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Nur77 and retinoid X receptors: critical factors in dopamine-related neuroadaptation

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Abstract

Dopaminergic systems in the brain adapt in response to a variety of stimuli from the internal and external world, but the mechanisms underlying this process are incompletely understood. In recent years, evidence has emerged that certain types of transcription factor of the nuclear receptor family, specifically *Nur77* and retinoid X receptors, play an important role in the Nuradaptation, and importantly, in the homeostatic regulation, of dopaminergic systems. These findings call for a reassessment of our fundamental understanding of the molecular and cellular basis of dopaminergic transmission. Given that diseases such as Parkinson's disease and schizophrenia are thought to involve maladaptation of dopamine signalling, these findings might lead new insight into these pathologies and offer new avenues for drug development.

Introduction

Dopamine neurotransmission plays an important role in a large series of physiological functions such as control of motor behaviour, learning, cognition, motivated behaviours and hormone production. Clinical evidences suggest that dopaminergic pathways are involved in several neurological and psychiatric disorders [1]. For example, a gradual loss of midbrain dopamine producing cells result in extensive dopamine depletion in the striatum and the characteristic motor symptoms observed in Parkinson's disease; i.e. bradykinesia, rigidity, resting tremors and postural instability. The main treatment for Parkinson's disease is based on dopamine replacement using the precursor L-DOPA for the biosynthesis of endogenous dopamine. At the other end of the spectrum, a hyperactivity of the mesolimbic dopamine system is thought to be a prominent driving force in the pathophysiology of schizophrenia. This hypothesis is based on the fact that the antagonism of the D_2 class of dopamine receptors is an essential prerequisite for the therapeutic efficacy of antipsychotic medications [2]. Dopamine neurotransmission is also deeply involved in drug addiction. The mesolimbic dopamine system, comprised of dopamine neurons in the ventral tegmental area (VTA) of the midbrain and their projections to the nucleus accumbens and prefrontal cortex, is the

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most important mediator of drug reward [3]. It is generally believed that drugs of abuse usurp the normal functioning of this neural circuitry, which normally controls responses to natural rewards, such as food, sex and social interactions.

The effects of dopamine are mediated through its interaction with G-protein-coupled membrane receptors. The dopamine receptor family contains five members distributed in two subfamilies; the D_1-like family, which includes D_1 and D_5 receptors, and the D_2-like family, which includes D_2, D_3 and D_4 receptors (reviewed in [4]). However, changes in dopamine neurotransmission are short-lived and therefore unlikely by themselves, to account for behavioural changes that are long lasting. Transcription factors are key elements that convert transient and reversible modulation of signal transduction molecules such as kinases (triggered by neurotransmitter receptor activation) to long lasting changes at the molecular and cellular levels. They represent a vast family of genes that encode regulatory factors, which modulate the expression of target genes. They play an important role during brain development and actively participate in adaptive responses following changes in the environment of neuronal cells, such as after ischemia, lesion or denervation and following exposure to drugs that affect neurotransmitter systems in mature brain [5]. The activation of immediate-early genes (IEGs) constitutes one of the initial steps of the mechanisms by which stimuli at the cell membrane are transduced into short and long-term neuronal responses [6]. In recent years, data supporting an important role for a class of transcription factors, namely *Nurs* and retinoid X receptor (RXR) subgroups, in dopamine-mediated effects have emerged. In this review, we will describe recent literature indicating that *Nur77* and RXR work in concert as adaptive and homeostatic regulators of dopamine functions in the context of dopamine-related neuropsychiatric and neurological disorders. Based on current knowledge, we would like to propose a model in which *Nur77* plays a key role as a molecular switch in dopamine-related neuroadaptation processes.

Nurs are versatile transcription factors that exert pleiotropic functions in periphery

Nurs are part of the nuclear hormone receptor superfamily and are defined as the orphan NR4A subgroup, which included *Nur77* (NR4A1 (also known as *Nerve Growth Factor-Inducible gene B* (*NGFI-B*))), *Nurr1* (NR4A2) and *Nor-1* (NR4A3). *Nurs* are classified as early response genes and are induced by a diverse range of signals, including growth factors, cytokines, peptide hormones, neurotransmitters and stress. Their ability to sense and rapidly respond to changes in the cellular environment appears to be a hallmark of this subgroup. These receptors bind as monomers, homodimers and heterodimers with RXR to different permutations of the canonical nuclear receptor binding motif (Fig. 1). In line with the pleiotropic physiological stimuli that induce the expression of members of the *Nurs* subgroup, they have been implicated in cell cycle regulation (and apoptosis), steroidogenesis, inflammation, carcinogenesis and atherogenesis (for review see [7]). For example, *Nur77* represents a key regulator of the negative selection of thymocytes. Nuclear export of *Nur77* plays an important role in modulation of retinoid signalling in PC12 phaeochromcytoma cells and in a Bcl-2-dependent apoptotic cascade in specific cancer cell contexts [8]. In the cardiovascular system, *Nur77* is involved in vascular cell functions by

regulating endothelial cell activation and vascular smooth muscle cell proliferation [9]. In the neuroendocrine system, *Nur77* is associated with the control of proopiomelanocortin expression and corticotropin-releasing hormone activity [10]. However, its role in the central nervous system (CNS) remains mostly unexplored.

Retinoic acids (RA) regulate the expression of numerous target genes by activating two specific transcription factors, Retinoic Acid Receptor (RAR) and RXR. These transcription factors are also members of the nuclear receptor superfamily. RARs are specifically involved in retinoid signalling, whereas RXRs serve as heterodimerization partners for other nuclear receptors including vitamin D receptor, thyroid hormone receptors, peroxisome-proliferator-activated receptors, liver X receptors, farnesoid X receptors and orphan members of the nuclear receptor family, such as *Nurr*1 and *Nur77* (Fig. 1) [11–13]. Again, these nuclear receptors interactions have been mainly observed in peripheral tissues.

Relationships between *Nurs*, retinoids and brain dopamine systems

Recent evidence suggests that orphan members of the *Nur* subgroup are closely associated with dopamine neurotransmission via their action as transcription factors (Fig. 2). In absence of *Nurr1*, dopamine midbrain precursors adopt normal localization and neuronal phenotype, but fail to differentiate into dopamine neuron phenotype, as demonstrated by the lack of tyrosine hydroxylase (TH) expression and all other analysed dopamine neuron markers [14]. In normal conditions, *Nur77* and *Nor*-1 are mainly expressed in target areas of dopamine neurons, such as the striatal complex and prefrontal cortex (Fig. 2A,B) [15–17]. Their mRNA levels are extremely low in the substantia nigra (SN) and VTA in basal conditions in the adult brain [15]. However, their expression can be significantly increased in the SN/VTA complex by administration of dopamine D_2 antagonists (Fig. 2C) [18] suggesting that their expression in this brain area is tonically repressed in normal conditions.

Several lines of evidence suggest a close relationship between retinoids and dopamine systems as well. First, brain areas receiving dopamine innervations such as the striatum, nucleus accumbens and olfactory tubercle expresses both RARβ and RXRγ isoforms [19–21]. In fact, the distribution of the RXRγ1 isoform is specifically associated with dopamine pathways in the mature CNS (Fig. 2) [22]. Second, genetic manipulations have shown that RARβ/RXRγ–deficient mice displayed impaired locomotion and dopamine signalling and prominent decreases in D_1 and D_2 receptor mRNA in the striatum [23], whereas RXRγ1–null mice exhibit an altered response to a typical neuroleptic [22]. Third, several lines of evidence support a role of retinoid signalling in schizophrenia [24]. Finally, it has been shown that RXR ligands can promote the survival of dopaminergic cells in a process mediated by *Nurr1*-RXR heterodimers [25]. Thus, anatomical and genetic data suggest that *Nurs* and retinoid receptors can be associated with dopamine systems.

A tremendous body of evidence indicates that transcription factors of the Fos family are involved in dopamine-mediated events [26]. For example, the *c-fos* mRNA and Fos-like proteins (FosB, ΔFosB) levels are strongly modulated by many products that altered dopamine neurotransmission [27]. However, recent data show that orphan nuclear receptors

Nur77 and *Nor*-1 represent other transcription factors whose expression is strongly modulated in response to dopamine transmission manipulation (see Fig. 3 and Table 1).

Nur77 and RXR in schizophrenia model and antipsychotic drug effects

Haloperidol, a typical neuroleptic, increased *Nur77* mRNA levels in a selective striatal cell population expressing the neuropeptide enkephalin (ENK) (Fig. 3 and Table 1) [16]. This striatal subpopulation, which also bears dopamine D_2 receptors, is specifically associated with the indirect striatal output pathway. We have recently shown that modulation of *Nur77* mRNA levels can be used to calculate an index predictive of the typical *vs* atypical profile of antipsychotic drugs [18] in a similar fashion to what has been observed with Fos-like protein expression [28]. Inductions of *Nurs* (*Nur77* or *Nor*-1) are correlated with dopamine D_2 and D_3 receptor affinities and 5-HT_{2A}/D_2 affinity ratios can also be used to predict *Nur77* and *Nor-1* patterns of expression [18]. Interestingly, *Nur77* mRNA up-regulation is maintained upon chronic typical antipsychotic drug treatments without any apparent desensitization, suggesting that *Nur77* not only participate in the initiation of a neuroadaptive signalling cascade but also to more prolonged effects [16, 19]. Thus, *Nurs* represent another important class of transcription factors that react to modification of dopamine neurotransmission. Although the patterns of expression of *c-fos* and *Nur77* are sometime similar, we do not know yet if these two classes of transcription factors act in synergy or if they have distinct subset of transcriptional targets.

Nur77 and RXR are also directly involved in motor side effects produced by typical antipsychotic drugs (Fig. 3 and Table 1). Moreover, the effects of antipsychotic drugs are significantly altered by genetic ablation of *Nur77*. *Nur77*(−/−) mice have a blunted cataleptic response to typical antipsychotics and this blunted response is restricted to dopamine D_2 antagonists [29]. The effects of haloperidol on the neuropeptide ENK and neurotensin mRNA are also significantly reduced in *Nur77*(−/−) mice [29], suggesting again a preferential effect on dopamine D_2-mediated processes. Mice display vacuous chewing movements (VCMs) following chronic haloperidol treatment. These VCMs share similarities with tardive dyskinesias in man. Interestingly, this response is exacerbated in *Nur77*(−/−) mice [30]. We have previously showed that *Nur77* transcripts are highly co-localized with RXRγ1 isoform in the striatum following haloperidol treatment [29]. This drug-induced co-localization of *Nur77*-RXRγ1 may have triggered new interactions between *Nur77* and RXR in striatal cells. Trying to decipher the mechanisms involved in haloperidol-induced behavioural effects, we have demonstrated that both the cataleptic and VCM responses are altered by retinoid ligands, such as 9-*cis* retinoic acid (9-*cis*RA), docosahexaenoic acid (DHA) (a polyunsaturated fatty acid that acts as an endogenous RXR ligand in the CNS [25, 31]) and HX531 (a synthetic RXR antagonist) [29, 30]. Interestingly, HX531 and DHA remain inactive on VCM responses in *Nur77*(−/−) mice, indicating that *Nur77* is needed for the expression of the effect of these compounds [30]. Taken together, these observations indicate that *Nur77* and RXR actively participate to antipsychotic drug effects and are associated with the generation of abnormal movements induced by dopamine receptor antagonists.

Additional data suggest that *Nur77* might also be involved in the expression of some schizophrenia symptoms (Table 1). Indeed, *Nur77* mRNA levels correlate with prefrontal cortex hypo-activity and sub-cortical hypersensitivity to psychostimulants in an animal model of schizophrenia. We have observed that *Nur77* mRNA levels are reduced in prefrontal and cingulate cortices of adult rats bearing a neonatal lesion of the ventral hippocampus [32]. Interestingly, a similar reduction of *Nur77* expression has been recently observed in prefrontal cortex of schizophrenic patients in a *post mortem* brain tissue analysis [33]. Neonatal ventral hippocampus lesioned animals also display an increased sensitivity to amphetamine and stronger induction of *Nur77* in subcortical brain regions [32]. These effects are reminiscent to the behavioural sensitization induced by psychostimulants in schizophrenic patients [34, 35]. *Nur77* and *Nor*-1 mRNA levels are also correlated with behavioural manifestations associated with cocaine and morphine administration (Table 1) [17, 36, 37].

Finally, *Nur77*(−/−) mice display alterations of dopamine neuron biochemical activity and disturbance of prefrontal cortex dopamine neurotransmission (Table 1). *Nur77*(−/−) mice are spontaneously hyperactive and are more sensitive to a low dose of a D_2 agonist acting mainly at pre-synaptic autoreceptor sites [38]. This suggests that dopamine neuron activity may be altered in these mice. Indeed, dopamine neuron biochemical activity and dopamine turnover are altered in *Nur77*(−/−) mice. These changes are accompanied by altered TH and catechol-O-methyltransferase (COMT) expression in *Nur77*(−/−) mice [38]. Since COMT gene polymorphisms that reduce its activity have consistently been linked with an increased risk of schizophrenia [39, 40], this observation suggests that *Nur77* might play a role in the regulation of mesocorticolimbic dopamine pathway and might be associated with generation of psychotic symptoms.

Nur77 and RXR in animal model of Parkinson's disease and anti-Parkinsonian drug effects

Several lines of evidence suggest the involvement of *Nur77* in Parkinson's disease and its therapeutic treatment (Table 1). We have observed important and complex modulations of striatal *Nur77* mRNA expression following denervation and L-DOPA treatment in two different animal models of Parkinson's disease; unilateral 6-hydroxydopamine (6-OHDA)-lesioned rats and *Aphakia* mutant mice [41–44]. In normal conditions, *Nur77* is expressed equally in both striatal output pathways. In unilateral 6-OHDA rats, denervation induces an up-regulation of *Nur77*, which takes place selectively in striatal ENK-containing cells (see Fig. 3 and Table 1). On the other hand, the percentage of striatal cells with co-localized *Nur77* and dynorphin (DYN), a selective marker of the direct striatal output pathway, is significantly reduced in the lesioned side [42]. However, in the intact side of the striatum, *Nur77* mRNA levels are increased in DYN-containing cells following L-DOPA treatment (Fig. 3 and Table 1) [42]. This imbalance between the two striatal output pathways that is first initiated by denervation then further exacerbated by repeated L-DOPA treatment suggests that these molecular changes may contribute the development of behavioural sensitization and long term effects of L-DOPA. This is supported by the fact that *Nur77*(−/−) mice show impaired behavioural and molecular adaptations to denervation and repeated L-

DOPA treatment [45]. It is interesting to note that *Nur77* can be selectively up-regulated in the DYN-containing cells by the co-administration of dopamine D_1 and D_2 agonists in normal rats (Fig. 3 and Table 1), suggesting that the specific expression of *Nur77* in the indirect striatal output pathway (ENK^+-cells) in 6-OHDA rats might be caused by a change in dopamine signalling cascade associated to the denervation process [46]. *Nur77* mRNA levels are also up-regulated in *Aphakia* mice, which bear a natural deletion of the homeobox Pitx3 gene locus that alters midbrain dopamine neuron development [43]. These mice display hypokinesia that can be restored with L-DOPA treatment and they show striatal biochemical alterations very similar to those observed in 6-OHDA animals [43].

Since RXR in association with *Nur77* are involved in haloperidol-induced VCMs and since L-DOPA-induced dyskinesias (LIDs) may share some homologies with neuroleptic-induced tardive dyskinesia, we investigated the effects of DHA, an endogenous activator of RXR, on LIDs in monkeys treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [47]. We have shown that DHA can reduce the severity or delay the appearance of LIDs in a non-human primate model of Parkinson's disease suggesting new targets for the improvement of the quality of life of people suffering from this debilitating disease. Although data obtained in rodent models clearly indicate that DHA activity can be dependent on *Nur77* expression [29, 30], additional experiments using more selective RXR ligands need to be performed since DHA may alter brain functions through other mechanisms [48]. Altogether these observations suggest that *Nur77* and RXR are associated with abnormal movements observed in Parkinson's disease and generated after classic dopamine replacement therapy.

Nur77 and RXR in dopamine-mediated neurotransmission

Current knowledge suggests a kind of yin-yang relationship between *Nur77* and dopamine; *Nur77* levels of expression are modulated by manipulation of dopamine neurotransmission and in turn, *Nur77* expression modulates dopamine-mediated effects (Table 1). Based on these observations, we can propose that; 1) *Nur77* and RXR are involved in a dopamine-mediated adaptive signalling pathway that tends to reduce the effect of alterations of the dopamine neurotransmission; 2) they are essential for maintaining the homeostasis of striatal dopamine functions by setting the threshold for the adaptive capacity of the striatal dopamine system; and 3) RXR ligands can be used to manipulate this *Nur77*-dependent pathway.

At first glance, *Nur77* can be viewed merely as another transcription factor, along with Fos and others, but its nuclear receptor nature and its putative interaction with RXR in brain dopamine system render it unique amongst other transcription factors involved in dopamine-mediated responses. Indeed, the absence (gene knockout) or reduction (animals bearing a neonatal lesion of the ventral hippocampus) of *Nur77* expression generates exacerbated responses of the dopamine system upon challenges. Therefore, *Nur77* seems essential for some neuroadaptive properties of the dopamine system. It represents a previously uncharacterized element in those dopamine-mediated responses.

Nurs are characterized by their ability to sense and rapidly respond to changes in the cellular environment. So far, modulation of *Nur77* mRNA levels in the CNS has been observed. Figure 4 shows modulation of the *Nur77* immunohistochemistry signal following challenge with dopaminergic drugs. Haloperidol increases *Nur77* immunostaining in the lateral portion of the striatum, whereas amphetamine had a more medial effect (Fig. 4). These patterns of *Nur77* immunostaining induction are similar to previously observed mRNA-induced patterns [16, 29, 32, 42].

Nur77 is a direct target of kinases, such as protein kinase A (PKA), that are associated with signalling pathways of G protein-coupled receptors [49, 50]. Additional signalling pathways have been shown to modulate *Nur77* expression and/or activity including; Mitogen-Activated Protein (MAP) Kinases (Extracellular signal-Regulated Kinases 1/2 (ERK1/2), c-Jun NH_2-terminal Kinase, (JNK) and p38 MAP kinase) [51–53], Mitogen- and Stress-activated Kinase (MSK) [54], Ribosomal S6 Kinase (RSK) [55] and Akt (Protein Kinase B) [56, 57] pathways in different cellular contexts (mostly in lymphocyte T cells). However, the signalling cascade leading to modulation of *Nur77* mRNA levels in the brain has never been investigated. The state of phosphorylation of *Nur77* is also critical for its function. Indeed, phosphorylation of *Nur77* can modulate its transcriptional activity, subcellular localization and heterodimerization with RXR [53, 55–57]. Outside the brain, translocation of *Nur77* from the nucleus to the cytoplasm is associated with apoptotic pathways and regulates retinoid-dependent signalling [8, 58]. We have previously shown that antipsychotic drugs increase the cellular co-localization of *Nur77* and RXRγ1 isoform in striatal cells [29] and that *Nur77* is mandatory for retinoid ligand activities over some dopamine-mediated effects [29, 30]. Thus, signalling events leading to phosphorylation of *Nur77* may have an important impact on its activity. Clearly, further studies will be necessary to identify signalling cascades leading to the modulation of *Nur77* expression as well on its phosphorylation state in the CNS.

Analysis of the functional role of members of the *Nur* family in the periphery is complicated by some functional redundancy [7]. For example, *Nor-1* can compensate for the genetic deletion of *Nur77* in T cell mediated apoptosis [59]. However, functional redundancy of *Nur77* and *Nor-1* has not been observed so far in dopamine systems. The cataleptic response to dopamine D_2 antagonists is not altered in *Nor-1* knockout mice [29] and they display behavioural alterations distinct from *Nur77*(−/−) mice in response to amphetamine (unpublished observations). Interestingly, it has been shown that *Nor-1* cannot form heterodimers with RXR [60]. Taken together, these results suggest that *Nor-1* and *Nur77* may have distinct functions in striatal dopamine-mediated effects. This may confer some brain selectivity for *Nur77*/RXR-related activities.

The close relationship between *Nur77*, RXR and dopamine system deduced from anatomical observations and altered responses to RXR ligands in *Nur77* knockout mice indicate that *Nur77* and RXRγ1 isoform might interact in striatal cells and form a transcriptional complex, which might modulate dopamine-mediated processes. The RARβ isoform is also largely express in the striatum [19, 20, 61] and both RARβ1-3 and RXRγ1 are highly co-expressed (near 100%) in striatum (Fig. 5). Thus, in basal conditions (in which *Nur77* expression remains low) transcriptional complexes composed of RAR/RXR might

predominate (Fig. 6). RXR is a silent partner in such a complex, i.e. this complex cannot respond to selective RXR ligands [60]. When *Nur77* is induced, it might favour the formation of *Nur77*/RXR heterodimers (Fig. 6). Hence, striatal cells now become responsive to RXR ligands, because RXR is an active partner in such an heterodimer complex [60]. Thus, *Nur77* could also be viewed as a molecular switch that allows striatal cells to become responsive to RXR ligands (Fig. 6). This model is consistent with the observations gathered so far in this system, but additional experiments will be required in order to demonstrate the presence of these transcriptional complexes in striatal cells.

Concluding remarks

Altogether, these findings call for a reassessment of our fundamental understanding of the molecular and cellular basis of dopaminergic transmission. Given that diseases such as Parkinson's disease and schizophrenia are thought to involve maladaptation of dopamine signalling, these findings might lead to new insight into these pathologies and offer new avenues for drug development. Indeed, synthetic retinoid ligands (also called rexinoids) or a new class of *Nur77* agonists recently identified [62] could eventually be used as new therapeutic targets for dopamine-related disorders. However, many important aspects remain to be further explored. Signalling pathways that trigger *Nur77* expression and/or phosphorylation in the brain needs to be documented. Genes targeted by a *Nur77*-RXR dependent transcriptional activity remain to be identified. Although we have identified some putative candidates, as discussed herein (enkephalin, neurotensin and COMT), a more global understanding of the role of these transcription factors into brain dopamine physiology is essential.

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Abbreviations

6-OHDA	6-hydroxydopamine
CNS	central nervous system
COMT	catechol-O-methyltransferase
DHA	docosahexaenoic acid
DYN	dynorphin
ENK	enkephalin
EPS	extrapyramidal symptoms
IEG	immediate-early gene

LID	L-DOPA-induced dyskinesias
NGFI-B	Nerve-Growth Factor Inducible gene B
RA	retinoic acid
RAR	retinoic acid receptor
RXR	retinoid X receptor
SN	substantia nigra
VCM	vacuous chewing movement
VTA	ventral tegmental area

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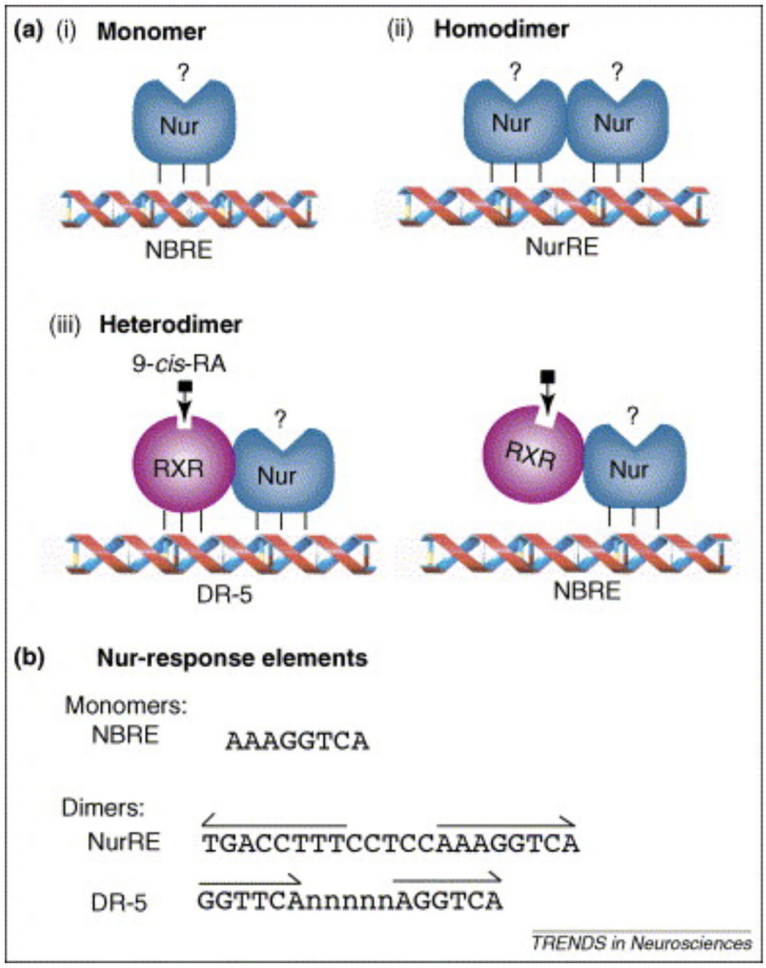

Figure 1. Transcriptional mechanisms of action of *Nurs*

Nurs can exert their transcriptional activity through multiple mechanisms. They can interact with the Nerve Growth-factor Inducible gene B (NGFI-B) Responsive Element (NBRE) as monomers **(A)**, as homodimers on the *Nur* Responsive Element (NurRE) **(B)** or as heterodimers with retinoid X receptor (RXR) as a partner on the retinoic acid direct repeat-5 (DR-5) responsive element or on the NBRE site **(C)**. Note however that *Nor*-1 cannot form heterodimer with RXR [60]. **(D)** DNA sequences of the various *Nur* response elements. The NurRE is composed of two canonical NBRE sites. The NurRE sequence presented corresponds to the previously characterized proopiomelanocortin promoter sequence [70]. The *Nur*-responsive DR-5 site is composed of two retinoid responsive half sites separated by 5 random nucleotides (n). This figure is adapted from [71] with the permission of Dr Jacques Drouin, IRCM, Montreal, Qc, Canada.

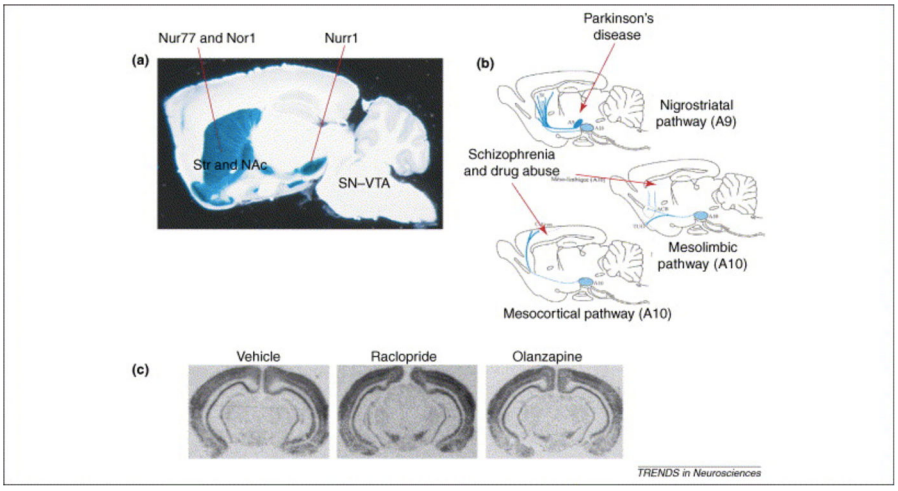

Figure 2. Relationships between Retinoid X Receptor γ1 (RXRγ1) isoform, *Nurs* and CNS dopamine systems

(**A**) RXRγ1 distribution is shown as blue staining on a sagittal section in the adult brain of RXRγ1(+/−) heterozygote mice (adapted with permission from [22]). *Nur77* is expressed in dopaminoceptive areas such as the striatum (Str) and nucleus accumbens (Acc), whereas *Nurr1* is expressed in dopamine neurons of the substantia nigra/ventral tegmental area (SN/VTA) region. (**B**) Note the similarities between the distribution of this RXR isoform in A with dopamine nigro-striatal (associated with the control of motor behaviors and Parkinson's disease), meso-limbic and meso-cortical (associated with associative and limbic functions in schizophrenia and drug abuse) pathways (adapted with permission from [72]). (**C**) *Nur77* is normally not expressed in the SN/VTA region, but typical (raclopride) and atypical (olanzapine) antipsychotic drugs induced high levels of the *Nur77* mRNA in midbrain dopamine cells (adapted with permission from [18]).

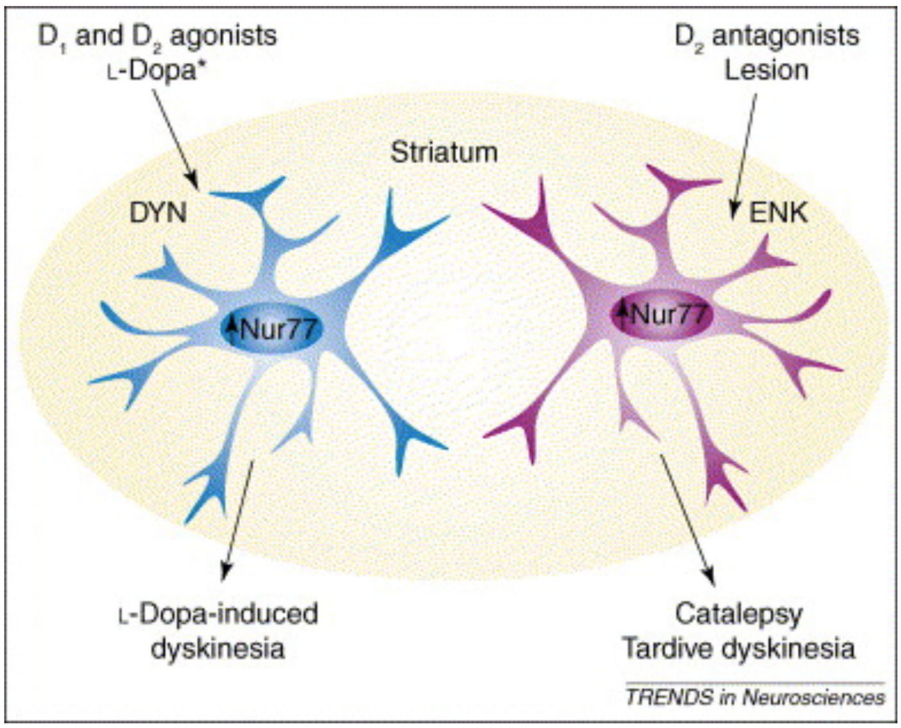

Figure 3. Modulation of *Nur77* mRNA levels in selective cell populations of the striatum is associated with specific locomotor effects

Combined administration of a D_1 and D_2 dopamine agonists, as well as chronic L-DOPA treatment in 6-OHDA-lesioned animals, modulates *Nur77* mRNA levels in dynorphin-containing (DYN) cells of the striatum [42, 44]. In contrast, after D_2 antagonists administration or following denervation *Nur77* mRNA levels are elevated in enkephalin-containing (ENK) cells of the striatum [16, 42]. Modulation of *Nur77* in ENK^+-cells of the striatum is associated with hypokinesia, catalepsy and vacuous chewing movements (tardive dyskinesias), whereas modulation of *Nur77* in DYN^+-cells of the striatum can be associated with L-DOPA-induced dyskinesia and turning behavior in unilaterally lesioned animals. * Note that in unilaterally 6-OHDA-lesioned animals treated with L-DOPA *Nur77* is increased in DYN^+-cells in the intact side of the striatum, whereas *Nur77* mRNA levels are reduced in DYN^+-cells in selective areas of the striatum in the lesioned side [42].

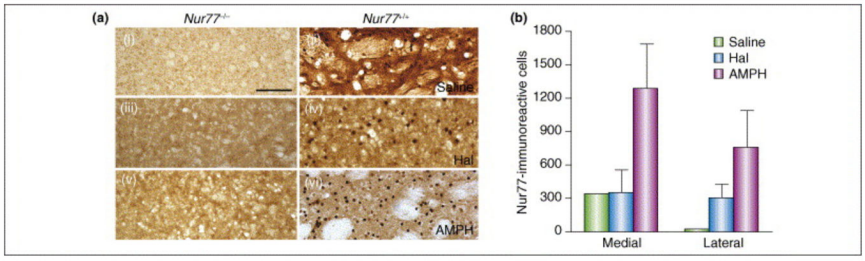

Figure 4. Modulation of *Nur77* proteins levels by dopaminergic drugs

Wild type (*Nur*77(+/+)) and *Nur77* knockout (*Nur77*(−/−)) mice treated with the vehicle (saline) (**A,B**), haloperidol (Haldol, 0.5 mg/kg, i.p.) (**C,D**) or d-amphetamine sulfate (AMPH, 2.5 mg/kg, i.p.) (**E,F**). Immunohistochemistry was performed with the *Nur77* antibody (M210, dilution 1:100, Santa Cruz Biotechnology). Note the absence of specific labelling in *Nur77*(−/−) mice (**A,C,E**). The immunohistochemistry procedure for *Nur77* immunostaining was adapted from [73] with minor modifications. Areas presented correspond to the ventrolateral portion of the striatum. These illustrations are representative of the labelling obtained in 3 animals for each group. Histograms of the **right panel** represent quantification of the total number of *Nur77* positive cells of the medial and lateral portions of the striatum of animals treated with saline (VEH), haloperidol (HAL) or amphetamine (AMPH) (unpublished data).

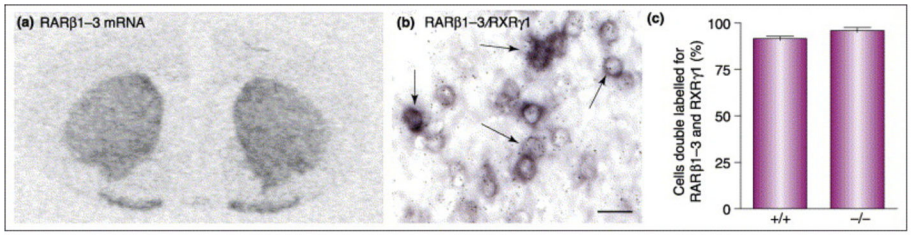

Figure 5. RAR and RXR mRNAs are highly co-localized in the striatum

(A) *In situ* hybridization of Retinoic Acid Receptor isoforms β1-3 (RARβ1-3) transcripts in the rat brain. The picture shows a coronal section of the rat brain illustrating RARβ1-3 mRNA levels in the striatum. (**B**) Representative double *in situ* hybridization using a radioactive-labeled RXRγ1 probe (sylver grains) in combination with a digoxigenin-labeled RARβ1-3 probe (purple depots) in the dorsolataral portion of the striatum (StDL) in wild type mice. (**C**) Quantification of RXRγ1 and RARβ1-3 mRNA levels in StDL of wild type (+/+) and *Nur77* knockout (−/−) mice. Co-localization of these transcripts is nearly 100% in this part of the brain and co-localization of these transcripts is not affected by *Nur77* gene ablation. Histogram bars represent mean ± SEM from 5 animals per groups (unpublished data).

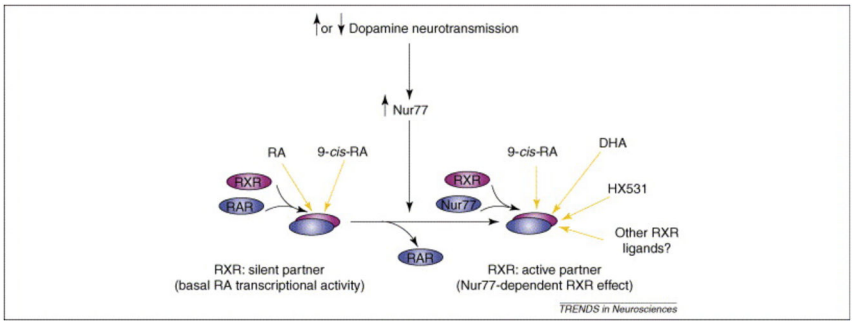

Figure 6. Schematic representation of the molecular switch property of *Nur77* in striatal cells

In basal conditions, co-localization of retinoid X receptors (RXR) along with retinoic acid receptors (RAR) and low expression of *Nur77* transcripts in striatal cells suggest that the transcriptional complex composed of RAR/RXR, in which RXR remains silent, is predominant. When dopamine neurotransmission is altered (antipsychotic agents, indirect agonists such as amphetamine or cocaine, denervation or dopamine replacement therapy), *Nur77* is induced in specific cell populations of the striatum. Then, competition between partnerships of RXR might occur (RAR/RXR vs *Nur77*/RXR). This allows the transcriptional complex *Nur77*/RXR, where RXR is an active partner, to be formed. In this condition, the system becomes responsive to RXR ligands such as docosahexaenoic acid (DHA), HX531 and other selective RXR ligands (to be tested). Note that all-*trans* retinoic acid (RA) only activates the RAR/RXR complex, whereas the derivative 9-*cis* retinoic acid (9-*cis*RA) can activate both complexes.

Table 1

Summary of the data on the relationship between *Nur77* and dopamine systems.

Type of data	Effect	References
Drug treatment		
Dopamine D_1 agonists:	No effect	[42, 63]
Dopamine D_2 agonists:	Decrease *Nur77* mRNA levels	[42, 63]
Combined D_1+D_2 agonists:	Increase *Nur77* mRNA levels (see Fig. 3 for more details)	[42]
Psychostimulants: (amphetamine, cocaine and high dose of caffeine)	Increase *Nur77* mRNA levels in the Str and NAcc	[17, 32, 37, 64, 65]
Typical antipsychotic drugs: (D_2 antagonists)	Strong increase of *Nur77* mRNA levels in the Str, NAcc, PFC and SN/VTA (**see** Fig. 3)	[16, 18, 19, 66]
Atypical antipsychotics:	Moderate to small increase of *Nur77* mRNA levels in the Str, NAcc, PFC and SN/VTA	[18]
Serotonin 5-HT_{1A} agonist:	Decrease *Nur77* mRNA levels	[63]
Serotonin 5-$HT_{2A/C}$ agonist:	Increase *Nur77* mRNA levels	[63]
Adenosine A_{2A} antagonist:	Decrease *Nur77* mRNA levels	[67]
Morphine:	Increase *Nur77* mRNA levels	[36, 68]
Naloxone: (opioid receptor antagonist)	Decrease *Nur77* mRNA levels	[36, 68]
Delta(9)-tetrahydrocannabinol: (THC)	Increase *Nur77* mRNA levels	[69]
Animal models		
Unilateral 6-OHDA lesion in rats (PD model):	Complex modulation of *Nur77* mRNA levels in selective striatal cell populations (see Fig. 3 for detail)	[42]
6-OHDA+L-DOPA:	Complex modulation of *Nur77* mRNA levels in selective striatal cell populations (see Fig. 3 for detail)	[42, 44]
Aphakia mice (PD model):	Increase *Nur77* mRNA levels	[43]
Aphakia mice + L-DOPA:	Decrease *Nur77* mRNA levels (restored to normal)	[43]
nVH lesion (schizophrenia):	Decrease *Nur77* mRNA levels in PFC	[32]
Post-mortem brain tissues in schizophrenics:	Decrease *Nur77* mRNA levels in PFC	[33]
***Nur77* gene knockout**		
Behaviors:	Reduce cataleptic response to typical antipsychotics	[29]
	No effect on the cataleptic response induced by a D_1 antagonist	[29]
	Generate spontaneous VCM and exacerbate antipsychotic-induced VCM	[30]
	Increase spontaneous locomotor activity	[38]
	Increase reactivity to D_2 autoreceptor stimulation	[38]
	Exacerbate L-DOPA-induced turning behavior in unilaterally 6-OHDA-lesioned mice	[45]
Gene expression:	Reduce COMT expression and alter dopamine turnover	[38]
	Reduce lesion- and antipsychotic-induced ENK and NT expression	[29, 45]
	Increase TH and *Nurr1* expression	[38]
	Increase D_2 receptor expression in Str, but not in SN/VTA	[29]

Data on *Nur77* mRNA level modulations are shown for the striatum (Str), when brain areas are not mentioned. Abbreviations: NAcc, nucleus accumbens; COMT, catechol-O-methyltransferase; ENK, enkephalin; NT, neurotensin; TH, tyrosine hydroxylase; PD, Parkinson's Disease; SN/VTA, substantia nigra/ventral tegmental area region; 6-OHDA, 6-hydroxydopamine; PFC, prefrontal cortex; AMPH, amphetamine, nVH lesion, neonatal ventral hippocampus lesion; VCM, vacuous chewing movements