Neurotoxicity Research (2018) 34:848–859
https://doi.org/10.1007/s12640-018-9889-z

REVIEW

Noradrenergic Modulation on Dopaminergic Neurons

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Received: 18 January 2018 / Revised: 5 March 2018 / Accepted: 8 March 2018 / Published online: 23 March 2018

Abstract

It is now well accepted that there is a close relationship between noradrenergic and dopaminergic neurons in the brain, especially referring to the modulation of the locus coeruleus–norepinephrine (LC-NE) system on dopamine transmission. The disturbance of this modulation may contribute to neurodegeneration of dopaminergic neurons in Parkinson's disease. In this article, we briefly review evidence related to such modulation. Firstly, we illustrated the noradrenergic innervation and functional implication for the LC-NE system and nigra–striatum dopaminergic system. Furthermore, we depicted neuroprotective effects of the LC-NE on dopaminergic neurons in vivo and in vitro. Moreover, we present data implicating the potential mechanisms underlying the modulation of the LC-NE system on dopaminergic neurons, in particular the effects of NE as a neurotrophic factor and through its ability to stimulate the expression of other neurotrophic factors, such as the brain-derived neurotrophic factor. Finally, we discussed other mechanisms intrinsic to NE's effects. A better understanding of the noradrenergic modulation on dopaminergic neurons may be rewarding by significant advances in etiologic study and promising treatment of Parkinson's disease.

Keywords Locus coeruleus · Norepinephrine · Dopamine · Neuroprotection · Neurotrophic factor · BDNF

Abbreviations

ARs	Adrenergic receptors
BDNF	Brain-derived neurotrophic factor
DA	Dopamine
CREB	cAMP response element binding
DBH	Dopamine β-hydroxylase
DSP4	*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine hydrochloride
LC	Locus coeruleus
NE	Norepinephrine
NET	NE transporter
PD	Parkinson's disease
SNpc	Substantia nigra pars compacta
TrkB	Tropomyosin receptor kinase B
VTA	Ventral tegmental area

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Introduction

Noradrenergic and dopaminergic systems are the major neuronal circuits in the brain. Their corresponding neurotransmitters norepinephrine (NE) and dopamine (DA) are the main catecholamines involved in a variety of physiological processes. The major noradrenergic nucleus in the brain is the locus coeruleus (LC, A6) located in the pons (Vijayashankar and Brody 1979; Brodal 1981) with wide afferents to the cortex, cerebellum, thalamus, and spinal cord (Moore and Bloom 1979; Morrison et al. 1979; Segal and Bloom 1976; Swanson and Hartman 1975). In particular, the LC is the sole noradrenergic source to innervate the hippocampus (Swanson and Hartman 1975; Haring and Davis 1985) and frontal cortex (Morrison et al. 1979; Samuels and Szabadi 2008). LC-NE neurons and released NE throughout the brain are involved in a variety of physiological functions and behaviors such as cognition (Sterpenich et al. 2006; Sara 2009), attention (Robbins 2000), locomotor control, and contributing to the affective state (Robbins and Everitt 1995). The substantia nigra pars compacta (SNpc, A9) (Anden et al. 1966; Domesick 1988) and ventral tegmental area (VTA,

A10) (Swanson 1982; Oades and Halliday 1987) represent two of the nine major dopaminergic neuron groups in the midbrain. Neurons from the SNpc and VTA are characterized by distinct but overlapping projection patterns. The majority of projections that originate from the SNpc innervate the dorsal striatum, and only some nigral fibers project to the ventral striatum and cortex. In contrast, neurons from the VTA mainly project to the ventral striatum as well as cortical areas, with significantly fewer projections innervating the dorsal striatum (Bjorklund and Dunnett 2007). While dopaminergic neurons in the SNpc are heavily involved in the control of movements, those in the VTA are responsible for the regulation of reward, emotional behavior and addiction (Satoh et al. 2003; Matsumoto and Hikosaka 2009; Bromberg-Martin et al. 2010). Nevertheless, although the LC-NE and DA systems have different characteristics, they have close relationship in anatomy, physiology, and functions, somewhat even overlapped. Therefore, their dysfunctions are also closely related to the pathogenesis of many neurodegenerative diseases.

It is a general knowledge that the degeneration in a clearly defined population of dopaminergic neurons in the brain is the main pathologic alteration in Parkinson's disease (PD) (Hirsch et al. 1988; Fearnley and Lees 1991). However, significant neuronal loss also occurs in the LC in PD. Neurodegeneration of LC neurons even starts earlier than that seen in the SNpc and at a greater magnitude (Gesi et al. 2000; Zarow et al. 2003). Furthermore, there is a correlation between NE deficiency and degenerated dopaminergic neurons with the severity of PD neurological symptoms, indicating that the LC-NE system shares a critical role with the DA system in the progression of PD. Moreover, the neuroprotective effects of an intact LC-NE neuronal system on nigrostriatal dopaminergic neurons and the contribution of endogenous NE to the recovery of the dopaminergic neurons have been reported in many studies (Delaville et al. 2011; Isaias et al. 2011). Therefore, understanding of their interaction, especially for the modulatory effects of the LC-NE system on dopaminergic neurons, may benefit the treatment of PD.

In this paper, we put emphasis on the modulatory effects of noradrenergic neurons on dopaminergic neurons. First, the anatomical and functional relationships between the LC-NE and dopaminergic system are illustrated. Second, the neuroprotective role of noradrenergic neurons on dopaminergic neurons is depicted. Finally, the potential mechanisms underlying the modulation of the LC-NE system on dopaminergic neurons, in particular NE as a neurotrophic factor and its ability to stimulate the expression of other neurotrophic factors, such as the neurotrophin brain-derived neurotrophic factor (BDNF), are discussed. Other potential mechanisms are taken into account of as well.

Noradrenergic Innervation and Functional Implication for the LC-NE System and Nigra Dopaminergic System

An important characteristic between the noradrenergic and dopaminergic systems is their anatomical correlation, which is the basis for the functional modulation of the LC-NE system on midbrain dopaminergic neurons. Anatomical analysis demonstrated that noradrenergic neurons from the LC widely innervate dopaminergic neurons in the midbrain by sending projections to the SNpc, VTA, and striatum in the vicinity of dopaminergic neuronal cell bodies (Simon et al. 1979; Berridge et al. 1997; Schroeter et al. 2000; Liprando et al. 2004; Mejias-Aponte et al. 2009). Furthermore, dopamine β-hydroxylase (DBH) and NE transporter (NET), as well as NE and its receptors such as β- (β1 and β2) and α- (α1 and α2) adrenergic receptors (ARs), can be detected in the most midbrain dopaminergic neurons including the VTA and striatum (Ross and Reis 1974; Chen and Reith 1994; Liprando et al. 2004; Mejias-Aponte 2016) by autoradiographic and immunostaining approaches (Jones et al. 1985; Lee et al. 1998). Such closely anatomical innervation raises the possibility that noradrenergic inputs play a role in modulating DA neuronal activity. For example, electrical stimulation of the LC results an excitation action showing by burst firing of dopaminergic neurons in the SNpc (Grenhoff et al. 1993), which can be attenuated by administration of the α1-AR antagonist prazosin (Grenhoff and Svensson 1993). Furthermore, either lesion of LC neurons or chronic NE depletion has been shown to reduce basal and amphetamine-induced release of DA in the striatum and SNpc (Lategan et al. 1990; Lategan et al. 1992). Consistently, the systemic administration of the selective NE reuptake inhibitor reboxetine enhanced the burst firing activity of dopaminergic neurons in the VTA (Linner et al. 2001). Stimulation of the LC facilitates firing rate in midbrain dopaminergic neurons (Grenhoff et al. 1993), which can also be reduced or increased by application of antagonists of α_1-ARs or α_2-ARs (Grenhoff and Svensson 1993).

However, there is a report that selective lesion of LC neurons increases the mean firing activity of dopaminergic neurons and their burst activity in the VTA (Guiard et al. 2008), suggesting a complexity in regulation of dopaminergic neuronal activity by noradrenergic inputs.

It is noteworthy that although NE terminals make close contacts onto midbrain DA neurons, the majority of contacts are not in direct synaptic apposition, as showing by an ultrastructural study (Liprando et al. 2004). That means, in the SNpc and VTA areas, there are predominant nonsynaptic appositions between NET-immunoreactive axons and dopaminergic neurons, which are separated by glia (Liprando et al. 2004). Although the real function of glia between these neurons is unknown, such glial separations may provide a selective physical barrier to transmission between some noradrenergic terminals and dopaminergic dendrites, allowing one subpopulation of dendrites to be modulated by NE, but not another. These ultrastructural observations suggest that their functional interactions between these two systems are more likely through extrasynaptic mechanisms and considered as a paracrine or volume transmission system (Mejias-Aponte 2016). Thus, NE released from noradrenergic terminals in this area seems to act as a neuromodulator on DA neurons more than a neurotransmitter (Gesi et al. 2000). The similar ultrastructural innervation between noradrenergic terminals and astrocytes is also found in the cortex and thymus (Vizi et al. 1995; Cohen et al. 1997). As NE induced expression of a range of growth factors such as BDNF, nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and fibroblast growth factor (FGF) in glial cells via an action on astrocytic β_2-ARs (Juric et al. 2006; Day et al. 2014), such innervation may be related to the modulatory effects of NE on neuronal plasticity.

In combination, these results not only establish a physiological and functional connection between the noradrenergic and dopaminergic systems, but also form the basis for the influence of NE on dopaminergic neurons in the neuropathology of degenerative diseases.

The Neuroprotection of LC-NE System on the Nigra Dopaminergic System

It is now known that the LC-NE system exhibits a neuronal protection on the nigra dopaminergic system, which has been revealed by a variety of studies. First, a functional and intact LC-NE system facilitates the survival of the dopaminergic system, which was revealed by the studies that the disturbance and/or a functional enhancement of the LC-NE system influences both the onset and the progression of neuronal damage to the DA nigrostriatal tract (Delaville et al. 2011; Isaias et al. 2011). For example, in neurotoxin-induced animal models of PD, concomitant lesions of the LC-NE system with 6-hydroxy-DA resulted in more dopaminergic neuronal loss or activity reduction in the SNpc and VTA areas caused by subsequent exposure to MPTP (Mavridis et al. 1991; Bing et al. 1994; Fornai et al. 1995; Srinivasan and Schmidt 2003). In line with these observations, neurotoxin such as DSP-4-induced reductions in LC activities and functions worsens DA deficit caused by MPTP in animal models of PD (Marien et al. 1993). In addition, these treatments resulted in a significant reduction in striatal concentrations of DA and its metabolites (Mavridis et al. 1991; Fornai et al. 1996; Srinivasan and Schmidt 2003) and an alteration in DA-related behavior (Antelman and Caggiula 1977; Wang et al. 2010). In contrast, administration of β2-AR agonists protects the MPTP-induced degeneration of dopaminergic neurons in the SNpc of mouse model and a β2-AR antagonist correlated with increased risk of developing PD (Mittal et al. 2017).

Second, the neuroprotection of noradrenergic neurons on dopaminergic neurons can be found by administration of NE or increase of NE synthesis, which has been evidenced by in vitro and in vivo studies. For example, in vitro administration of NE (0.3–1 μM) confers substantial and long-term protection to dopaminergic neurons by reducing spontaneously occurring oxidative stress in primary cultured mesencephalic cells (Troadec et al. 2001). Similarly, elevation of extracellular NE levels by treatment with α2-AR antagonists (Martel et al. 1998) or by genetic methods (Kilbourn et al. 1998) protected dopaminergic neurons from neurotoxin-induced cell death. NE hyperinnervation of target areas or treatment of rats with NE has led to resistance to experimental parkinsonism (Marien et al. 1994; Rommelfanger et al. 2004; Rommelfanger et al. 2007). It is well known that methamphetamine can cause degeneration of dopaminergic axon in nigra-striatal regions (Hotchkiss and Gibb 1980; Hirata et al. 1996). Such methamphetamine-induced dopaminergic degeneration is exacerbated after experimental lesion of LC neurons with enhanced methamphetamine toxicity and damage to these neurons (Fornai et al.

1995; Fornai et al. 1998; Weinshenker et al. 2008). In addition, a postmortem survey from persons with PD revealed that the brain areas that were high in NE tended to be spared from DA loss, consistent to a neuroprotective role of NE, with an exception being the putamen (Tong et al. 2006). In clinic trials, to increase extracellular NE concentrations has been used for treatment of PD patients, including use of α_2- and β_2-AR antagonists, NET inhibitor, and increase NE synthesis (Espay et al. 2014; Mittal et al. 2017).

The Role of NE in the Modulation of the LC-NE on Dopaminergic Neurons

As a classic neurotransmitter of the LC-NE system, NE plays a critical role for the noradrenergic functions and behaviors in the homeostasis of body (Berridge and Waterhouse 2003). In addition, NE may act as a modulator for the modulation to other neuronal circuits especially for the dopaminergic neurons. It has been suggested that the neuronal beneficial effects of NE on other neurons can be direct and indirect. For the direct effect, NE is considered to act as a neurotrophic factor. For the indirect effect, it refers to its ability to facilitate the expression of other neurotrophic factors such as the BDNF (Aloyz et al. 1999; Chen et al. 2007; Counts and Mufson 2010), FGF-2 (Kajitani et al. 2012), Bcl-2 (Huang et al. 2007), and NGF (Culmsee et al. 1999; Counts and Mufson 2010). However, both mechanisms can be overlapped. This review focusses on the mediator role of BDNF for NE's effects, although other growth factors are also often associated with an ability of NE to protect dopaminergic neurons from toxicity (Timmer et al. 2007; Xing et al. 2010; Dobolyi et al. 2012).

NE Operates as an Endogenous Neurotrophic Substance

Acting as a neurotrophic factor, NE can influence both development and adulthood. For these effects, NE has been considered to drive DNA synthesis in the mature and developing nervous system (Lauder 1993), which induces neurite outgrowth in primary cultured neurons (Day et al. 2014). For instance, stimulation of α_2-ARs expressed within proliferative germinal zones decreases DNA synthesis in the developing forebrain (Lidow and Rakic 1994; Kreider et al. 2004). Such effect of NE to drive DNA synthesis has been suggested possibly as a common mechanism in the developing and adult brain.

During the development period, NE is thought to be required for the critical period plasticity in development of the cerebral cortex and olfactory. For instance, NE can participate in the formation and organization of neuronal circuits in the olfactory bulb, as injection of either NE or β-AR agonists into rat pups increased odor experience and the differentiation of olfactory bulb plasticity (Sullivan et al. 1989; Sullivan et al. 1991). In contrast, early NE depletion induced by cytotoxic lesion of the LC in rat pups impaired the development of the cerebral cortex (Felten et al. 1982; Siciliano et al. 1999). Furthermore, the use of $dbh^{-/-}$ mice verified NE's necessary effect on the development of auditory cortex (Shepard et al. 2015). In addition, in vitro studies demonstrated that NE increases embryonic neuroepithelial cell division during early development and in cultured neurons from embryonic rodent brain via the α_1-ARs (Popovik and Haynes 2000), promotes differentiation and neurite outgrowth, and increases expression of genes related to neuronal sprouting (Day et al. 2014) and differentiation (Laifenfeld et al. 2002). Similarly, the facilitative effects of NE on synaptic plasticity during development period were confirmed by ex vivo experiments (Hu et al. 2007; Liu et al. 2010).

Similarly, the LC-NE system also plays a prominent role to maintain its neurotrophic influence on adulthood period. This effect mainly exhibits as its action on the cellular plasticity through neurogenesis. For example, in adult rats, administration of NE markedly increased hippocampal synaptic plasticity in adult rats (Katsuki et al. 1997) and directly activated self-renewing and multipotent neuronal precursors, including stem cells from the hippocampus of adult mice (Jhaveri et al. 2010). BrdU-positive cells in the adult hippocampus were significantly enhanced by increased extracellular NE resulted from administration of reboxetine (Malberg et al. 2000). L-Dihydroxyphenylserine (L-DOPS), a NE prodrug, is reported to stimulate neuronal sprouting and synaptogenesis (Stroemer et al. 1998). Furthermore, NE could affect neurogenesis indirectly through α_1-ARs on interneurons (Hillman et al. 2009). In contrast, a significant reduction in hippocampal neurogenesis was observed by neurotoxin DSP-4-induced depletion of NE (Kulkarni et al. 2002), by bilateral infusions of the anti-DBH-saporin into the LC (Coradazzi et al. 2016), or by administration of α_2-AR agonists (Yanpallewar et al. 2010) which can be reversed by α_2-AR antagonist yohimbine via increasing NE release (Yanpallewar et al. 2010). Similarly, noradrenergic activation resulted from LC stimulation increased plasticity in the auditory cortex and auditory thalamus neurons in the adult rats (Edeline et al. 2011). The neurotrophic benefit of the LC-NE system on dopaminergic neurons is supported from investigations related to PD patients and PD animal models. A plague of the DA replacement therapy for PD patients is the onset of abnormal involuntary movements (AIMs, also called L-DOPA-induced dyskinesia) (Blin et al. 1988). It appeared to be a result of an aberrant synaptic plasticity of dopaminergic neurons in the striatum (Calabresi et al. 2000; Picconi et al. 2005).

However, it is considered to be associated with the loss of a trophic support of the NE system for the growth, differentiation, and repair of the nigrostriatal DA pathway, as the use of α2-AR antagonists yohimbine and idazoxan to increase NE availability can dramatically reduce the AIMs in PD patients and PD animal models (Henry et al. 1999; Rascol et al. 2001; Lundblad et al. 2002). Furthermore, a loss of LC-ascending NE axons forestalls the onset, worsens the severity, and decides the ultrastructural correlates of L-DOPA-induced AIMs (Fulceri et al. 2006; Fulceri et al. 2007). Together, these findings clearly demonstrated the robust impact of the LC-NE system on dopaminergic neuronal plasticity in the adult brain.

The neurotrophic effects of NE have been also explained as one of the mechanisms underlying NE's neuroprotective role. Although ARs are involved in NE neurotrophic actions, several observations revealed that in some cases, NE's effects are independent of ARs. Instead, the catechol moiety of NE plays an important role. For example, the neuroprotective effect of NE against oxidative stress in cultured cholinergic neurons and SK-N-SH cells appears to be related to its catechol moiety, as a compound that reproduces the diphenolic structure of NE without binding affinity for ARs (Vauquelin et al. 1979) mimicked NE's neuroprotective effects (Traver et al. 2005; Jhang et al. 2014). The similar phenomenon was also found on the dopaminergic neurons (Troadec et al. 2001). The diphenolic structure in NE may be at the origin of the trophic effect on DA and responsible for the neuroprotective effect of NE, possibly via the production of corresponding metabolites by autoxidation (Troadec et al. 2001). These indicate that the precursors and metabolites of NE, which exhibited on their aromatic ring two free hydroxyl groups in the orthoposion, afford neuroprotection. It is such diphenolic structure that is responsible for the neuroprotective/antioxidant activity of NE. Consistent with this view, the compounds which possess a catechol moiety, such as the β- and β_1-AR agonists isoproterenol and dobutamine, as well as *o*-catechol (pyrocatechol), mimicked the protective effects of NE in dopaminergic and other cultures (Ancerewicz et al. 1998; Noh et al. 1999; Troadec et al. 2001).

NE's Effects May Be Mediated Through BDNF

BDNF is a member of the neurotrophin family (Barde et al. 1982; Leibrock et al. 1989). It is predominantly produced by neurons (Zafra et al. 1992; da Penha Berzaghi et al. 1993; Lindholm et al. 1994; Thoenen 1995) and astrocytes (Miklic et al. 2004). Binding BDNF and its preferred receptor, the tropomyosin receptor kinase B (TrkB) (Reichardt 2006), triggers the activation of diverse signaling cascades, further regulating neuronal development and survival, as well as neurogenesis in the central nervous system (Ghosh et al. 1994; Jones et al. 1994; Nawa et al. 1994; Cabelli et al. 1995; McAllister et al. 1995, 1996; Zuccato and Cattaneo 2009). Accumulating evidence shows that NE can facilitate the expression of several neurotrophic factors. However, BDNF can be a main mediator for the trophic signal derived from noradrenergic afferents (Fawcett et al. 1998), for which the extensive studies have well documented.

First, BDNF is synthesized by LC neurons (Castren et al. 1995; Smith et al. 1995; Conner et al. 1997; Numan et al. 1998). DBH and BDNF are co-localized in the noradrenergic axons and terminal nerve fibers in the brain (Castren et al. 1995; Fawcett et al. 1998). Second, BDNF is anterogradely transported (from the cell soma) by afferents to fibers in noradrenergic terminals and then secreted onto target neurons (Conner et al. 1997; Fawcett et al. 1998). Such anterogradely transported BDNF causes activation of TrkB in target regions such as the neocortex for neurons survival and differentiation (Fawcett et al. 1998). This presynaptic secretion of BDNF may provide a cellular mechanism for noradrenergic modulating on other neural circuitries, in either developing or mature nervous systems. An in vivo study demonstrated that mice overexpression BDNF in DBH-positive neurons exhibited a 52% increase of TH-positive neurons in the SNpc (Alonso-Vanegas et al. 1999), suggesting that an increased anterograde transport of BDNF through coeruleus-nigral projection could benefit the growth of mesencephalic DA neurons (Vitalis et al. 2005). Third, NE stimulates the synthesis of BDNF in neurons and astrocytes, which has been confirmed in vivo (Fawcett et al. 1998; Ivy et al. 2003) and in vitro (Zafra et al. 1992; Schwartz and Nishiyama 1994; Schwartz et al. 1994; Inoue et al. 1997; Juric et al. 2006; Chen et al. 2007; Musazzi et al. 2014). In contrast, the antagonists of α_1- and β_1/β_2-ARs inhibited this stimulatory effect of NE (Juric et al. 2008). Fourth, the neuroprotective effects of NE require TrkB activation. NE triggers TrkB phosphorylation. It has been reported that the TrkB, but not ARs, is essential for the ability of NE to protect cultured neurons from rat cortex, hippocampus, and LC, as well as human hNT neurons following Aβ exposure (Counts and Mufson 2010; Liu et al. 2015). The ability of NE to prevent Aβ-induced cells death was fully prevented by the TrkB antagonist k252a. Fifth, NE may transactivate TrkB via Src family kinase activity, which has been indicated in the studies using adenosine, pituitary adenylate cyclase-activating peptide, and zinc (Lee and Chao 2001; Lee et al. 2002; Rajagopal et al. 2004; Huang et al. 2008), as NE and the small molecule TrkB agonist 7,8-dihydroxyphenylserine share structural similarities (a catechol ring).

Both NE and BDNF Act Through Survival Signaling Pathways

Neuronal viability is maintained through a complex interacting network of signaling pathways. While these diverse cascades are critical for the proper formation of the central nervous system (Yuan and Yankner 2000), they are associated with neuronal protections for affected neurons

and called as the neuronal survival signaling pathways. For example, the phoshpatidyloinositol-3-kinase (PI3K)/Akt pathway is a major mediator of cell survival signaling leading to the transcription of many pro-survival genes (Datta et al. 1999; Brunet et al. 2001; Kang et al. 2004; Patel et al. 2010). The mitogen-activated protein kinase/extracellular signal regulated kinase 1/2 (MAPK/ERK) pathways promote neuronal growth and neuroplasticity and influence gene expression through activation of transcription factor such as CREB (Shaywitz and Greenberg 1999; Troadec et al. 2002; Einat et al. 2003; Chen et al. 2007; Cottingham et al. 2012). In addition to increasing cellular survival, the PI3K and MAPK pathways play principal roles in promoting neurite growth, synaptic strength and plasticity (Heerssen and Segal 2002). NE and BDNF are not transcriptional factors and cannot directly act on transactivation of related genes (Ruiz et al. 2014). As such, these pathways have been shown to mediate the neurotrophic effects of NE and BDNF. As one of the consequences, activation of these signaling pathways leads to the binding of transcription factors with *cis*-acting elements such as *AP-1*, *CRE*, and *Egr1/SP1* on the TH promoter and transactivation of the TH gene (Nagamoto-Combs et al. 1997; Lim et al. 2000; Suzuki et al. 2004; Kalashnikova et al. 2006; Fukuchi et al. 2010).

Many lines of investigations have revealed these survival pathways as an important mean for NE to enhance neuronal growth or protections. For instance, administration of NE dose-dependently induces a robust activation of ERK1/2 (Cottingham et al. 2012), PI3K, and CREB proteins (Chen et al. 2007). Similarly, desipramine, which increases extracellular NE levels, not only can act as a signaling potentiator to selectively enhance NE-induced ERK1/2 signaling (Cottingham et al. 2012), but also activate the MAPK/ERK pathway (Huang et al. 2007). Cyclic adenosine monophosphate (cAMP) was described as a prosurvival molecule for several populations of catecholaminergic neurons. The neuroprotective effect of NE on dopaminergic neuronal cells is strongly enhanced by forskolin, a cAMP-elevating agent, which did not involve ARs (Troadec et al. 2002). However, this effect involves cAMP-dependent MAPK, as forskolin stimulated the phosphorylation of extracellular ERK1/2 in dopaminergic neurons (Troadec et al. 2002). Nevertheless, other studies showed that α_{2A}-AR (Cottingham et al. 2012) or β-ARs (Counts and Mufson 2010) are involved in NE-induced neuroprotective properties through stimulation of cAMP production and pCREB signaling. The activation of these signal pathways is believed to promote cell survival both in vivo (Chen and Russo-Neustadt 2005) and in vitro (Chen and Russo-Neustadt 2007).

As mentioned above, activation of diverse signaling cascades trigged by binding of BDNF and TrkB also has critical roles in neuronal plasticity, survival, and neurogenesis (Zuccato and Cattaneo 2009). The three major pathways include the phospholipase C-γ (PLC-γ), PI3K)/Akt, and MAPK/ERK pathway (Baydyuk and Xu 2014). By activating these diverse signaling cascades in neurons, BDNF can regulate neuronal development and progenitor cell survival, proliferation, initiation of neurite outgrowth, and path-finding (Bonni et al. 1999; Encinas et al. 1999; Yamada et al. 1999). It can mediate various structural plasticities of neurons, including dendrite formation and maintenance (Widmer et al. 1993; McAllister et al. 1999; Berghuis et al. 2006; Sciarretta et al. 2010; Orefice et al. 2013). The MAPK/ERK pathway also activates regulators of protein translation (Segal 2003). Deletion of either the *TrkB* or *Bdnf* gene leads to cell atrophy, dendritic degeneration, and neuronal loss, as shown in the excitatory neurons of the dorsal forebrain (Gorski et al. 2003). BDNF-activated ERK1/2 protects cultured rat cortical neurons against apoptosis induced by DNA damage, which is necessary and sufficient for the anti-apoptotic action of BDNF (Hetman et al. 1999; Gozdz et al. 2003).

A foundation of previous studies as described above has illustrated the potential mechanisms underlying effects of NE on dopaminergic neurons through its neurotrophic action and through other neurotrophic factors such as BDNF. The LC-NE system can affect neuronal growth, survival and plasticity of dopaminergic neurons, indicating that NE must activate the translation of pro-growth or plasticity-related protein synthesis. Therefore, activation of signaling pathways as listed above is a necessary step and thus leads to transcription of the TH gene acting on some *cis*-elements in the TH promoter (Kim et al. 1993; Tinti et al. 1996; Suzuki et al. 2004).

Other Potential Mechanisms Underlying Effects of NE on Dopaminergic System

NE Has Anti-inflammatory Properties: Suppress Mediators of Inflammation

Accumulating evidence suggests that inflammation contributes to the onset and evolution of degeneration in dopaminergic neurons (Mosley et al. 2012). Therefore, the neuroprotective effects of NE on dopaminergic neurons may also be related to its ability to maintain the immunosuppressive environment in the brain as a repression of proinflammatory mediators (Feinstein 1998; Heneka et al. 2002). In vivo studies show that increasing NE levels reduce inflammation (Kalinin et al. 2006) and provide neuroprotection (Troadec et al. 2002). First, NE can reduce damage during neuroinflammatory and neurodegenerative conditions by inducing expression of neurotrophic factors as mentioned in the above section. Second, NE or stimulation of ARs promotes anti-inflammatory phenotypes. For example, the β_2-AR agonist protects neurons from kainic acid-induced inflammatory damage (Gleeson et al. 2010), as activation of the β_2-ARs promotes the M2 macrophage phenotypes (Grailer et al. 2014) and Th2-type immune responses by reduced cytokine secretion (Anderson and Mosser 2002).

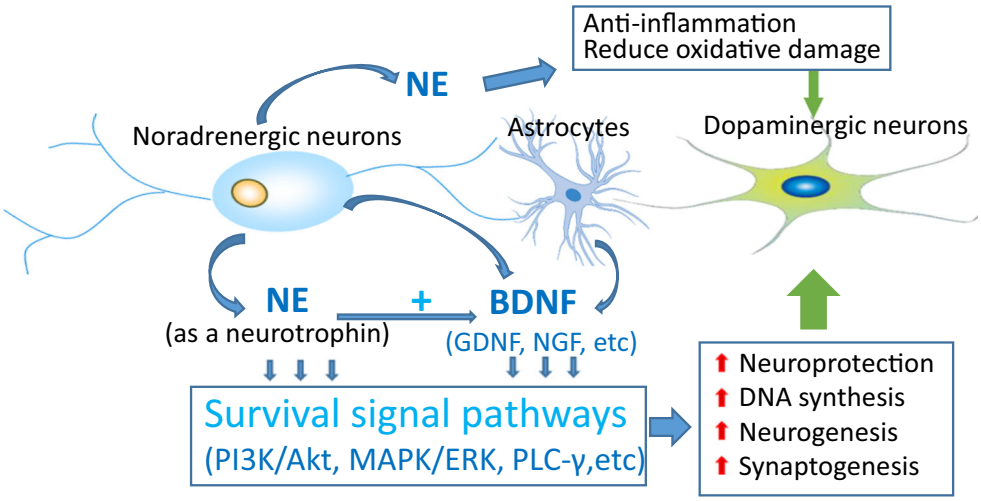

Fig. 1 Schematic representation of potential mechanisms underlying the protective role of the LC-NE system on dopaminergic neurons through trophic influence and positive signaling

Third, NE can suppress inflammatory gene expression from astrocytes. For example, in vitro studies have shown that NE or β-AR agonists suppresses glial expression of proinflammatory cytokines such as IL-1β (Thastrup et al. 1985; Dello Russo et al. 2004), MIP1-α and TNF-α from macrophages (Spengler et al. 1994; Hasko et al. 1998), and the inducible nitric oxide synthase (iNOS) (Feinstein et al. 1993; Gleeson et al. 2010). Similarly, these treatments reduce system levels of TNF-α, IL-6, and nitric oxide during endotoxemia (Elenkov et al. 1995; Szabo et al. 1997). Also, NE reuptake inhibitors desipramine and atomoxetine suppress expression of inflammation-related chemokine and cell adhesion molecule in vivo and in vitro (O'Sullivan et al. 2009, 2010). Other in vivo studies demonstrated that experimental LC destruction resulted in a robust increase and prolonged expression of both IL-1β and iNOS (Heneka et al. 2002).

NE's Protection May Be Related to the Reduction of Oxidative Stress-Induced Damage

Oxidative stress has been considered as a causative factor for degeneration of dopaminergic neurons in PD. One protective role of NE on dopaminergic neurons may be related to its ability to reduce oxidative stress (Noh et al. 1999). For example, treatment with NE markedly reduced the production of free radical species, which can be mimicked by treatment with catalase (Troadec et al. 2001), an enzyme that blocks the conversion of H_2O_2 into the highly reactive hydroxyl radicals (Takahashi and Niki 1998). Further, NE and its putative active metabolites are hydrophilic, and they can exert their protective action at the level of the outer plasma membrane by preventing the propagation of lipid peroxidation (Andorn and Pappolla 2001). Moreover, NE was shown to act as both a scavenger of hydroxyl radicals and an inhibitor of lipid peroxidation in cell-free system (Liu and Mori 1993). Finally, trolox is a vitamin E analogue known to protect cell membranes from hydroxyl radical-mediated lipid peroxidation and showed its neuronal protection (Buettner 1993). NE has been showed as potent as trolox in reducing the levels of reactive oxygen species produced in degenerating neurons (Troadec et al. 2001; Alvarez-Diduk and Galano 2015). Therefore, NE exerts its protective action at the levels of the outer plasma membrane by preventing the propagation of lipid peroxidation.

Conclusions

It is well known that the LC-NE system plays a critical role in homeostatic control of brain functions and is involved in a variety of physiological process and behaviors. Furthermore, there are a number of lines of studies revealed the crosstalk between the LC-NE and dopaminergic neurons. However, the neuroprotective effects of the LC-NE system on dopaminergic neurons, especially the involved mechanisms, have not been discussed in detail. Based on the evidence reviewed above, a functional and activity deficiency in the LC-NE system has been taken as a critical factor in determining the evolution of progressive degeneration in dopaminergic neurons in the brain. An intact LC-NE system provides an important role for the survival and normal function of dopaminergic neurons. Among these effects, NE as a potential modulator for dopaminergic neurons plays a central role through its neurotrophic factor and by means of other neuronal growth factors especially BDNF (Fig. 1). Extensive and appropriate studies will be necessary to elucidate the mechanisms involved in NE's neurotrophic effects, which will improve our understanding the modulation of the LC-NE on dopaminergic neurons and benefit for the strategy in paving a path to drug development and treatment of neurodegenerative diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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