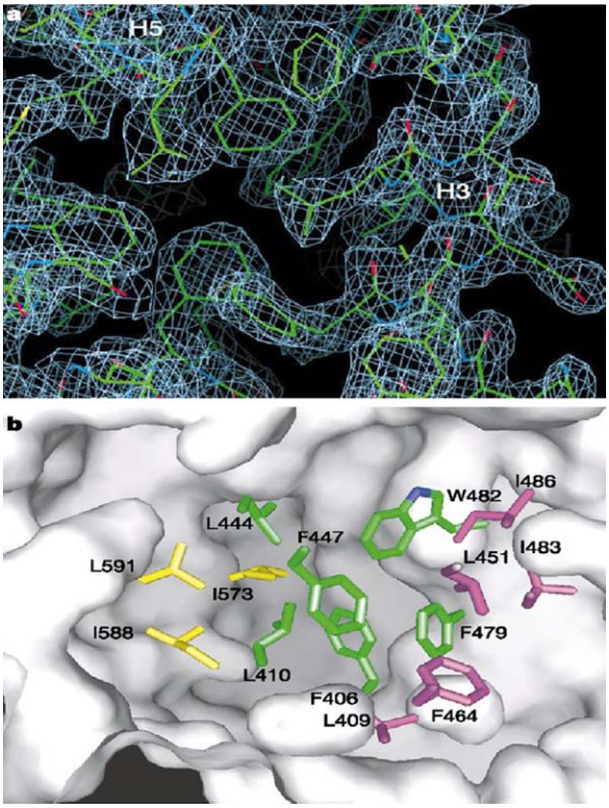

Fig. 2. Crystal structure diagram of Nurr1 shows no ligand-binding cavity in Nurr1. (a) The σ_A-weighted $2F_o–F_c$ electron density map (contoured at 1.5σ) of the Nurr1 LBP behind α-helix H3. (b) The six residues that completely block the ligand passage behind H3 (F406 and L410 from H3, L444 and F447 from H5, F479 from loop 6–7 and W482 from H7) are shown in green. The pocket is further sealed by residues L409 from H3, L451 from H5, I483 and I486 from H7 and F464 from the β-turn on one side the structure, and residues I573 from H11, and I588 and L591 from H12 on the other side, shown in pink and yellow, respectively. The internal surface of the protein, after removing these side chains, is shown in grey (replicated from Wang et al., 2003).

response element by homodimers form. Nurr1 binding to NBRE sequence can also activate the transcription of TH and DAT gene (Sakurada et al., 1999; Sacchetti et al., 2001), thus providing further evidence that Nurr1 is essential for the development of the dopaminergic neuron. In addition, Nurr1 can also form heterodimers with retinoid X receptor (RXR) and binding to RXR response element (Renaud et al., 1995). Nurr1 as well as Nor-1 can bind and activate transcription as homodimers.

Recent research has found that N-terminal region (AF1) of Nurr1 is important for regulating transcription (Nordzell et al., 2004). This region is highly conserved in NGFI-B/Nurr1/Nor-1 family members and can be activated by mitogen-activated protein kinase (MAPK) pathway as a consequence of several stimuli (Fig. 1A and B). Nurr1, when appropriately activated, can be rapidly upregulated through MAPK pathway or other pathways. Because of multiplicity of cleavage and splicing, there are several isoforms of Nurr1 (Ichinose et al., 1999; Xu and Le, 2004). Ichinose et al. (1999) have found three isoforms (hcNurr1–2, hcNurr1–3, hcNurr1–8) in mesencephalic neurons. The ability of DNA-binding is reduced by 36–50% in hcNurr1–2 and hcNurr1–8 and reduced by 94% in hcNurr1–3 as compared to full length Nurr1. The multiplicity of isoforms and transcriptions gives Nurr1 ability to react differently to different forms of stimulation. A novel splicing variant of Nurr1, named Nurr1-c, has been identified in non-neuronal tissues including lymphocytes, liver, muscle, and kidney, which has 25 amino acids deletion in the C-terminal region of exon 5. This splicing variant shows a significant reduction of luciferase activity in vitro as compared to Nurr1, indicating that Nurr1 can act alternately in transcriptional regulation (Xu and Le, 2004).

3. Nurr1 in the development of dopaminergic neurons

3.1. Nurr1 distribution in central nervous system

Nurr1 is distributed widely in cell nucleus in central nervous system (CNS), especially in dopaminergic neurons. The proportion of neurons that expressed Nurr1 is 96% in SN, 95% VTA, 91% in liner nucleus raphe, 85% in olfactory bulb, and 61% in cortex (Backman et al., 1999). Neurons of paraventricular area and nucleus of hypothalamus only modestly express Nurr1 and TH, whereas the noradrenaline neurons in the brainstem do not express Nurr1 (Zetterstrom et al., 1996; Backman et al., 1999; Wang et al., 2003) even though these neurons are involved in PD. Thus, the expression of Nurr1 is confined to periglomerular cells of the olfactory bulb and dopaminergic neurons in mesencephalon (Backman et al., 1999; Le et al., 1999a). The level of Nurr1 expression is different in the different stages of development. While it is highest in the embryonic stage than other stages, its expression remains high in dopaminergic neurons through life, suggesting its importance not only in dopaminergic neuron development but also in maintenance (Zetterstrom et al., 1997; Le et al., 1999a).

3.2. Genes and factors involved in central dopaminergic neuron development

The development of mesencephalic dopaminergic neurons is a complex process that requires the participation of numerous genes and factors, including Shh, En1, En2, Pax-2, Pax5, Lmx1-b, Pitx-3, Wnt1, Wnt-3, and Wnt-5 (Castelo-Branco et al., 2003; Nunes et al., 2003; Smidt et al., 2003). Fig. 3 illustrates the different stages of mensencephalic dopaminergic neurons: (a) Shh and Fgf8, expressed first, appear to be involved in the formation of dopaminergic progenitor cells (Roussa and Krieglstein, 2004b; Yan et al., 2005); (b) En1, En2, Pax2, Pax5, Wnt1 are subsequently expressed and these factors appear to participate in the differentiation of dopaminergic progenitor cells (Castelo-Branco et al., 2003; Perrier et al., 2004; Yan et al., 2005); (c) Lmx1b, expressed subsequently, also participates in the differentiation of dopaminergic progenitor cells (Smidt et al., 2000); (d) Nurr1 is first expressed at E10.5 in the mouse, just before Pitx-3 and TH (E11.5) (Saucedo-Cardenas et al., 1998; Smits et al., 2003) (Fig. 3A), and it interacts with Pitx-3 and other factors in the induction of TH-positive cells, giving birth to the dopaminergic neurons. Thus, Nurr1 primarily functions in the late stage of development of

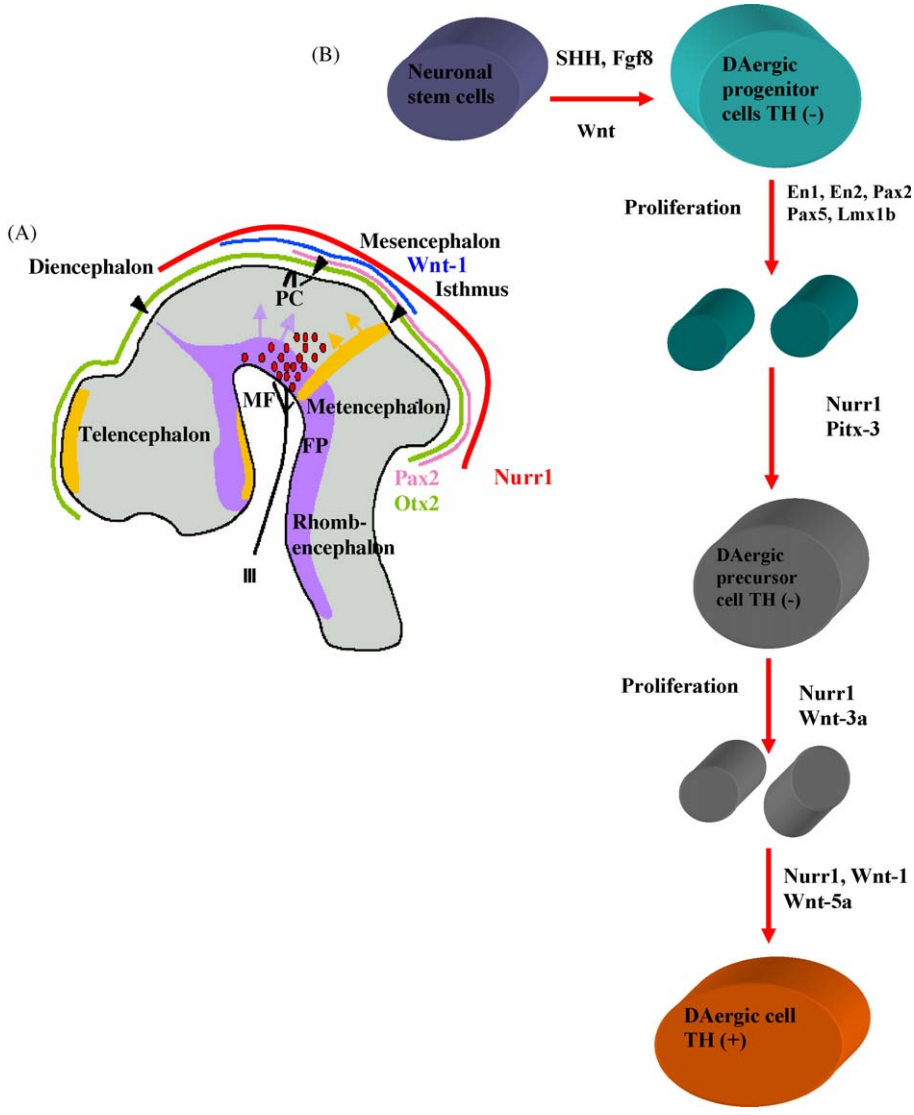

Fig. 3. (A) Schematic representation of the developing mouse central nervous system at E11.5. Mesencephalic dopaminergic (DAergic) neurons are generated in the immediate vicinity of two organizing centers, the floorplate (FP) in the ventral midline, and the isthmus at the midbrain–hindbrain boundary. Pax2, Otx2 and Wnt-1 are expressed. Nurr1 is expressed at E11.5. Differentiation and proliferation of DAergic cells have begun with the help of these factors. MF: mesencephalic flexure; PC: posterior commissure (replicated from Vitalis et al., 2005). (B) Development of DAergic neuron from neuronal stem cells. Expression cooperates with other factors promotes TH (−) DAergic precursor cells into TH (+) DAergic cells.

dopaminergic neuron and, along with other essential factors (e.g., Pitx-3, Wnt-1a, Wnt-5a), is involved in the differentiation of Nurr1(+) precursors into dopaminergic neurons (Le et al., 1999b; Castelo-Branco et al., 2003; Nunes et al., 2003).

3.3. Role of Nurr1 in the central dopaminergic neuron development

Numerous studies have documented that Nurr1 is essential for both the survival and differentiation of the mesencephalic dopaminergic precursor cells. Zetterstrom et al. (1997) found that mice with a targeted deletion of the Nurr1 gene die 1day after birth. They have also observed that the mice with deletion of the Nurr1 gene (Nurr−/−) cannot suck milk and have poor motor function. The histopathological examination has found a lack of dopaminergic neurons in SN and VTA in the midbrain, but other areas are spared, including diencephalon, hypothalamus and olfactory bulb (Le et al., 1999a). The TH as well as AADC and dopaminergic neuron transmitter dopamine in the nigro-striatal pathway are also absent (Zetterstrom et al., 1997; Baffi et al., 1999; Le et al., 1999a), but there was no significant alteration of other catecholamines. Subsequent studies have found that in the absence of Nurr1 in mice at embryonic day 11.5, dopaminergic neurons adopt a normal localization in VTA (Zetterstrom et al., 1997; Saucedo-Cardenas et al., 1998) (Fig. 3B), but the late prescursors fail to induce a dopaminergic phenotype (Castillo et al., 1998). Furthermore, the dopaminergic precursor cells in midbrain degenerate, and the levels of Pitx-3 decrease as a result of apoptosis of the mesencephalic dopaminergic precursor cells (Saucedo-Cardenas et al., 1998). In contrast to the Nurr1−/− mice, the heterozygous adult mice (Nurr1+/−) have normal

levels of dopamine level in the corpus striatum, but the level of Nurr1 protein is obviously decreased as compared to normal (Nurr1+/+) mice (Le et al., 1999b).

3.4. Nurr1 regulates other dopaminergic neuron-related gene expression during development

We and others have documented that *Nurr1* can regulate several other gene expressions including TH, AADC, DAT, and VMAT-2 (Sakurada et al., 1999; Schimmel et al., 1999; Sacchetti et al., 2001; Hermanson et al., 2003; Kim et al., 2003) (Fig. 4). Nurr1 interacts with other transcription factors to regulate the transcription of the TH gene by binding to the NBRE sequence in 5′-untranslated region (Schimmel et al., 1999; Hermanson et al., 2003). DAT gene also has NBRE sequence in 5′-untranslated region and, therefore, Nurr1 can also regulate the transcription of DAT gene through its binding to NBRE sequence. Furthermore, Nurr1 can bind to the RXR receptor (retinoid receptor) of ADH2 (retinoic acid converting enzyme) and form heterodimers, which is an important factor in the development and maturation of neuron cells (Sacchetti et al., 2002; Wallen-Mackenzie et al., 2003).

In addition to its effects on the dopaminergic system, Nurr1 can directly transactivate the osteocalcin gene (Pirih et al., 2004) and regulate adrenal aldosterone production (Bassett et al., 2004).

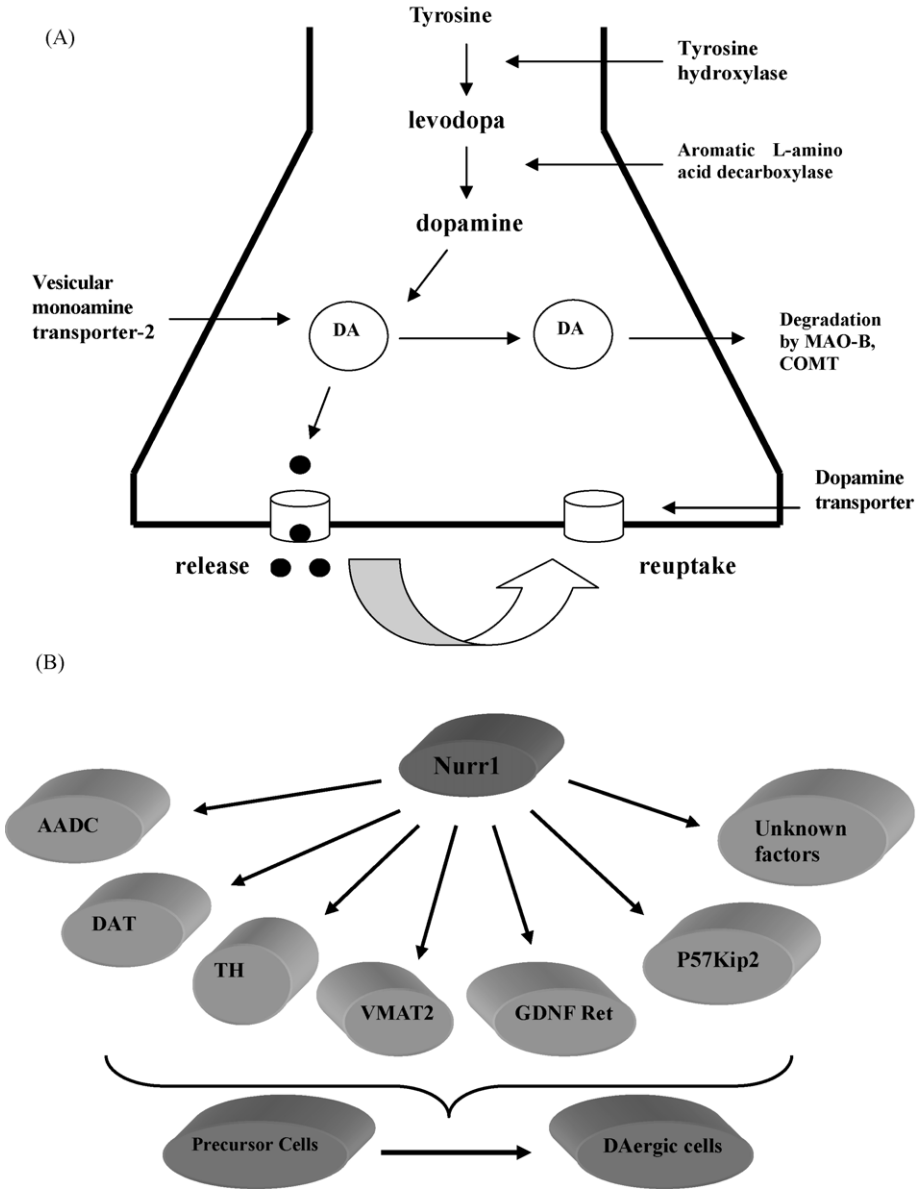

Fig. 4. Nurr1 regulates expression of AADC, DAT, TH, VMAT-2 Ret and P57Kip2 that are essential in DAergic phenotype and functional maintenance. (A) Shows the process of synthesis of dopamine. TH and AADC are critical enzymes for biosynthesis of dopamine. VMAT-2 participates in the storage of dopamine and DAT takes part in reuptake of dopamine. (B) Introduction of AADC, DAT, GDNF Ret, TH, P57Kip2, VMAT-2 and other unknown factors in mensencephalic DA neurons requires Nurr1.

4. Interaction between Nurr1 and other essential factors in dopaminergic neuron development

4.1. Pitx-3

There is an emerging body of evidence that suggests that a ''cross-talk'' between Nurr1 and several other transcriptional factors and neurotrophic growth factors may exist in different development and maturation stages of mensencephalic dopaminergic neurons. Pitx-3 is the bicoid-related homeodomain-containing transcription factor that is only expressed in mesencephalic dopaminergic neurons (van den Munckhof et al., 2003) (Fig. 3). High levels of Pitx-3 are detected in Nurr1−/− mice at embryonic day 11.5, which indicates that the expression of Pitx-3 is independent of Nurr1 in early development stages; as development progresses, these Nurr1−/− mice display loss of Pitx-3 expression and increase in apoptosis of ventral midbrain neurons, which suggests that Nurr1 may be critical for the maintenance of Pitx-3 in the late stages of dopamine neuron development (Saucedo-Cardenas et al., 1998). The Pitx-3 gene is mutated in the Aphakia (ak) mice model, characterized by abnormal anatomical organization of the mesencephalic dopaminergic system, loss of nigrostriatal fibers and dopaminergic neurons specific to the SN, and impaired innervation of the striatum (Hwang et al., 2003; van den Munckhof et al., 2003). In addition, homeodomain transcription factor Pitx3 has been demonstrated to facilitate the differentiation of mouse embryonic stem cells into AHD2-expressing dopaminergic neurons (Chung et al., 2005).

4.2. Lmx1b

Lmx1b is a member of the LIM hemodomain family that is an essential factor in development of dopaminergic neurons (Smidt et al., 2000) (Fig. 3B). Lmx1b expression starts at E7.5, earlier than Nurr1 (E10.5) and Pitx-3 (E11.5), and its expression is independent of Nurr1 (Smidt et al., 2000). Lmx1b is not required for the expression of TH, but it is necessary for the expression of Pitx3, which is essential for the specification of the midbrain dopaminergic neurons (Saucedo-Cardenas et al., 1998; van den Munckhof et al., 2003). Lmx1b−/− mice lack the necessary molecular signals to differentiate and maintain mesencephalic dopaminergic neurons in ventral midbrain (Smidt et al., 2000).

4.3. GDNF receptor

Nurr1 might be associated with several neurotrophic factors that participate in the development of dopaminergic neurons. These neurotrophic factors include GDNF, BDNF and fibroblast growth factor (FGF). Nurr1 regulates these factors probably by acting as a transcription regulator. Nurr1 is essential for the expression of Ret, a GDNF receptor in the midbrain dopaminergic neurons and in the brain stem (Wallen et al., 2001). GDNF promotes differentiation and development of dopaminergic neurons in rats and primates (Ai et al., 2003). Intraputaminal infusion of GDNF in aged rhesus monkeys shows an 18% increase in the number of TH-positive dopamine neurons and a 28% increase in perikaryal size of dopaminergic neurons (Ai et al., 2003). This process partly relies on the expression of Nurr1 as the expression of Nurr1 (and Pitx3) was significantly higher in GDNF-treated rats (Roussa and Krieglstein, 2004a,b). In addition, Grothe et al. have found that FGF-20 promotes the differentiation of neural stem cells that express Nurr1 into TH-positive neurons (Grothe et al., 2004). The interaction between Nurr1 and neurotrophic factors may play an important role in the development of dopaminergic neurons.

4.4. Other essential factors

Nurr1 also interacts with Wnts, a family of glycoproteins that regulates cell proliferation and differentiation (Castelo-Branco et al., 2003) (Fig. 3). Another factor with which Nurr1 interacts is p57kip2, a kinase inhibitor of the CIP/KIP family, whose expression in postmitotic differentiating midbrain dopaminergic neurons partly depends on Nurr1 (Joseph et al., 2003). Nurr1 may also interact with the GRIK5 gene, which codes for kainate receptor (KA2), a subunit of the glutamate receptor (Chew et al., 1999).

5. The role of Nurr1 in the pathogenesis of PD and related disorders

5.1. Pathogenesis of PD

PD is a progressive neurodegenerative disease, characterized by motor symptoms such as tremor, rigidity, bradykinesia and postural instability, as well as a variety of non-motor symptoms, that occurs in all ethnic groups and is increasingly common with advanced age (Jankovic, 2005). The pathologic examination shows the loss of pigmentation cells in SN and the presence of Lewy bodies that stain with α-synuclein, ubiquitin, synphilin-1, Parkin, UCH-1 and other proteins that accumulate and aggregate to form the cytoplasmic inclusions (Dawson and Dawson, 2003). Dysfunction of mitochondria and impairment of ubiquitin proteasome system have been thought as leading causes to dopaminergic neuron degeneration (Olanow, 2002; Dawson and Dawson, 2003). The early diagnosis of PD is based on recognition of typical symptoms, although functional imaging, such as DAT-SPECT and F-DOPA PET, is currently studied as a potential marker for early diagnosis and progression of the disease (Jankovic, 2005). In addition to sporadic PD, an increasing number of genetically-defined forms of PD has been reported (Vila and Przedborski, 2004).

5.2. Association of Nurr1 gene with PD

Several studies have found that abnormalities in Nurr1 gene might be risk factors for both familial PD and sporadic PD. Nurr1 gene contains at least four single nucleotide polymorphisms (SNP) (Xu et al., 2002; Le et al., 2003). One of the SNP is in the BseRI restriction site resulting in a homozygous

7048G7049 in intron 6 (NI6P), which shows a significantly higher frequency in familial and sporadic PD (Xu et al., 2002) and diffuse Lewy body disease (Zheng et al., 2003). Furthermore, variants in Nurr1 gene have been found in association with familial PD (Le et al., 2003). Genetic analyses in 201 individuals with PD identified two variants in Nurr1 (−291T del and −245 T → G), mapping to the first exon of Nurr1 and affect one allele in individuals with familial PD with apparently autosomal dominant form but not in individuals with sporadic PD (Le et al., 2003). These affected PD patients are Caucasians of European descent. Phenotypes of patients with variants in the Nurr1 gene are identical to those of late-onset PD but no pathological data are currently available. These variants are found to decrease Nurr1 mRNA level in lymphocytes and affect the transcription of gene that encodes TH. It is postulated that these variants could cause dysfunction of dopaminergic neurons and lead to PD. The variants in Nurr1 in PD seem to be very rare and population-restricted (Carmine et al., 2003; Tan et al., 2003; Wellenbrock et al., 2003; Hering et al., 2004). Recently, two novel variants at exon3 of Nurr1 gene were identified in two non-familial PD patients (Grimes et al., 2004). The first, a heterozygous C–G transvertion at exon3 (−253), changes the amino acid serine to cysteine and the second is a −223C → T sequence. Either or both of these mutations may affect phosphorylation procedure in transcription of the gene encoding TH. Further studies including haplotype analysis and pathophysiology determination are needed to clarify whether the reported variants are disease causing mutations or susceptible polymorphisms to PD.

5.3. Reduced Nurr1 expression in PD

Decline of Nurr1-ir neuronal number and optical density (OD) has been observed in SN neurons but not within hippocampal neurons in PD (Chu et al., in press). In PD, the OD of Nurr1-ir is significantly decreased in nigral neurons that contained α-synuclein inclusions but not inclusion-negative neurons. The decline in Nurr1-ir expression is correlated with loss of TH-ir in PD. However, in the nigra of Alzheimer's disease and progressive supranuclear palsy, the OD of Nurr1-ir was decreased in neurons with neurofibrillary tangles (Chu et al., in press). These data demonstrate that Nurr1 is a sensitive marker for dopaminergic neuronal degeneration in both α-synucleinopathies and tauopathies, and the loss of Nurr1 is associated with the intracellular pathology of these diseases.

Quantitatively measuring the level of Nurr1 mRNA in human peripheral blood lymphocytes has revealed a significant decrease in individuals with PD and parkinsonian syndromes (Pan et al., 2005a). Therefore, detection of Nurr1 mRNA levels in peripheral blood could be used as a peripheral biomarker of dopaminergic system and as an early method in the diagnosis of PD and parkinsonian syndromes in the future.

5.4. Dopaminergic dysfunction in Nurr1 knock-out animals

Heterozygous Nurr1 knock-down mice (Nurr1+/−) have been used to study the correlation between the levels of Nurr1 expression and nigral dopaminergic neuron function (Le et al., 1999b; Jiang et al., 2005). Changes in locomotor activity, thought to be related to reduced mesolimbic and mesocortical dopamine levels without obviously altered striatal dopamine levels, have been reported in adult Nurr1+/− mice (Eells et al., 2002; Backman et al., 2003), and these Nurr1+/− mice have been found to have increased vulnerability to neurotoxin MPTP-induced nigral injury (Le et al., 1999b). Old Nurr1+/− mice (>15 month) displayed a significant decrease in the rotarod performance and locomotor performance compared with the normal Nurr1+/+ mice and adult Nurr1+/− mice (Jiang et al., 2005). The reduction of rotarod and locomotor performance correlates with the decreased striatal dopamine and Nurr1 mRNA levels in an age-dependent manner (Jiang et al., 2005). In contrast, over-expression of Nurr1 in mouse neuronal stem cells have been found to have neuroprotective effects against neurotoxin 1,2,3,6-methyl-phenyl-tetrahydro-pyridine (MPTP)-induced cell death (Lee et al., 2002).

5.5. Interaction of Nurr1 with PD-related genes

It is suspected that Nurr1 may interact with PD-related genes. Using siRNA interference to suppress Nurr1 expression at least 75% in human dopaminergic cell line SH-SY5Y, the mRNA levels of dopaminergic neuron associated genes TH, DAT, AADC, and VMAT2 are markedly decreased by 50–72% (Deng et al., 2005). Interestingly, the PD-related gene PINK1 expression is also decreased by 70% while α-synuclein expression is moderately but significantly increased by 25% (Deng et al., 2005). Baptista et al. (2003) have investigated transcriptional changes of genes known to be involved in dopamine synthesis in dopaminergic neuroblastoma cell line transfected with either normal or mutant (A30P or A53T) α-synuclein. They have found that expression of Nurr1 is significantly reduced in the cells transfected with either normal or mutant (A30P or A53T) α-synuclein, suggesting that dopamine synthesis is, at least in part, regulated by this transcription factor. It is possible that some patients with PD start with fewer dopaminergic neurons and as a result of age related attrition coupled with neurodegeneration related to toxic effects of accumulated misfolded protein, the threshold for dopamine depletion severe enough to produce parkinsonian symptoms is reached earlier than otherwise (Jankovic, 2005). Besides genetically determined lack of dopaminergic neurons, there is some evidence that other prenatal factors may predispose some individuals to an age-related dopaminergic deficiency and parkinsonism. Carvey et al. (2003) have demonstrated that dopaminergic neurons are damaged in offspring as a result of prenatal exposure to the bacteriotoxin lipopolysaccharide. In addition, several drugs may affect the expression of Nurr1. Lithium, an anti-neuropsychiatric disorders drug, has been identified to reduce the expression of Nurr1 in rat model (Al et al., 2004).

5.6. Possible role of Nurr1 in mental disorders

To investigate whether defects in Nurr1 contribute to mental disorders, Buervenich et al. (2000) have examined over 300

patients and found two different missense mutations in the third exon of Nurr1 in two schizophrenic patients and another missense mutation in the same exon in an individual with manic-depressive disorder. All three mutations cause a similar reduction of in vitro transcriptional activity of Nurr1 dimers by about 30–40% (Buervenich et al., 2000).

5.7. Nurr1 and cocaine abusers

Chronic exposure to cocaine induces long-term adaptations resulting in markedly decreased Nurr1 expression within the dopamine neurons of human cocaine abusers (Bannon et al., 2002). Nurr1 is known to regulate transcription of the gene encoding the cocaine-sensitive DAT and DAT gene expression is markedly reduced in the dopamine neurons of Nurr1-deficient cocaine abusers (Bannon et al., 2002), suggesting that Nurr1 plays a critical role in controlling human DAT gene expression and adaptation to repeated exposure to cocaine.

6. The role of Nurr1 in the treatment of PD

6.1. Nurr1-gene engineered stem cells

In recent years, gene therapy and stem cell therapy in PD and other neurodegenerative diseases have been at center stage of public and scientific interest. Cells derived from the fetal midbrain can modify the expression of the disease, but they are not an adequate or stable source of dopamine-synthesizing neurons. In contrast, embryonic stem (ES) cells proliferate extensively and can generate dopamine neurons. Kim et al. (2002) and Chung et al. (2002) have reported that a highly enriched population of midbrain neural stem cells can be derived from mouse ES cells after transfection with Nurr1 gene. These genetically engineered dopaminergic ES cells show electrophysiological and behavioral properties expected of SN-derived dopaminergic neurons (Kim et al., 2002).

6.2. Drugs that induce Nurr1 expression

Dopamine receptors D2 may have influence on the Nurr1 expression. In dopamine receptor D2-deficient mice the Nurr1 mRNA expression is found to be significantly increased in the SN region probably as a compensatory consequence of an impaired dopamine autoreceptor function (Tseng et al., 2000).

Dopamine receptor agonist pramipexole is found to have the capability of enhancing the expression of mRNA and protein of Nurr1 and other dopaminergic neuron associated genes in human dopaminergic cell line SH-5YSY via D3 activation mechanism (Pan et al., 2005b). Another dopaminergic receptor agonist ropinirole has been documented to prevent the progression of PD in Nurr1 deficient mouse model (Jiang et al., 2004). In SH-5YSY cell cultures, treatment with radicicol, a heat shock protein inducer, at 1–10 μM can enhance the expression of Nurr1, correlating with the inhibition of rotenone-mediated apoptosis (Pan et al., 2005c). Furthermore, several small molecules (MW around 200) of Nurr1-like agonists that can mimic Nurr1 transcription activity with excellent bioavailability and can easily cross blood-brain barrier are currently being tested in in vitro and in vivo models of PD (Le et al., 2004). In primary mensencephalic cultures these Nurr1-like agonists can enhance TH and DAT mRNA levels by 2-5-fold. Further studies of these Nurr1-like agonists in animal models of PD have shown promising results (Le et al., 2004). Whether these findings will translate into clinically useful therapy of PD requires further investigation.

7. Conclusion

The reviewed experiments and studies provide evidence that Nurr1 is an important transcription factor in the CNS. Nurr1 is highly expressed in dopaminergic neurons in the midbrain and is essential for the development of midbrain dopaminergic neurons. Nurr1 may also be critical for maintenance of dopaminergic neuron function in adulthood. Dysfunction of the gene may have a pathological role in several neurological and psychiatric disorders. Furthermore, Nurr1 can be a potential target for the study of novel therapeutic strategies in PD.

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