

REVIEW ARTICLE

Progress and Promise of Nur77-based Therapeutics for Central Nervous System Disorders

Lu Liu¹, Di Ma¹, La Zhuo¹, Xinyuan Pang¹, Jiulin You¹ and Jiachun Feng^{1,*}¹Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Changchun, 130021, Jilin Province, China

Abstract: Nur77 belongs to the NR4A subgroup of the nuclear receptor superfamily. Unlike other nuclear receptors, a natural ligand for Nur77 has not been identified yet. However, a few small molecules can interact with this receptor and induce a conformational change to mediate its activity. The expression and activation of Nur77 can be rapidly increased using various physiological and pathological stimuli. *In vivo* and *in vitro* studies have demonstrated its regulatory role in tissues and cells of multiple systems by means of participation in cell differentiation, apoptosis, metabolism, mitochondrial homeostasis, and other processes. Although research on Nur77 in the pathophysiology of the central nervous system (CNS) is currently limited, the present data support the fact that Nur77 is involved in many neurological disorders such as stroke, multiple sclerosis, Parkinson's disease. This indicates that activation of Nur77 has considerable potential in treating these diseases. This review summarizes the regulatory mechanisms of Nur77 in CNS diseases and presents available evidence for its potential as targeted therapy, especially for cerebrovascular and inflammation-related CNS diseases.

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1. INTRODUCTION

Nur77, a member of the nuclear receptor family, is found in a variety of tissues and cells. The regulation of its expression is both cell-dependent and time-dependent, resulting in different influences on gene expression and transcription, according to tissue requirements. For instance, the colocalization and overexpression of Nur77 in the nucleus and cytoplasm of high grade serous ovarian cancers (HGSOC) cells was in accordance with significantly shorter survival time in ovarian cancer patients [1], while Nur77 in the cardiovascular system reduced the risk of atherosclerosis [2]. Odila *et al.* revealed that in the central nervous system (CNS), Nur77 had a widespread expression throughout all regions of the cerebral cortex and selective expression in the limbic system and cerebellum, suggesting that it may have shared roles in the regulation of limbic-associated behavioral, cognitive, and motor function [3]. In recent years, several studies have focused on the relation between Nur77 and CNS. Therefore, this article reviews the functions of Nur77 in the CNS, its association with the diseases involved, and its potential as therapeutic targets.

2. STRUCTURAL CHARACTERISTICS OF NUR77

Nur77 is a member of NR4A subgroup in the nuclear receptor family, also called human homologue testicular

receptor 3(TR3) [4] or rat homologue nerve growth factor inducible gene B (NGFI-B) [5]. Here, we refer to them collectively as Nur77. Like other members of this orphan nuclear receptor, such as NR4A2 (Nur-related factor 1, Nurr1) and NR4A3 (Neuron-derived orphan receptor 1, NOR-1), Nur77 has a transcriptional domain with variable lengths of amino acids at the amino terminal, which contains (a) a ligand-independent activation function 1(AF-1) responsible for interacting with other transcription factors and regulating transcription activity, (b) a DNA-binding domain (DBD) in the middle which consists of two zinc-finger motifs that can interact specifically with DNA sequences, in which high homology amino acid sequences can recognize highly conserved DNA regions, and (c) a ligand binding domain (LBD) at the carboxyl terminus containing a ligand-dependent activation function 1 (AF-2) which can specially connect with corresponding ligands to change molecular conformation to make Nur77 have transcriptional activity [3, 6-8].

3. BIOLOGICAL FUNCTIONS OF NUR77

There has been no identification of a natural ligand for Nur77 yet. It can be initially cloned as an immediate-early response gene when treated by growth factors [9], cytokines, peptide hormones, neurotransmitters [10] and stress [11], and it also interacts with multiple transcription factors, transcription co-regulators, or kinases to form homodimers or heterodimers [12]. Hence, the activity and function of Nur77 are regulated by its expression level, post-translational modification and subcellular location. It can also participate in the

*Address correspondence to this author at the Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Changchun, 130021, Jilin Province, China; E-mail: fengjcf@163.com

control of various cellular events including proliferation, differentiation, apoptosis, metabolism, and inflammation.

3.1. Cell Differentiation, Survival, and Apoptosis

Several studies have confirmed that Nur77 can regulate the activation of cells by changing the expression level, when exposed to extracellular stimuli, thereby affecting cell differentiation and phenotype. For example, Tomioka *et al.* reported that trichostatin A (TSA) can induce neurite outgrowth in PC12 cells and stimulate mRNA and protein expression of the Nur77 gene. The deletion of the Nur77 gene inhibited the growth of neurites induced by TSA. Moreover, the ectopic expression of Nur77 significantly induced the formation of neuronal projections in PC12 cells. Thus, Nur77 is crucial for TSA-induced neuronal differentiation [13]. Hanna *et al.* found that the deletion of the Nur77 gene from hematopoietic cells in Nur77 knockout mice resulted in the loss of monocytes, especially patrolling Ly6C⁺ monocytes. At the same time, the few remaining cells in the bone marrow still remained in the S phase of the cell cycle and underwent apoptosis, suggesting that Nur77 is the master regulator of the differentiation and survival of patrolling Ly6C⁺ monocytes [14]. In contrast, Nur77 can affect macrophages or microglia to show two different phenotypes, namely type 1 (M1) and type 2 (M2) macrophages/microglia. The Nur77-deficient microglia were polarized to an enhanced type 1 (M1) and secreted pro-inflammatory cytokines such as TNF- α , interferon (IFN)- γ , interleukin (IL)-12, IL-23, IL-6, and iNOS [15]. T cells are another type of cells influenced by Nur77. While the proper expression of Nur77 can promote the development of Treg cells by stimulating Foxp3 expression in an experimental autoimmune encephalomyelitis (EAE) model [16], the abnormal regulation of Nur77 leads to changes in T cell subsets, which are manifested as increased Th1/Th17 cells and decreased Treg cells [15]. In general, Nur77-mediated signaling pathways may be a key target for the development of therapies that regulate cell differentiation and control inflammatory events in the early stages of the disease.

Many studies have suggested that Nur77 mediates apoptosis as a transcription factor when subjected to pathological stimulation or even under normal physiological conditions. We believe that Nur77 can lead to apoptosis in neurological diseases owing to many reasons. One reason is the specificity of cell expression. Hao *et al.* found that Nur77-deleted N2a cells (a type of mouse neuroblastoma cells) after hypoxia-reoxygenation (HR) treatment, had decreased expression and activity of the apoptosis-related caspase-3, and caspase-9, when compared with the control group [17]. This study demonstrated that Nur77 is indispensable for the induction of apoptosis. Interestingly, in an *in vitro* cerebral ischemia model, both overexpression and lack of Nur77 influenced the activity and apoptosis of primary neural cells. Increasing the expression of Nur77 even reduced caspase-9 and cytochrome C (cyto C) to inhibit apoptosis [18]. In addition, as a nuclear transcription factor, Nur77 is located in the nucleus in the resting state. The earliest studies showed that apoptosis of cells, induced by cyto C release after activation of Nur77 localized to mitochondria, was the main form of apoptosis caused by Nur77 heterotopia [18]. It can be seen

that changes in intracellular localization of Nur77 are necessary for the pro-apoptotic activity of Nur77. Therefore, some studies have paid attention to factors affecting the subcellular localization of Nur77 [19]. Retinoid X receptor (RXR) is required for Nur77 to be transferred from the nucleus and targeted into the mitochondria. Studies have shown that IGFBP-3 (Insulin-like growth factor binding protein-3) can interact with Nur77 in the cytoplasm, resulting in rapid mitochondrial translocation of RXR α -Nur77 dimer, thereby increasing mitochondrial membrane permeability. This leads to the leakage of cyto C from the mitochondrial matrix into the cytoplasm and activation of the caspase-9/caspase-3 pathway, which in turn mediates apoptosis [20]. Previous studies have also claimed that various signaling pathways that cause Nur77 activation are involved in Nur77-regulated apoptosis, including NF- κ B, MAPK, ERK/ JUK, PKC, PI3K-AKT, among others. Activation of MAPK and phosphorylation at different sites can affect the activity of Nur77 [21]. NF- κ B in the nucleus can bind to the promoter of Nur77 and upregulate its expression, participating in the downstream apoptosis pathway [22]. PKC and phosphorylation of JUK promote the cytoplasmic localization of Nur77 from the nucleus [23, 24]. Nur77 then converts B cell lymphoma 2 (Bcl-2) from an anti-apoptotic molecule to a pro-apoptotic molecule through its interaction with Bcl-2 on the mitochondria [19] and endoplasmic reticulum (ER) [25], thus triggering mitochondria dysfunction and caspase activation [19]. In general, Nur77 has a dual role in mediating cell apoptosis and survival/proliferation (Fig. 1), which can be the focus in future research, especially in the CNS.

3.2. Autophagy

Autophagy is a catabolic process that maintains cell homeostasis. Under physiological and pathological conditions, its effects are bidirectional. On the one hand, phagocytosis of misfolded proteins and clearance of functionally impaired macromolecules and organelles are crucial to maintaining cell survival [26]. For example, autophagy (mitophagy) can remove the damaged mitochondria, and thus alleviate inflammation when organelles such as mitochondria are prone to dysfunction due to inflammatory mediators. Since Nur77 can translocate from the nucleus to the cytoplasm under stress and other conditions, some studies have demonstrated its participation in the regulation of autophagy through different mechanisms (Fig. 1). Hu *et al.* found that ubiquitinated Nur77 can translocate from the nucleus to the mitochondria, causing mitochondria-associated apoptotic pathways, and making mitochondria more sensitive to autophagy at the same time. Mitochondria with ubiquitinated Nur77 were more susceptible to interaction with lysosomal p62/SQSTM1 for autophagy, leading to the clearing of dysfunctional mitochondria in order to protect cells and alleviate inflammation [27]. Parkin on mitochondria may also initiate mitochondrial autophagy by interacting with Nur77. translocated into the mitochondria, and then recruiting Pink1 [28]. On the other hand, the persistence of autophagy or activation of autophagy under abnormal conditions may lead to the transformation of the original pro-survival effect to a pro-death effect. Thus, studying autophagy is also of great significance, especially in some infections and inflammation of cancer and neurodegenerative-related diseases [26]. Previous studies

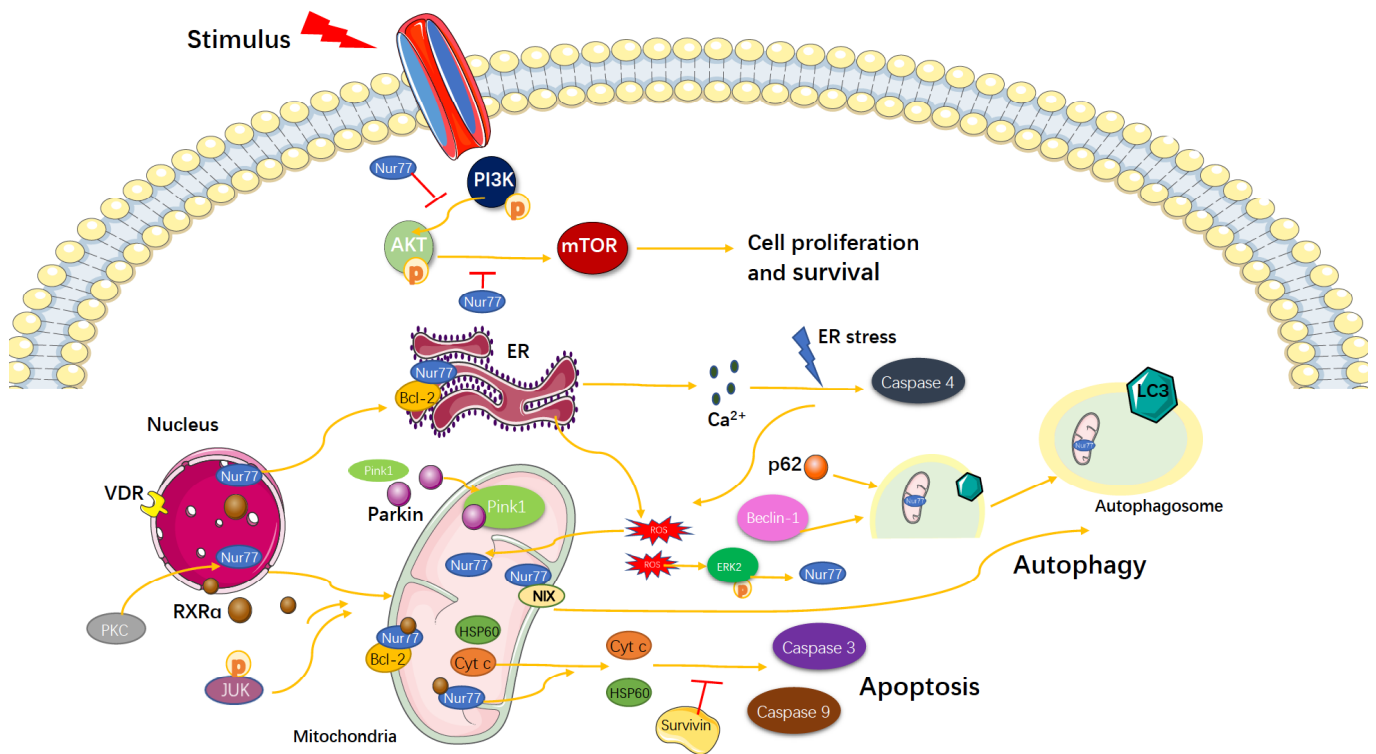


Fig. (1). The mechanism of Nur77 regulating cell survival and apoptosis in CNS. Nur77 mediates cell apoptosis through caspase, endoplasmic reticulum stress, and mitochondrial autophagy, while the PI3K/AKT pathway is involved in Nur77-mediated cell survival. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

have also suggested that Nur77 can participate in caspase-dependent cell death by regulating autophagy, making Nur77 a mediator of programmed cell death, bridging apoptotic, and nonapoptotic pathways. Nur77 translocated to the mitochondria can interact with the mitochondrial outer membrane Nix, and then enter the mitochondrial inner membrane through the Tom40 and Tom70 channel proteins. The permeability transition pore complex ANTI-VDAC1 induces autophagy by dissipating the mitochondrial membrane potential. This process leads to excessive mitochondrial clearance and irreversible cell death [29]. Jimena *et al.* demonstrated that mutations in the transcriptional domain of Nur77 can prevent cell death by modulating NK1R/SP- or IGF1R-mediated autophagy [30]. This suggests that Nur77 may affect autophagic cell death in a protective or destructive role.

3.3. Nur77 and Inflammation

Inflammation is the normal physiological process of stress in the body. In this process, various immune mediators are recruited to damaged tissues to eliminate toxins and other harmful substances produced by them, so as to promote the restoration of normal tissue structure and function. However, the persistence of the inflammatory process or the body's inability to eliminate it normally leads to a pathological inflammatory response, which is manifested as an imbalance between pro-inflammatory and anti-inflammatory factors. Many diseases in the CNS have abnormal elimination or persistence of inflammatory response. Various studies have shown that Nur77 has the potential to alleviate inflammatory diseases, and its anti-inflammatory effect has been confirmed

in several experimental models. Therefore, the different expression of Nur77 in different cells, can regulate different processes in cytopathological pathogenesis to achieve anti-inflammatory goals. Firstly, by regulating cell differentiation, cells are transformed into anti-inflammatory phenotypes. For example, Nur77 increased the anti-inflammatory phenotype of microglia or macrophages and reduced the production of pro-inflammatory factors such as IL-1 β , IL-6, TNF- α , and iNOS in a mouse model of sepsis [21]. The second goal is to change the expression of key molecules involved in the inflammatory pathways. In the lipopolysaccharide (LPS) -stimulated inflammatory model, Nur77 can inhibit the binding of NF- κ B p65 with DNA and NF- κ B activity, and antagonize the inflammatory response caused by the up-regulation of NF- κ B expression [21]. The third goal is to regulate the metabolic state of cells involved in the inflammatory response. Liebmann *et al.* have proven that Nur77 controls a complex metabolic network partly *via* interaction with the transcription factor ERRA mechanistically in T cells. Moreover, the loss of Nur77 expression in T cells influences the key processes of cell metabolism, such as mitochondrial respiration or glycolysis, which affect the recruitment of T cells to the CNS, thereby facilitating the development of T cell-mediated autoimmunity [31].

4. NUR77 AND CNS DISEASES

Several studies have reported the protective anti-inflammatory role of Nur77 in multiple system diseases, but studies pertaining to its role in the CNS are still limited. Many CNS disease models in existing research show that

lack of Nur77 leads to worsening of corresponding symptoms in mice and increases mortality, indicating that Nur77 can play a protective role in neurological disease, and stressing the need for further research into its corresponding mechanisms of regulation.

4.1. Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune inflammatory disease that occurs in the CNS [32]. The EAE animal model of MS in humans is characterized by T cell-driven initiation of inflammation, which then migrates through the destructed blood-brain barrier (BBB) and infiltrates into the CNS parenchyma. Infiltrated T cells can produce pro-inflammatory molecules that activate and chemoattract the CNS-resident microglia and peripheral macrophages, thus amplifying the CNS inflammatory response and leading to myelin destruction and axonal loss [32, 33]. Achiron *et al.* found that MS patients have reduced apoptosis of peripheral blood mononuclear cells (PBMC), and further microarray results showed that the expression of Nur77 is down-regulated in peripheral blood mononuclear cells in the early stage of MS patients [34]. EAE rats with Nur77 deficiency produce more severe symptoms, and vitamin D3 treatment reduces the corresponding symptoms by increasing the expression of Nur77 in the spleen and PBMC of EAE rats [35], suggesting that the occurrence of MS may be associated with abnormal regulation of Nur77.

There are various regulatory mechanisms driven by Nur77 in the development of MS. It is well known that the key nodes of cell cycle and proliferation regulation are controlled by cell metabolism [36]. Liebmann *et al.* experimentally verified that Esrra promoter could directly bind to the Nur77 protein, significantly altering metabolic processes such as mitochondrial oxidative respiration of T cells and glycolysis. Nur77-deficient T cells can play a flexible transformation in these two key energy pathways (mitochondrial respiration and glycolysis). Blocking these pathways using drugs and inhibiting Esrra expression can affect the proliferation of T cells in mice with Nur77 deficiency, leading to the inhibition of the energy sources generated by the processes such as the change of T cell activation threshold and the production of pro-inflammatory factors caused by Nur77 deficiency [31]. It can be seen that the role of Nur77 as the main regulatory gene in T cell metabolism is most likely in close interaction with other transcription factors. In addition, previous studies have suggested a link between the adrenal signaling system and the development of MS [37, 38]. Shaked *et al.* have further proven that the macrophages that produce norepinephrine (NE) are likely to be the link between the two [39]. At the early stage of EAE, monocytes and macrophages induced tyrosine hydroxylase (TH) and secreted NE. NE released by autocrine signaling caused a neuroinflammatory cascade, and produced IL-6 and other related chemokines, thus driving leukocytes to be raised in the CNS. Further experiments demonstrated that Nur77 expressed by monocyte-derived macrophages directly inhibited the transcription of the TH gene in macrophages by recruiting the co-repressor CoREST complex to bind to the TH promoter. Furthermore, it restricted CNS inflammation caused by the passive transfer of brain-derived T cells. The

Nur77 deletion prevented the assembly of the CoREST complex, resulting in increased TH gene expression and NE secretion, following NE and pro-inflammatory IL-6 reactivated mononuclear cell-derived macrophages by $\alpha 1$ adrenergic receptors and gp130 receptors respectively, resulting in an aggravated vicious cycle of the inflammatory response, promoting the recruitment of inflammatory cells such as T cells to the CNS [39]. The above-mentioned experimental results suggest that Nur77 could act as a regulator of both inflammation and sympathetic systems, especially in cases of neuroinflammation. It is known that microglia play an important role in the occurrence and resolution of MS. The resident microglia of the CNS are instructed and activated by immune mediators, upregulation of the pattern recognition receptors, and costimulatory molecules. NO and other substances produced by microglia activation can produce neurotoxic effects in CNS, leading to the destruction of the BBB, the transport and activation of peripheral T cells, initiation and expansion of inflammation, and eventually, the occurrence of diseases [40, 41]. In contrast, the phagocytosis of microglia and the synaptic interaction with neurons or other cells can help remove apoptotic neurons in the later stage of inflammation, therefore promoting remyelination by clearing the myelin stasis [42, 43]. By measuring the expression of Nur77 in organs, it was found that Nur77 mRNA levels were the most abundant in the brain and spinal cord under the resting state. Further experiments through Nur77 knock out mice and *in vitro* experiments verified that Nur77 prevented excessive activation of microglia by regulating the activation threshold of microglia in the early stage of EAE, regulated the ability of microglia to recruit T cells into the CNS, and inhibited the production of chronic inflammation. It could also affect arginine metabolism and NO production by regulating the expression of arginase-1 and iNOS. Thus, the neurotoxic effect caused by microglia was eliminated and the ability of microglia to recruit T cells to enter CNS was inhibited [44]. In this study, Nur77 had no positive effect on the differentiation of T cells themselves, probably because this study focused on the regulation of Nur77 in the early stages of inflammation. Many studies have confirmed that Nur77 plays a complicated role in T cell-mediated CNS autoimmunity. Wang *et al.* found enhanced clinical signs and pathologies in Nur77^{-/-} EAE mice, accompanied by a decrease in regulatory T cells, an increase in pro-inflammatory Th1/Th17 cells in the CNS, and Th1 cells in the spleen. IFN- γ and IL-17 in splenocytes also increased in number. The data were collected at the peak of day 21 of EAE induction, hence Nur77-mediated immunomodulatory mechanism such as T cell apoptosis and Treg induction may not have occurred at the early stage of T cell activation, but at the stage when the T cells are fully activated and differentiated [15]. Liebmann *et al.* crossed Nur77KO mice with 2D2 mice to generate Nur77KO-2D2 mice, which developed a higher cumulative EAE score and had an increased number of CD4⁺ T cells in the CNS *in vivo*. Accordingly, restimulation of CNS-derived CD4⁺ T cells showed that Nur77-deficient CD4⁺ T cells produced significantly more IFN- γ than Nur77-competent counterparts. Along these lines, Nur77KO mice in the active MOG₃₅₋₅₅-induced EAE model also showed consistent results, whereas Treg frequencies remained unaffected. It is worth noting that in this research, the increased

production of proinflammatory cytokines by MOG_{35–55}-activated CD4⁺ T cells was already evident before disease onset (*i.e.*, on day 10) [31]. Therefore, Nur77 seems to limit T cell responses very early in the initiation of T cell-mediated autoimmunity. To sum up, the correlation between Nur77 and T cell-related autoimmunity is definite, which provides a new research direction for the treatment of inflammatory diseases of the nervous system. Further evidence is needed to confirm the relationship between the influence of Nur77 on T cell activation and differentiation and the occurrence and development of the disease. In addition, the molecular pathways and transcriptional events involved in the Nur77-mediated microglia and T cells still need to be studied in detail. Decreased expression of transcriptional activators or increased expression of transcriptional inhibitors may alter Nur77 to be implicated in the pathogenesis of autoimmunity. Moreover, in the absence of genetic changes in the Nur77 gene, functional changes in Nur77 such as phosphorylation may affect autoimmunity, suggesting that Nur77-related molecules may become a new treatment for MS as well as other autoimmune diseases.

4.2. Cerebrovascular Diseases

Cerebrovascular diseases refer to a variety of brain vascular diseases, including cerebral atherosclerosis, stroke, cerebral hemorrhage, cerebral artery injury, cerebral aneurysm, arteriovenous malformation, cerebral arteriovenous fistula, cerebral arteritis and so on, most of which are commonly characterized by ischemic or hemorrhagic accidents in brain tissue. Arterial remodeling is considered to be a key process in vascular diseases such as aneurysm formation and atherosclerosis [45]. In atherosclerosis, outward or expansive remodelling can compensate for luminal narrowing, and is a process that is beneficial to preserve local blood flow, and is associated with plaque instability [46, 47]. Bonta *et al.* demonstrated that Nur77-transgenic mice exposed to flow-induced, left carotid artery outward remodeling, post contralateral carotid artery ligation showed reduced macrophage accumulation and caused lower MMP1 and MMP9 mRNA levels when compared with DTA or wild-type mice, which may explain a substantial reduction in outward remodeling [45]. Yang *et al.* found that overexpression of Nur77 firmly increased the thrombomodulin expression, weakened the TNF- α -induced prothrombotic states in endothelial cells (ECs), and suppressed arterial thrombus formation *in vivo*. Furthermore, Nur77 deficiency increased susceptibility to arterial thrombus formation greatly, which proves the essential roles of the NR4A receptor in maintaining vascular homeostasis of ECs and suggests that Nur77 may be a potential therapeutic target for inflammatory and thrombotic diseases [48]. Since Nur77 has different roles in inducing apoptosis, mediating cell differentiation and vascular remodeling, whether it has a protective effect in cerebrovascular disease is still unclear. Ischemic stroke caused by cerebrovascular obstruction accounts for 80% of all types of stroke, and can reduce cerebral blood flow. The subsequent hypoglycemic and hypoxic processes increase brain injury and lead to permanent neurological loss, making it one of the important causes of death in middle-aged and elderly patients worldwide. Nowadays, an increasing number of studies have considered Nur77 as an important factor in the regulation of the

pathological process of cerebrovascular disease. A few studies have proven that local cerebral ischemia can induce the expression of immediate early genes such as Nur77 mRNA and protein in the ischemic areas and in the ipsilateral cortex, and delayed expression of Nur77 in areas remote from the injury, prompting that Nur77 can participate in the regulation of late response gene expression and may affect the formation of neuronal remodeling, ischemia tolerance, and neuro-psychosis after ischemia [11]. Further *in vitro* simulated cerebral ischemia experiments confirmed that up-regulated expression of Nur77 decreased apoptosis and apoptotic related protein expression. Therefore, active regulation of Nur77 protein expression or transcriptional activity may have beneficial effects on nerve self-protection [18]. The expression of Nur77 is also increased in hemorrhagic stroke; however, it is accompanied by an increase in the corresponding apoptotic proteins including Bcl-2, cyto C, and caspase-3. After using the Cyclosporin A (CsA), Nur77 localization was found to be restricted to the nucleus by immunohistochemical analysis, and the expression and phosphorylation level of Nur77 were reduced. Thus, CsA can inhibit the transfer of Nur77 from the nucleus to the mitochondria-mediated apoptosis pathway. It is suggested that the neuro-protective effect of CsA may be related to the inhibition of the Nur77-dependent apoptotic pathway [49]. In another study in rats which were experimentally induced with subarachnoid hemorrhage (SAH), researchers also found that after induction of SAH and injection of Cyclosporin B (Csn-B), an agonist for Nur77, Nur77 could promote cerebral cell apoptosis by mediating early brain injury and stimulating a conformational change in Bcl-2, leading to cyto C release [50]. Therefore, the effect of Nur77-mediated apoptosis on the prognosis of a stroke may be influenced by the type of stroke. Increased expression of Nur77 in ischemic stroke tends to reduce apoptosis while increased apoptosis is induced in hemorrhagic stroke. Cerebral ischemia-reperfusion (IR) markedly augments mitochondrial stress, resulting in oxidative stress and ATP depletion [51, 52]. Zhao *et al.* confirmed the existence of mitochondrial fragmentation with up-regulated Nur77 and INF2 under IR injury in *in vitro* and *in vivo* experiments. They provided evidence that Nur77 activation influenced the activity of the Wnt pathway *via* the promotion of β -catenin phosphorylation and INF2 activation, finally leading to an imbalance between mitochondrial fission and fusion. Mitochondrial dysfunction led to the production of ROS and the downstream antioxidants GPX, SOD, and GSH, the release of cyto C, as well as the increased expression and activity of caspase-3 and 9. Nevertheless, the loss of Nur77 could reverse the outcomes above. This finding indicates that a reduction in Nur77 could improve brain resistance to reperfusion-mediated damage *via* regulating mitochondrial homeostasis and neuron viability [17]. A latest experimental study found that Nur77 deficient mice showed a lighter neurobehavioral disorder than normal mice after the occurrence of stroke, suggesting that the knockdown of Nur77 reduced microglia activation after the infarction. The expression of M1 microglia in the peri-infarct area was reduced. Further experiments found that Nur77 was colocalized with p65 of NF- κ B directly, and the deletion of Nur77 also markedly reduced the MCAO-induced p65 activation around the infarction area. Inhibition of NF- κ B/p65

activation reversed the increasing expression level of Nur77 induced in OGD/R microglia cells, accompanied by decreased M1 polarization, chemokine expression and increased anti-inflammatory gene expression [53]. This result was the first to conclude that Nur77 activates microglia cells to differentiate them into the M1 phenotype through colocalization with NF- κ B /p65 in an acute cerebral ischemia model, which is a strong contradiction to many studies suggesting Nur77 to be a protective transcription factor. Future investigation is necessary to clarify the obvious discrepancy between the studies mentioned. One plausible explanation is that the influence of Nur77 on the balance between physiology and pathology, apoptosis and necrosis, inflammation and anti-inflammatory functions of cells is complex. The physiological and pathological changes of different cells and corresponding organelles such as mitochondria, also lead to different directions of disease development, which may be related to the inflammatory state after a stroke at that time.

4.3. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is characterized by the formation of senile plaques and neurofibrillary tangles composed of tau amyloid fibrils, accompanied by progressive memory loss that eventually leads to dementia [54]. The expression of Nur77 is essential for the normal maintenance of cognitive function, and inhibition of its transcriptional activity will lead to severe impairment of long-term memory [55]. In a simulated AD model constructed from the amyloid precursor protein and presenilin-1 (APP+PS1) transgenic mouse, Dickey *et al.* found that the expression of the Nur77 gene was only decreased in the APP region. On the contrary, the mRNA expression level of presynaptic markers (synaptic vesicle proteins, synaptic fusion proteins, and so on) was relatively stable, suggesting that the synaptic structure remained unchanged, further suggesting that Nur77 may regulate the generation of cognitive dysfunction before the degeneration of synapses and neurons [56]. Their subsequent experiments further explored the relationship between the expression of immediate early genes (IEG - Nur77, Arc, and Zif268) and amyloid deposition. The results showed that the progressive deposition of amyloid resulted in significant under-expression of Nur77, Arc and Zif268 at mRNA and protein expression levels, which are essential for neuronal plasticity and memory function. It turns out that the hypothesis that amyloid itself impairs the induction of the IEGs, therefore resulting in further gliosis and onset of memory loss, is validated [57]. In terms of gene expression in the NR4A family in peripheral blood of AD patients, only Nur77 gene expression was significantly down-regulated [58]. However, in another early study of the brains of AD patients, Nur77 levels were elevated, and its expression was limited to vertebral neurons and dentate granule cells in the cortex and hippocampus. Since obvious regional neurodegeneration in AD patients exists, it suggests that a Nur77-mediated pathway may be involved with neuronal loss [59]. In a nutshell, Nur77 participates in the pathological process of the brains in AD patients, and the normal expression of its transcriptional activity is conducive to protect the normal function of brain neurons. A study using a genome-wide scan for NBREs in human promoter regions has found that SerpinA3 (α 1-antichymotrypsin), a major constituent of the plaque that

interacts with neurotoxic amyloid peptide A β in the generation of AD, could be identified as a novel Nur77-regulated gene [60]. These results shed light on possible mechanisms of Nur77 gene regulation. Further research is needed to investigate the mechanism by which Nur77 regulates cognitive function and mediates AD. Moreover, the confirmation of an apoptotic role of Nur77 in AD may trigger more interesting therapeutic interventions, like 9-cis retinoic acid (9cRA), which can inhibit the RXR α /Nur77 nuclear export induced by A β ₂₅₋₃₅ and decrease the apoptotic rate of N2a cells through mediation in Bcl-2 and Bcl-2 associated X (Bax) expression [61].

4.4. Parkinson's Disease (PD)

Parkinson's disease (PD) is a neurodegenerative disease characterized by degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) region of the brain. The causes of PD are complex and not yet fully understood. DA precursor Levodopa (L-Dopa) and DA agonists can significantly improve the symptoms of PD, whereas long-term use of these pharmacological approaches is inevitably associated with the side effects including motor fluctuations like L-Dopa-induced dyskinesia (LID) and other non-motor symptoms [62]. Observations made from the peripheral blood of individuals who suffered from PD indicated that expression levels of Nur77, Nurr1 and NR4A3 were significantly down-regulated [58]. In recent years, research has thrown light on an important role of Nur77 in DA neurotransmission in the developing and mature CNS. Striatal Nur77 expression is strongly modulated after perturbation of DA neurotransmission, such as unilateral DA denervation and subsequent L-Dopa treatment [63, 64]. Denervation reduced Nur77 mRNA levels, while chronic L-Dopa treatment strongly induced Nur77 transcription, suggesting that Nur77 might be involved in the movement disorders in rodent models of PD [65]. In an experimental PD mouse model, Nur77 deficiency after MPTP treatment regulated by the calpain-CDK5-MEF2 pathway could induce hypersensitization of dopaminergic neurons to exogenous stress and degeneration, and this sensitivity was reversed by ectopic Nur77 re-expression [66]. Rouillard *et al.* also observed a rapid Nur77 ectopic expression in the SNc after 6-hydroxydopamine (OHDA) exposition in rats, whereas genetic disruption of Nur77 reduced dopamine cell loss and the development of LID, suggesting that striatal Nur77 expression is associated with the production of LID in experimental PD [67]. It is consistent with the finding that Nur77 expression has a significant inverse correlation with dyskinesia score [65]. Since excessive microglia and astrocyte activation in the SNc are associated with damage to neurons and pathogenesis of PD [68-70], Nur77 has been further proven to protect dopaminergic neurons from inflammation-induced death by attenuating both microglia and astrocytes activation [69, 70]. In the PD model constructed by 6-OHDA-lesioned PC12 cells or SH-SY5Y cells, cytosolic Nur77 and translocation from the nucleus to the cytoplasm were increased together with formation of the subcellular co-localization of Nur77/cyto C/HSP60. Mitochondrial autophagy and ER stress were then aggravated, suggesting that Nur77 can be a crucial modulator in mediating mitochondrial impairment and cellular death in the pathogenesis of PD [28, 71, 72].

Table 1. Summary of potential functions of Nur77 in different cells in the CNS.

Associated Diseases	Models and Cells Studied	Functions of Active Nur77 Expression	Key Molecules or Effector Signaling Pathways	Refs.	
Alzheimer's disease (AD)	Human brain and tonsil tissue	Involved in AD-associated neuronal loss	-	[59]	
	Mouse N2a neuroblastoma cells	Induces AD-associated neuronal loss	Co-translocates with RXRa Decreases Bcl-2 and increases Bax expression	[61]	
Parkinson's disease (PD)	Mouse astrocytes	Inhibits inflammatory gene expression Inhibits inflammation	Inhibits the transcriptional activity of NF-κB	[69]	
	Mouse microglial cells	Inhibits inflammation Inhibits dopaminergic neurotoxicity of microglia	Suppresses the LPS-induced NF-κB activation, which is partly dependent on p38 MAPK activity	[70]	
	Rat/Mice DA neurons	Decreases dopamine cell loss and L-Dopa-induced dyskinesia	-	[67]	
	PC12 cells		Increases mitochondrial impairment Induces neurodegeneration	Induces co-localization of cyto C/HSP60/Nur77 Upregulated by ERK/JNK inhibitors	[72]
			Exacerbates neuronal cellular death Increases ER Stress Induces autophagy and mitochondrial impairment	Regulates the Bcl-2/cyto C/cleaved caspase-3 pathway Aggravates intracellular Ca ²⁺ , ROS levels, regulates the PI3K/AKT viability pathway, CHOP, and ATF3 Mediates up-regulation of PINK1/Beclin-1/LC-3 and downregulation of p62/Parkin	[28]
Stroke	Mouse microglial cells	Exacerbates inflammation Mediates microglia polarization	Interacts with NF-κB/p65	[53]	
	Rat cerebellar granule neurons	Increases neuron apoptosis	Forms heterodimerization with RXR	[73]	
	PC12 cells WG32 cells (superoxide dismutase over-expressed PC12 cells)	Induces neuronal toxicity	Regulates phosphorylation of MAP kinase including ERK1/2, p38, and JNK	[74]	
	Rat neural cells	Decreases neural apoptosis	Induces survivin after OGD	[18]	
	Mouse N2a neuroblastoma cells	Increases mitochondrial fragmentation Increases neuron apoptosis	Upregulates INF2 <i>via</i> the Wnt/β-catenin signaling pathway	[17]	
Subarachnoid hemorrhage (SAH)	Rat brain tissues	Increases cell apoptosis	Regulates the Bcl-2/cyto C/ caspase-3 pathway	[49]	
	Rat cerebral cells	Induces cell apoptosis	Regulates the Bcl-2/cyto C pathway	[50]	
		Induces cell apoptosis	Activates JNK signaling pathway	[75]	
Traumatic brain injury (TBI)	PC12 cells rat nerve cell	Induces cell apoptosis	Regulates the Bcl-2/cyto C/ caspase-3 pathway	[76]	
Multiple sclerosis (MS)	Mouse microglial cells	Promotes microglia activation and polarization Inhibits inflammation	Downregulates arginase-1 expression and upregulates NO expression	[44]	
	Mouse macrophages Mouse microglia Mouse T lymphocytes	Regulates polarization of macrophages/microglia Decreases Th1/Th17 cell differentiation Inhibits inflammation	Regulates cytokines expression	[15]	
	RAW 264. 7 cells Mouse myeloid cells	Inhibits microglia activation and immune cell infiltration Inhibits expression of norepinephrine in macrophages Inhibits inflammation	Suppresses transcription by recruiting the CoREST complex	[39]	

(Table 1) contd....

Associated Diseases	Models and Cells Studied	Functions of Active Nur77 Expression	Key Molecules or Effector Signaling Pathways	Refs.
	Human Peripheral blood mononuclear cells (PBMC) from MS patients	Induces PBMC apoptosis Inhibits inflammation	Upregulates the VDR /calpain/ROS/ caspase dependent apoptosis	[35]
	Mouse T lymphocytes	Restricts proliferation and activation of T cells Restricts T Cell-Mediated CNS autoimmunity Limits cell cycle progression and metabolic activity of activated CD4 ⁺ T cells Regulates metabolic gene expression in activated T cells	Regulates ERRA inhibition	[31]
Sciatic Nerve Injury	Rat Schwann cells PC12 cells	Involved in Schwann cell differentiation <i>in vitro</i> , SC myelination and axonal regeneration <i>in vivo</i>	-	[77]
Glioblastoma multiform (GBM)	Human GBM cells DBTRG-05MG and GBM 8401	Increases tumor cell apoptosis	Activates the PKC signaling pathway via AP-1 motifs in the Nur77 promoter	[23]
			Activates the JNK pathway via AP-1 motifs in the Nur77 promoter	[24]
	Human neuroblastoma SK-N-SH cells	Increases apoptosis Induces ER stress Induces mitochondrial stress	Initiates an early release of Ca ²⁺ from ER and activate caspase 4 Activates the Bcl-2/cyto C/ caspase-9 pathway	[25]
LPS-induced inflammation	Mouse microglial cells Murine BV-2 microglial cells	Inhibits inflammation	Downregulates NF-κB transcriptional efficiency by inhibiting p65 phosphorylation and acetylation	[78]
	PC12 cells	Promotes neurite outgrowth after treatment of TSA	Associated with acetylation of Lys14 on histone H3	[13]
	Mouse monocytes	Regulates differentiation and survival of 'patrolling' Ly6C ⁺ monocytes	Decreases NF-κB activation Increases expression of CX3CR1 and CCR2	[39]

The above reactions can be significantly altered by interfering Nur77 expression with microRNA and memantine treatment [72], which means that regulating Nur77 expression may have a similar effect to anti-Parkinson drugs. These studies suggest that Nur77 is expected to be a new therapeutic target for PD.

4.5. Brain Tumors

Several studies have shown that Nur77 may have a role in mediating apoptosis of brain tumor cells [23-25]. After treating human neuroblastoma SK-N-SH cells with the retinoid-related molecule CD437, mitochondrial stress and caspase-9 activation were observed after the transfer of Nur77 from the nucleus to mitochondria. In addition, the transfer of Nur77 to the endoplasmic reticulum was also confirmed. Nur77 then interacted with ER-targeting Bcl-2 on the ER, and initiated early release of calcium ions from the ER to induce ER stress and subsequent activation of caspase-4, thereby promoting apoptosis of neuroblastoma cells [25], which suggests that Nur77 can also regulate ER homeostasis and affect tumor cell survival. Some drugs such as n-butylidenephthalide (BP) or one derivative of BP (PCH4) treating glioblastoma multiform (GBM) cells activated the PKC or JNK pathway and regulated Nur77 activity via AP-1 motifs in the Nur77 promoter region to increase tumor cell

apoptosis. This shows that blocking the Nur77 promoter can reduce apoptosis induced by these drugs [23, 24]. This also suggests that Nur77 can be used as the target gene in drug research to treat brain tumors.

CONCLUSION AND PERSPECTIVES

We have summarized the current knowledge of Nur77 in national and international studies, including its regulatory functions and possible mechanisms in a variety of CNS diseases, as listed in (Table 1). Evidence regarding the therapeutic potential of Nur77-targeting molecules in these diseases has also been discussed.

Although the regulatory effect of Nur77 in CNS diseases has been proven in many *in vivo* and *in vitro* experiments, its mechanism of action still needs to be studied in further detail. What factors affect the balance of Nur77 in cell survival and death, anti-inflammatory, pro-inflammatory, and other cellular events should be the focus of future research. Sub-cellular localization, cell types, the cellular environment, other signaling molecules that have cross-talks with Nur77, as well as the types of stimuli that regulate their expression and activity are all factors that need to be considered. Nur77 acts as a bridge connecting mitochondria-mediated apoptosis and autophagy in CNS-related inflammatory and metabolic

diseases, perhaps, depending on whether Nur77 is localized to the mitochondrial outer or the inner membrane. Therefore, any factors that can affect the translocation of Nur77 from the nucleus to the mitochondria and its mitochondrial localization should be investigated. In addition, it is essential to know how the genomic and non-genomic functions of Nur77 are influenced by specific or different conditions. Looking into the potential influence of Nur77 in other NR4A members and the functional consequences thereof, may also prove meaningful, providing more alternatives for the development of corresponding drugs.

Above all, Nur77 has great therapeutic potential to treat CNS diseases and should be considered while carrying out future research on drugs that work on the CNS.

LIST OF ABBREVIATIONS

BRE	=	Brain and Reproductive Organ-Expressed Protein
ERK	=	Extracellular Signal-Regulated Kinase
iNOS	=	Inducible Nitric Oxide Synthase
JNK	=	Jun N-terminal Kinases
MCAO	=	Middle Cerebral Artery Occlusion
MPTP	=	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
NBREs	=	Nerve Growth Factor-Responsive Elements
NF- κ B	=	Nuclear Factor- κ B
NR4A	=	Orphan Nuclear Receptor 4A Protein
p38 MAPK	=	p38 Mitogen-Activated Protein Kinase
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
Th17	=	T-helper 17 Cells
TNF- α	=	Tumor Necrosis Factor- α
Treg	=	CD4 ⁺ CD25 ⁺ Regulatory T Cells

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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