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α-Synuclein and Noradrenergic Modulation of Immune Cells in Parkinson's Disease Pathogenesis

*Laura M. Butkovich, Madelyn C. Houser and Malú G. Tansey**

Tansey Laboratory, Department of Physiology, School of Medicine, Emory University, Atlanta, GA, United States

α-synuclein (α-syn) pathology and loss of noradrenergic neurons in the locus coeruleus (LC) are among the most ubiquitous features of Parkinson's disease (PD). While noradrenergic dysfunction is associated with non-motor symptoms of PD, preclinical research suggests that the loss of LC norepinephrine (NE), and subsequently its immune modulatory and neuroprotective actions, may exacerbate or even accelerate disease progression. In this review, we discuss the mechanisms by which α-syn pathology and loss of central NE may directly impact brain health by interrupting neurotrophic factor signaling, exacerbating neuroinflammation, and altering regulation of innate and adaptive immune cells.

Keywords: α-synuclein, locus coeruleus, Parkinson's disease, neuroinflammation, norepinephrine, immune cell

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***Correspondence:**
Malú G. Tansey
malu.tansey@emory.edu

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INTRODUCTION

Locus coeruleus (LC) degeneration and α-synuclein (α-syn) aggregation are among the most ubiquitous features of Parkinson's disease (PD) (Chui et al., 1986; German et al., 1992; Zarow et al., 2003). Brain regions affected in PD, including the LC, contain large protein-rich intracellular inclusions known as Lewy bodies (LB) or Lewy neurites (LN) accompanied by chronic inflammation and neuron loss (den Hartog and Bethlem, 1960; Spillantini et al., 1997; Tansey and Goldberg, 2010). While LBs and LNs contain numerous proteins, α-syn is the predominant component (Spillantini et al., 1997), and α-syn is the major pathological protein underlying PD pathogenesis. α-syn is a 140-amino acid protein encoded by the *SNCA* gene, which is expressed in many tissue types and which accounts for approximately 1% of cytosolic proteins in neurons (Shibayama-Imazu et al., 1993; Iwai et al., 1995; Stefanis, 2012). It is highly expressed in the presynaptic terminals where it acts as a molecular chaperone in SNARE formation and vesicular trafficking (Burre et al., 2010). Genetic evidence comes from individuals carrying *SNCA* mutations, which confer increased risk of PD, or autosomal dominant forms of PD (Klein and Schlossmacher, 2006). Finally, animal models overexpressing α-syn develop age-dependent α-syn aggregates and PD-like behavioral abnormalities (Masliah et al., 2000; Giasson et al., 2002). The initiating event in α-syn aggregation is unknown, but Lewy pathology (LP) and cell loss are common within discrete neuronal populations in PD.

Extensive dysfunction of catecholaminergic neurons is a well-established feature of PD, and a major hallmark is LP and loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) which induces motor impairments including tremor, muscle rigidity, bradykinesia, and postural instability (Hirsch et al., 1988; Fearnley and Lees, 1991; Parkinson, 2002). A diagnosis of PD is currently dependent on the presence of motor symptoms and striatal dopamine deficiency; however, PD is a multifactorial disease with non-motor symptoms that are associated with alterations in cholinergic, serotonergic, and noradrenergic systems occurring years or even decades prior to the onset of motor dysfunction (Gonera et al., 1997; Abbott et al., 2005; Ross et al., 2008).

LP and degeneration of several pontine and medullary nuclei (including the dorsal raphe, dorsal motor nucleus of the vagus, pedunculopontine nucleus, and LC) are ubiquitous features of PD (Halliday et al., 1990). The LC is the major source of norepinephrine (NE) to the CNS, and it is among the first brain regions to be affected in PD (Iversen et al., 1983; Mann and Yates, 1983; Braak et al., 2001). NE is the ligand for the adrenergic receptors (ARs) comprised of seven G-protein coupled receptors that are G_q-, $G_{i/o}$-, or G_s-coupled, allowing NE to have diverse functional effects dependent on receptor expression and cell type (Strosberg, 1993). LC neurons are constitutively active and innervate virtually every brain region via extensive and complex axonal arborization that facilitates the release of both synaptic NE and extra-synaptic NE at axonal varicosities (Freedman et al., 1975; Grzanna and Molliver, 1980; Jones and Yang, 1985; Agnati et al., 1995) where LC-NE can be neuroprotective by both direct and indirect mechanisms. Here, we will review evidence that LC dysfunction may exacerbate PD pathophysiology and may represent a tipping point in disease progression.

LC-NE DYSREGULATION COULD PROMOTE THE PROGRESSION OF PD PATHOLOGY

It is unclear why certain neuronal populations like the LC are vulnerable to α-syn pathology, but sensitivity to oxidative stress, pacemaker activity, and extensive contact with blood vessels that may expose LC neurons to circulating toxins have been implicated (Jenner, 2003; Cho, 2014; Pamphlett, 2014). The degree of noradrenergic innervation to a brain region is negatively correlated with DA loss (Tong et al., 2006), indicating that the loss of central NE and its neuroprotective actions may directly influence the rate of PD progression. In PD, loss of LC neurons begins prior to nigral pathology and appears to be of greater magnitude (German et al., 1992; Zarow et al., 2003; Szot et al., 2006; Brunnstrom et al., 2011). Per the Braak staging hypothesis of PD pathology, LP first appears in brainstem nuclei (stage 1), and, as PD progresses, continues along a caudo-rostral axis with LC pathology appearing at stage 2 and SNpc pathology at stage 3, before ultimately extending into cortical regions (Braak et al., 2003). PD brain tissue has marked LC denervation in many brain regions and loss of LC cell bodies that extends throughout its rostral-caudal axis (Javoy-Agid et al., 1984; German et al., 1992; Pavese et al., 2011). Imaging and postmortem histological studies of PD patients reveal a progressive loss of central NE throughout the brain (Pifl et al., 2012) along with accumulation of α-syn and loss of LC neurons (Halliday et al., 1990; Chen et al., 2014; Keren et al., 2015; Isaias et al., 2016). LC neuron vulnerability to α-syn pathology can be replicated experimentally. A recent model targeted viral vector-mediated overexpression of a familial PD mutant α-syn variant to the murine LC region (Henrich et al., 2018). While transgene expression was not restricted to neuronal cells, the resulting progressive α-syn aggregation, gliosis, and LC degeneration are reminiscent of LC pathology found in PD. Enzymes responsible for NE synthesis and NE metabolite levels are reduced in the CSF of PD patients, also supporting these central changes in NE metabolism (Hurst et al., 1985; Goldstein et al., 2012). Evidence of early LC dysfunction can be found in patients who do not meet the diagnostic criteria for PD. In such individuals, decreased neuron density in the LC, but not VTA or dorsal raphe, corresponds to the severity of global parkinsonism (Buchman et al., 2012), suggesting that this state may represent prodromal/preclinical PD. Patients who had LP at autopsy but lacked any of the clinical signs of PD also had reduced LC neuron density as compared to DA neurons in the SNpc, further highlighting the possible early role of LC neuron loss in PD (Dickson et al., 2008).

There is also evidence that α-syn may directly affect NE homeostasis by two separate mechanisms. First, norepinephrine transporter (NET)-expressing cells transfected for α-syn expression reveal that high levels of α-syn negatively regulate NET expression on the cell surface, while relatively lower levels increase NET expression (Wersinger et al., 2006). Second, when α-syn is overexpressed in an NE-producing cell line or transgenic rodent model, it can translocate to the nucleus and directly interfere with transcription of dopamine ß-hydroxylase (DBH), the enzyme involved in the final step of NE synthesis, reducing NE production (Kim et al., 2011, 2014). It is possible that interfering in NE neurotransmission could, in turn, impact α-syn expression as ß-adrenergic receptor (ß-AR) agonists reduce *SNCA* mRNA and α-syn protein expression in induced pluripotent stem cells derived from individuals carrying the *SNCA* triplication mutation (Mittal et al., 2017). Together, these data indicate that α-syn can influence NE metabolism, and that this, in turn, could impact α-syn expression, although additional work is required to determine if this is clinically relevant.

PD NON-MOTOR SYMPTOMS

The LC is the major source of NE to the CNS (Mouton et al., 1994), and dysregulated noradrenergic innervation is associated with many of the non-motor symptoms of PD including anxiety (Casacchia et al., 1975; Stein et al., 1990; Nuti et al., 2004), depression (Shulman et al., 2002; Ravina et al., 2007), rapid eye movement (REM) sleep behavioral disorder (RBD) (Sixel-Doring et al., 2011; Kalaitzakis et al., 2013), and dementia (Chui et al., 1986).

Up to 60% of PD patients report experiencing some form of anxiety (Chaudhuri and Schapira, 2009; Lin et al., 2015; Houser and Tansey, 2017). Dopamine, serotonin, and NE have been implicated in PD anxiety, suggesting that its neurobiological origins are complex (Eskow Jaunarajs et al., 2011; Thobois et al., 2017; Joling et al., 2018). LC neurons are highly active during stress exposure (Bingham et al., 2011; Curtis et al., 2012) and innervate all corticolimbic regions involved in the anxiety response (Aston-Jones et al., 1991, 1999). In PD patients, anxiety severity is inversely correlated with dopamine/NE transporter binding in the LC (Remy et al., 2005), and experimentally, selectively inhibiting LC neurons during stress exposure blocks the subsequent anxiety-like behavior (McCall et al., 2015).

Around 35% of PD patients suffer from depression (Reijnders et al., 2008; Houser and Tansey, 2017). Dysfunction of LC-NE is known to be associated with depression (Moriguchi et al., 2017) and is a common pharmacological target in the treatment of depression (Ressler and Nemeroff, 2001; Remy et al., 2005). Indeed, early investigation of NET expression in the LC reported decreased NET in major depressive disorder (Klimek et al., 1997), although results from subsequent studies have been inconsistent (Moriguchi et al., 2017). While it is unclear if NET is downregulated due to lack of available NE or in order to increase synaptic NE levels, it is clear that NE dysfunction can contribute to depressive symptoms.

LC neuron activity fluctuates diurnally with increased activity immediately prior to waking and during waking hours (Hobson et al., 1975). Sleep disturbances are one of the most common complaints from PD patients (Smith et al., 1997) and can include insomnia (Gjerstad et al., 2007), excessive daytime sleepiness (Rye et al., 2000), and RBD (Comella et al., 1998; Gagnon et al., 2002). A recent study reported that disturbed sleep is positively correlated with anxiety and depression in PD (Rana et al., 2018). In fact, RBD is the most predictive non-motor symptom of synucleinopathies with up to 92% of idiopathic RBD patients receiving a synucleinopathy diagnosis within 14 years (Iranzo et al., 2006; Postuma et al., 2009; Schenck et al., 2013). There is evidence that LC neurons in individuals that have PD with disturbed sleep contain more LP than in those without (Kalaitzakis et al., 2013), and mice lacking DBH (and subsequently, NE) have significantly disturbed sleep behavior (Hunsley and Palmiter, 2003). Together, these data suggest that loss of central NE may directly contribute to the development of sleep disturbances in PD.

An estimated 83% of PD patients will experience some sort of cognitive dysfunction, including dementia (Hely et al., 2008). Dementia is characterized by cognitive impairment, including memory loss, attentional deficits, and loss of executive function (Elizan et al., 1986; Aarsland et al., 2003). While dementia is generally associated with cholinergic deficits and late-stage PD, early executive disturbances may arise from deregulation of LC-NE. PD patients with dementia have more extensive loss of LC-NE in cortical regions than those without (Chan-Palay and Asan, 1989). In fact, degeneration of LC neurons and loss of cortical NE is a central component of dementia of Alzheimer's type (Mann and Yates, 1983; Zarow et al., 2003). In animal models, hippocampal LC-NE is essential for proper memory acquisition and retrieval (Devauges and Sara, 1991; Mello-Carpes et al., 2016), and loss of LC neurons can impact memory and enhance cognitive deficits (Ohno et al., 1997; Chalermpalanupap et al., 2018).

BEYOND THE NON-MOTOR SYMPTOMS

The temporal relationship between LC and SNpc pathology suggests that loss of LC-NE may leave SNpc neurons more vulnerable to α-syn toxicity and potentiate the rate of PD progression. Experimentally, loss of LC-NE exacerbates 6-OHDA- and MPTP-mediated nigral degeneration in rodent and primate models (Mavridis et al., 1991; Srinivasan and Schmidt, 2003; Rommelfanger et al., 2007; Yao et al., 2015), while increasing synaptic NE by genetic deletion or pharmacological blockade of the NE transporter (NET) confers resistance (Kilbourn et al., 1998; Rommelfanger et al., 2004). Indeed, individuals with a functional polymorphism in the promoter regions of the *DBH* gene have reduced risk of developing PD (Healy et al., 2004). In sum, these data demonstrate that loss of NE may exacerbate nigral pathology.

NEUROPROTECTIVE EFFECTS

NE can directly act as a neurotrophic factor but can also indirectly stimulate neurotrophic factor expression. Primary mesencephalic cultures treated chronically with NE have a significantly reduced rate of cell death, increased neuritic processes, and reduced production of reactive oxygen species when compared to untreated cultures, and this phenotype resembles cultures treated with traditional antioxidants (Troadec et al., 2001, 2002). Increasing synaptic NE was shown to be protective against neuron loss and inflammation in a model of hypoxic-ischemia (Toshimitsu et al., 2018). While NE ligation of ARs directly facilitates neuroprotection by several mechanisms, the neuroprotective effects are not always blocked by AR antagonists, suggesting NE-mediated protection may also occur indirectly. One candidate mechanism of interest is the neuropeptide brain-derived neurotrophic factor (BDNF), which is synthesized and released by astrocytes and neurons, including those in the LC (Castren et al., 1995). BDNF signaling is primarily mediated by binding to the high affinity tropomyosin-related kinase B receptor (TrkB), which can protect SNpc neurons in experimental models, and BDNF mRNA is reduced in the SNpc in PD (Hyman et al., 1991; Spina et al., 1992; Howells et al., 2000). NE can also enhance BDNF transcription and BDNF/TrkB kinetics (Chen et al., 2007). Activation of the β1-adrenergic receptor stimulates BDNF transcription in astrocytes (Koppel et al., 2018). When BDNF binds to TrkB, signal transduction is mediated by TrkB dimerizing and autophosphorylating (Haniu et al., 1997). NE can induce autophosphorylation of TrkB and is protective against cell death in primary culture (Liu et al., 2015). In addition to loss of NE, α-syn may also directly disrupt the neuroprotective effects of BDNF. A recent study demonstrated that α-syn has the potential to bind the kinase domain on TrkB receptors, preventing the neurotrophic signaling of BDNF/TrkB, and that this exacerbates degeneration of DA neurons (Kang et al., 2017).

CENTRAL INFLAMMATION

Neuroinflammation is a vital mechanism in restoring brain integrity following neuronal insult but is also a core component of PD pathology. In a healthy brain, the inflammatory response resolves relatively quickly, with normal brain function restored (Roth et al., 2014; Laumet et al., 2018). In neurodegenerative diseases, such as PD, sustained neuroinflammation can become

cytotoxic, aggravating neuronal degeneration. It is unclear what triggers the initial inflammation in PD, but extracellular monomeric or aggregated α-syn can be phagocytosed by microglia and induce their activation (Zhang et al., 2005; Hoenen et al., 2016), and neuronal overexpression of α-syn aggravates and prolongs neuroinflammation (Miller et al., 2007; Gao et al., 2011; Sanchez-Guajardo et al., 2013). In PD patients, immune mediators such as IL-1ß, TGFß, IFNγ, and IL-6 are increased in the cerebral spinal fluid (CSF) and nigrostriatal regions (Mogi et al., 1994; Blum-Degen et al., 1995; Mount et al., 2007), and SNpc DA neurons appear particularly sensitive to pro-inflammatory cytokines (McGuire et al., 2001; Mount et al., 2007; Tansey and Goldberg, 2010). In fact, neuroinflammation is detectable prior to signs of neuronal degeneration, suggesting a potential early role for inflammation in PD pathogenesis (Theodore et al., 2008; Watson et al., 2012).

Research indicates that dysregulation of noradrenergic signaling may also play a role in driving inflammation. Like overexpression of neuronal α-syn, lesioning LC neurons using a noradrenergic-specific toxin also induces inflammation (Theodore et al., 2008; Watson et al., 2012; Yao et al., 2015; Song et al., 2018). NE can have activating or inhibitory effects on immune cells depending on adrenergic receptor expression, which varies depending on the cellular environment (Khan et al., 1985; Tanaka et al., 2002). Therefore, LC degeneration and subsequent deficient brain NE may contribute to PD pathology by loss of normal immune cell modulation. Microglia, the brain-resident macrophages, are the sentinels of brain parenchyma, monitoring tissue integrity and responding to infection or injury (Nimmerjahn et al., 2005). When ramified (resting) microglia are activated, they adopt an amoeboid morphology, proliferate, and become phagocytic, releasing pro-inflammatory cytokines which can recruit central and peripheral immune cells to the site of insult (Hayes et al., 1987). There is extensive evidence of sustained microglial over-activation in degenerating brain regions in PD (Kim and Joh, 2006; Tansey and Goldberg, 2010), and inhibiting microglia activation with minocycline prevents DA neuronal loss in mice treated with a DA neuron-specific toxin (Wu et al., 2002).

Microglia express many neurotransmitter receptors, including ARs (Pocock and Kettenmann, 2007). While more studies are required to understand how AR activation affects microglial phenotypes, depletion of NE, as is found in PD, exacerbates microglial inflammatory responses (Heneka et al., 2002; Bharani et al., 2017). AR-mediated modulation of microglia is well documented, although reports of the functional outcome are inconsistent. In murine brain slices, resting microglia appear to preferentially express the excitatory ß2-AR, but shift toward the inhibitory α2-AR receptor expression following activation with the canonical microglial activator lipopolysaccharide (LPS) (Gyoneva and Traynelis, 2013). However, microglial treatment with an ß2-AR agonist is reported to have anti- or pro-inflammatory effects. For example, cultured primary microglia treated with a ß2-AR agonist suppressed microglial proliferation (Fujita et al., 1998), while a subsequent study reported that priming microglia with a ß2-AR agonist prior to LPS treatment significantly increased pro-inflammatory IL-1ß and IL-6 expression (Johnson et al., 2013). The functional outcome of microglial AR activation appears dependent on the physiological context, and further examination is needed to determine how this may influence PD pathology.

PERIPHERAL INFLAMMATION

There is abundant evidence that the inflammatory manifestations of PD are not confined to the CNS. Indicators of inflammation have been found in the colon tissue, stool, and blood as well as in the CSF. Colonic expression of the genes encoding pro-inflammatory cytokines TNF, IFNy, IL-6, and IL-1β is increased in PD, accompanied by evidence of gliosis (Devos et al., 2013). Recently, we reported that IL-1α, IL-1β, CXCL8, and CRP are significantly elevated in stool from PD patients compared to controls (Houser et al., 2018), and that serum levels of TNF, IFNy, and neutrophil gelatinase-associated lipocalin levels are significantly and consistently different in PD over a 24-h period (Eidson et al., 2017). Local α-syn expression has been found to increase under inflammatory conditions in the periphery (Stolzenberg et al., 2017), and α-syn pathology has been observed in the enteric nervous system of PD patients, even from the earliest stages of disease (Stokholm et al., 2016; Barrenschee et al., 2017; Punsoni et al., 2017). These findings demonstrate that similar pathological processes are active in the CNS and the periphery in PD, and there is almost certainly significant crosstalk between them.

Degradation of the blood-brain-barrier (BBB) has been well documented in PD (Kortekaas et al., 2005; Pisani et al., 2012; Gray and Woulfe, 2015), and it has been proposed that this impaired barrier function exposes the CNS to circulating factors that could promote α-syn aggregation (Gray and Woulfe, 2015), immune cell infiltration, neuroinflammation, and, ultimately, neurodegeneration (Rite et al., 2007). Whether through direct effects of reduced signaling through endothelial β-ARs or through increases in vascular permeability-promoting inflammation, LC neurodegeneration compromises the integrity of tight junctions (Kalinin et al., 2006) and increases permeability of the BBB (Nag and Harik, 1987). BBB leakiness enables greater interaction between central and peripheral immune activities, allowing exchange of cytokines, chemokines, and other circulating molecules and potentially even facilitating infiltration of peripheral immune cells into the CNS where loss of central NE modulation could result in aberrant immune cell activity.

As with brain-resident microglia, immune cells originating in the periphery can also be modulated by NE. Peripheral immune cells infiltrate the brain parenchyma in PD (Kannarkat et al., 2013), and these will likely be directly impacted by reduced levels of central NE. Peripheral NE levels may also play important immunomodulatory roles in PD. The NE deficiency found in the CNS in PD is not consistently recapitulated in the periphery, with several studies reporting no difference in NE levels in plasma from PD patients compared to healthy controls (Eldrup et al., 1995; Goldstein et al., 2003). It is likely, however, that at least a subset of PD patients is affected by peripheral NE dysregulation as evinced by the prevalence of neurogenic orthostatic hypotension (NOH) associated with this

disease. NOH is a condition in which insufficient noradrenergic activity results in failure to appropriately increase blood pressure (BP) in response to a postural change such as sitting up or standing. This results in insufficient cerebral blood supply and can produce lightheadedness and dizziness, which increase fall risk (Merola et al., 2016). NOH occurs frequently in conditions involving synucleinopathy, and roughly 30% of PD patients are affected. NOH in PD is attributed to noradrenergic postganglionic sympathetic denervation associated with LP and a subsequent failure to induce sufficient NE production when transitioning to an upright position (reviewed by Loavenbruck and Sandroni, 2015). PD patients with orthostatic hypotension exhibit lower levels of NE in plasma compared to PD patients without NOH that reach levels significantly lower than non-PD controls (Senard et al., 1990; Niimi et al., 1999; Goldstein et al., 2005). This creates the potential for PD-associated NE deficiency to modulate peripheral immune responses as well as central.

Nearly every lymphoid tissue in the body has postganglionic sympathetic innervation, and peripheral innate and adaptive immune cells express ARs, rendering them responsive to NE. Excitatory β2-ARs are the most highly expressed ARs on peripheral immune cells, and their activity likely dominates the immune response to NE. β-AR signaling has potent anti-inflammatory effects on innate immune cells (reviewed by Qiao et al., 2018). In macrophages, which bear close functional resemblance to microglia, it suppresses pro-inflammatory activity and promotes tolerogenic and homeostatic phenotypes (Grailer et al., 2014; Noh et al., 2017). It also limits the number and the effector functions of natural killer (NK) cells (Whalen and Bankhurst, 1990; Takamoto et al., 1991). Adrenergic signaling has been shown to impair the functions of neutrophils and eosinophils as well (Gosain et al., 2009; Brunskole Hummel et al., 2013; Noguchi et al., 2015). Dendritic cells connect the innate and adaptive immune responses by sampling antigens in the local environment and then presenting them with appropriate polarization signals to T cells. β2-AR activation profoundly suppresses dendritic cell functionality, inhibiting their maturation, migration, antigen presentation including cross presentation, and proinflammatory cytokine production while inducing expression of anti-inflammatory factors (Seiffert et al., 2002; Herve et al., 2013; Chen et al., 2016; Qiao et al., 2018). It is important to note that while these anti-inflammatory effects on innate immune cells are well-documented, study designs differ widely, and the effects they observe on these cells vary depending on physiological context, time, AR agonist, and dose. Further research will be necessary to better characterize the relationship between NE and innate immune responses.

CD4+ T helper (Th) cells are indirectly affected by AR agonists due to their suppressive effects on dendritic cells which result in diminished differentiation of effector T cells, particularly Th1s (Wu et al., 2016). Th1 cells also express β2-ARs (McAlees et al., 2011), and their proliferation and activity are inhibited upon ligation of this receptor (Ramer-Quinn et al., 1997; Riether et al., 2011). Since Th2 cells do not express ARs (McAlees et al., 2011), their functionality is not directly modulated by exposure to NE, but NE-mediated suppression of Th1 cells would relieve their negative regulatory pressure on Th2 cells, indirectly promoting Th2-mediated immune activity, which is canonically involved in anti-helminth and allergic immune responses but not classic inflammation (Huang et al., 2015). β2-AR signaling also impairs the activity of CD8+ memory and effector T cells (Chen et al., 2016; Estrada et al., 2016; Bucsek et al., 2017).

The consequences of AR ligation on other T cell subsets are less straightforward. The intricacies of the potential effects of NE on CD4+ Th17 cells are just beginning to be elucidated. These cells are important actors in normal mucosal immunity, but they are also implicated in autoimmune pathology. Several studies have reported that treatment of CD4+ cells with NE promotes differentiation of Th17 cells and increases their activity (IL-17 production) while simultaneously inhibiting Th1 differentiation and activity (IFNγ production) (Carvajal Gonczi et al., 2017; Xu et al., 2018). On the other hand, studies of Th17 cells from both mice and humans with Th17-mediated autoimmune diseases found that treating CD4+ T cells with NE inhibited the differentiation and activity of Th17 cells (IFNγ production was also still reduced) (Boyko et al., 2016; Liu et al., 2018). This indicates that the immunoregulatory effects of NE on Th17 cells are dependent on the physiological context. It is also possible that autoimmune conditions in which pathology is mediated in part by IL-17-producing cells might constitute a unique context in which this alternative regulatory action of NE is observed. For instance, in such conditions, a highly inflammatory cell type that exhibits characteristics of both Th1 and Th17 cells is typically present (Murphy et al., 2010), and it may be that the actions of NE on this particular cell type rather than on canonical Th17s dominate its observed effects in these autoimmune diseases.

Findings on NE modulation of CD4+ T regulatory (Treg) cells, an anti-inflammatory subset which counteracts effector functions of other types of T cells, are even more ambiguous. One study reports that treatment of Tregs with NE prior to transfer in an autoimmune arthritis mouse model rendered them pathological and worsened the disease (Harle et al., 2008). In the same vein, another study found that NE exposure decreased the regulatory activity of Tregs and even induced their apoptosis (Wirth et al., 2014). On the other hand, a study in humans reported that Treg frequencies were elevated under conditions which increased circulating NE levels and that treatment of Tregs with epinephrine, which is chemically similar to NE and binds the same receptors, stimulated Treg proliferation. This effect was blocked by treatment with a β-AR antagonist (Inoue et al., 2017). A final study reported no detectable effects of treatment with NE or epinephrine on human Tregs, though they did determine that they could express three different types of ARs (Cosentino et al., 2007). Obviously, more research is needed to determine the effect of NE on Tregs.

B cells also express β2-ARs, and there is evidence that NE can negatively regulate the magnitude of antibody responses. The effects are highly varied, however, as they are influenced by the effects of NE on T cells, by the stimuli used to activate B cells, and by the immunological and physiological context of the experiment (extensively reviewed by Kin and Sanders, 2006). A couple of more recent studies suggest that, under conditions of autoimmune disease in which B cells contribute to inflammatory activity and pathology, NE exerts a suppressive effect on these

cells which is mediated by decreased IL-7 receptor signaling and enhanced production of anti-inflammatory IL-10 (Pongratz et al., 2012, 2014).

The effects described here do not represent the full extent of peripheral NE-mediated neuroimmune interactions. Most studies to date have focused on the results of β2-AR signaling, but immune cells express other ARs as well which can mediate different effects (Lorton and Bellinger, 2015), and, as in the brain, the relative levels of these receptors change in different immune environments. Activation of the same AR can even produce distinct responses depending on the concentration of the ligand and its temporal relationship to immunogenic stimuli (reviewed by Lorton and Bellinger, 2015). This provides important plasticity for neuroimmune regulatory mechanisms. Nonetheless, many functional studies support the existing literature that indicates a primarily anti-inflammatory impact of peripheral NE. Vagus nerve stimulation is known to have clear immunosuppressive effects (Inoue et al., 2017) and to reduce synuclein expression in the brain (Farrand et al., 2017), and these effects are mediated in large part by NE signaling through β-ARs (Vida et al., 2011). A recent review (Bucsek et al., 2018) summarized numerous studies showing that chemical ablation of sympathetic neurons or β-AR blockade enhanced immune responses to different bacterial, viral, and parasitic infections while AR agonist treatment impaired anti-viral and anti-parasite responses. Several of the studies found that these effects were specific to modulation of peripheral adrenergic activity, but it was also demonstrated that this could induce corresponding immune responses in the CNS. Similarly, another study found that ablation of peripheral and LC noradrenergic neurons prompted an exaggerated acute inflammatory response to peripheral LPS that was observed both in the brain and in the circulation (Bharani et al., 2017).

Taken together, the data on peripheral immune cells and their function when challenged indicate that NE is immunosuppressive, and as such, postganglionic sympathetic denervation and NE deficiency in PD could stimulate pro-inflammatory immune activity. This has implications for PD pathogenesis and the progression of disease pathology. Peripheral and systemic inflammation have been well documented in PD, and it has been proposed that inflammatory mechanisms may contribute to non-motor symptoms and also be responsible for the development and spread of synucleinopathy and the induction of neuroinflammation and neurodegeneration in this disorder (Qin et al., 2016; Houser and Tansey, 2017). PD-associated gastrointestinal abnormalities and dysfunction are consistent with inflammatory conditions in the gut (Houser and Tansey, 2017), and levels of proinflammatory cytokines in the blood correlate positively with the severity of anxiety and depression in PD patients (Wang et al., 2016). α-syn levels increase in the context of immune activation, and some data suggest that peripheral inflammation can induce elevated α-syn expression in the brain (Kelly et al., 2014) and that peripheral α-syn can migrate to the brain through the vagus nerve (Holmqvist et al., 2014). α-syn has also been shown to exert chemoattractant properties on peripheral myeloid cells, including recruiting them into the brain in a rodent PD model (Stolzenberg et al., 2017; Harms et al., 2018). Infiltration of peripheral CD4+ and CD8+ T cells into the brain has also been observed in PD (Brochard et al., 2009), and it has been shown that these T cells (primarily the CD4+ subset) in peripheral blood from PD patients recognize and respond to peptides derived from α-syn (Sulzer et al., 2017). In animal models of parkinsonian neuropathology, invading monocytes and CD4+ T cells have been identified as key mediators of neurodegeneration (Brochard et al., 2009; Harms et al., 2018).

NE deficiency, centrally and/or in the periphery, could potentiate all of these immune-mediated effects in PD. It would impair anti-inflammatory regulatory functions, shifting immune cells toward more pro-inflammatory phenotypes. Innate immune cells affected in this way would be less able to clear α-syn aggregates and neuronal debris effectively and in a toleragenic manner and more likely to recruit additional effector cells, stimulate their pro-inflammatory activities, and perhaps even present α-syn and other neuronal antigens in a context which could induce autoimmune responses (Sulzer et al., 2017). Furthermore, the activity of at least some T cell subsets which may be pathologically involved in PD could be potentiated by a loss of inhibitory NE signaling. Especially in the context of a compromised BBB, these pro-inflammatory immune cells and their products would have greater access to the CNS and could infiltrate and mediate damaging effects on neurons there.

DISCUSSION

Extensive dysfunction of catecholaminergic neurons is a well-established feature of PD, and while a major hallmark is LP and loss of DA neurons in the SNpc, PD is a multifactorial disease with alterations in cholinergic, serotinergic, and noradrenergic systems occurring years earlier and generally associated with PD's non-motor symptoms (Halliday et al., 1990; Braak et al., 2003). α-syn pathology and a progressive decline in LC-NE have been well characterized; still it is unclear why these neurons are among the most vulnerable in PD. Still less is known about how the deficits in LC-NE and the loss of its neuroprotective and neuroimmune modulatory effects could influence the development of synucleinopathy and exacerbate PD pathology (summarized in **Figure 1**). Preclinical research has provided compelling evidence supporting the neuroprotective functions of NE. Experimentally, depletion of NE renders SNpc neurons vulnerable in toxin models of PD (Mavridis et al., 1991; Srinivasan and Schmidt, 2003; Rommelfanger et al., 2007), while NE enhancement is protective (Kilbourn et al., 1998; Rommelfanger et al., 2004). Additionally, there is a reciprocal modulatory relationship between α-syn and NE whereby α-syn can modulate NE neurotransmission, both at the level of synthesis (Kim et al., 2014), and by modulating NET expression at the cell surface (Wersinger et al., 2006), and NE can attenuate *SNCA* transcription and α-syn protein expression (Mittal et al., 2017). As PD pathophysiology progresses, LP develops in the SNpc and other brain regions, and LC-NE denervation may exacerbate the rate and/or degree of degeneration during this premotor phase of PD. Experimentally, NE drives BDNF/TrkB

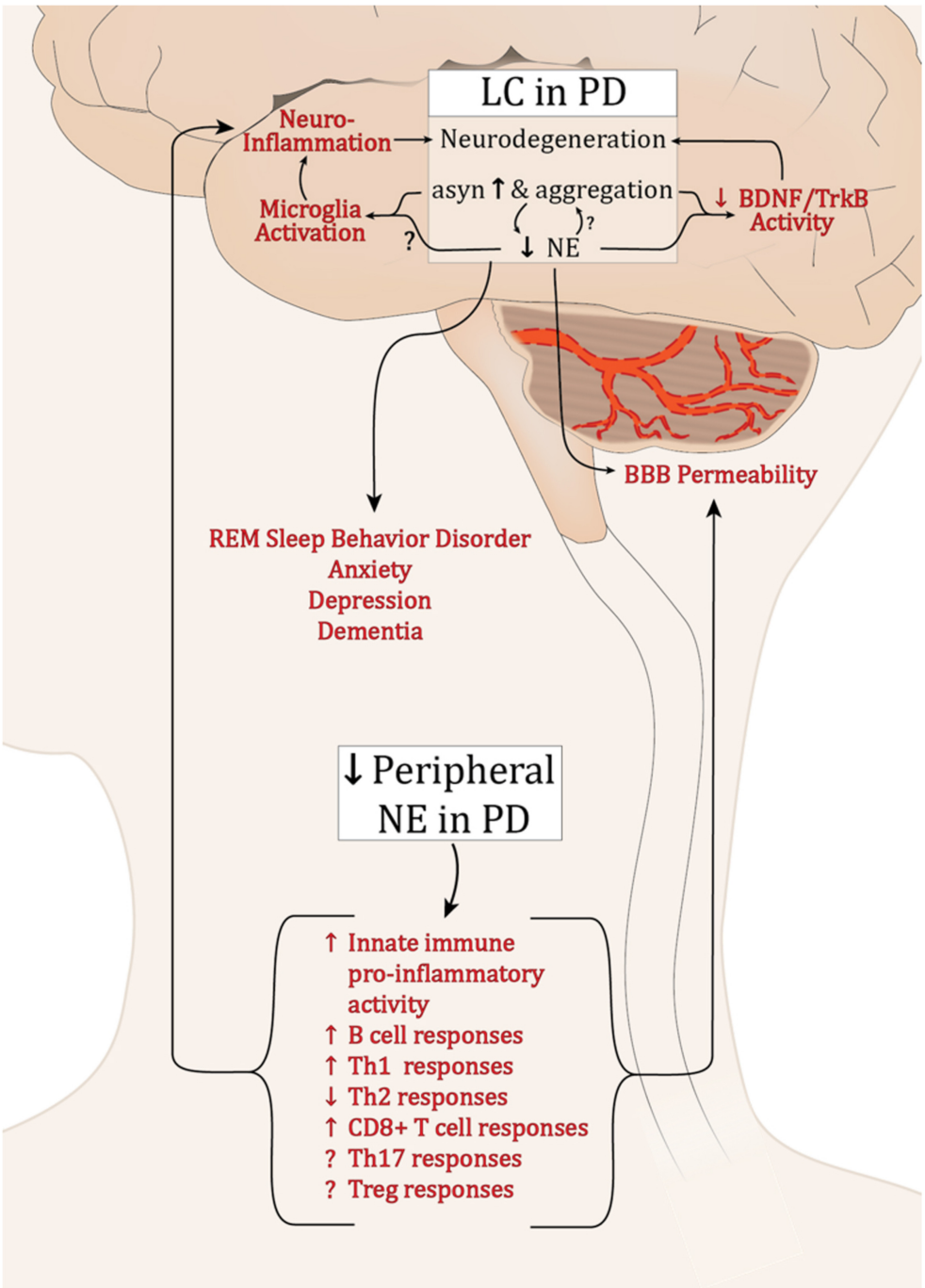

FIGURE 1 | Potential effects of dysregulated NE in PD. Abbreviations: α-syn, α-synuclein; BBB, blood brain barrier; B cell, B lymphocytes; BDNF, brain derived neurotrophic factor; LC, locus coeruleus; PD, Parkinson's disease; NE, norepinephrine; Th1, T helper 1 lymphocytes; Th17, IL-17 producing T helper lymphocytes; Th2, T helper 2 lymphocytes; CD8+, cytotoxic T lymphocytes; Treg, T regulatory lymphocytes; Trkb, tropomyosin-related kinase B receptor.

signal transduction (Liu et al., 2015), while α-syn can interrupt it (Kang et al., 2017). The detrimental effects of declining NE in PD may be compounded by the inhibition of BDNF-mediated neuroprotection by α-syn. This could contribute to the low serum BDNF levels that negatively correlate with motor impairment in later PD (Scalzo et al., 2010).

Neuroinflammation is a cardinal feature of PD and experimentally, both α-syn overexpression and lesion of the LC neurons result in inflammation (Theodore et al., 2008; Watson et al., 2012; Yao et al., 2015). While the experimental outcomes are currently inconsistent, it is clear that NE can modulate microglia activation status (Fujita et al., 1998;

Gyoneva and Traynelis, 2013; Johnson et al., 2013). The decline in brain NE, increase in synucleinopathy, and subsequent modulation of microglia may contribute to the chronic inflammation found in PD brain tissue. Such inflammation is sufficient to induce parkinsonian neurodegeneration (Duffy et al., 2018; Song et al., 2018).

While the brain was once believed to be "immune privileged," the entry of peripheral immune cells through the BBB is now a well-established feature of PD. Numerous immune cell populations are responsive to NE, and its deficiency in the periphery would diminish what seems to be a largely anti-inflammatory regulatory influence. This could promote exaggerated pro-inflammatory immune responses systemically. If the peripheral immune cells were recruited to the brain, reduced local NE levels combined with synuclein pathology would serve to augment and sustain inflammatory activity.

The physiological effects of neuroimmune interactions both centrally and peripherally are myriad, and their subtleties are just beginning to be appreciated and studied in detail. They may have the potential, however, to offer new therapeutic approaches for disorders such as PD for which effective treatments remain elusive. Future research evaluating the incidence of PD among individuals taking β-AR blockers (Mittal et al., 2017), for instance, and the rate of disease progression in PD patients treated with drugs that raise peripheral NE levels, such as droxidopa, could reveal new information about the role of NE in PD pathology.

AUTHOR CONTRIBUTIONS

LB contributed to conception and wrote the first draft of the manuscript. MH wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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