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Review

Targeting the norepinephrinergic system in Parkinson's disease and related disorders: The locus coeruleus story

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ABSTRACT

Parkinson's disease (PD), dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are related, progressive and debilitating neurodegenerative disorders with hallmark features that include a variety of motor and non-motor symptoms (behavioral, autonomic and cognitive dysfunction). For almost half a century, the motor aspects have been attributed to Lewy pathology (LP) predominantly in the substantia nigra (SN), causing a major loss of dopaminergic neurons. However, the relative success of dopaminergic replacement therapies for alleviation of solely the parkinsonian features has prompted researchers to further explore other monoaminergic strategies which may tackle all PD-related aspects. In this regard, recent evidence suggests that LP in the locus coeruleus (LC), the brain's main source of norepinephrine (NE), precedes that of the SN, and, may be one of the very first etiological events in PD. Interestingly, oxidized NE has neuroprotective properties and may even prevent the formation of toxic and higher molecular weight α-synuclein oligomers associated with PD. Moreover, norepinephrinergic neurons directly innervate the SN, and, LC lesioning causes more severe dopaminergic cell loss and supplementary motor manifestations, as shown in preclinical research. In fact, the LC may be considered one of the main orchestrators that controls the other major monoaminergic nuclei, such as the SN and raphe nuclei. Apart from its regulating function, disruption of such a sustainable but vulnerable LC-NE system has been linked to the cognitive pathophysiology of dementia as well. Consequently, LC neuronal loss and the accompanying norepinephrinergic deficiency constitute an important pharmacological target for the (symptomatic) treatment of PD/DLB/PDD. This review, therefore, summarizes and discusses all relevant neurochemical research, including the intriguing link with (prodromal) dementia, several biomarker opportunities, the latest therapeutic strategies to enhance NE signaling, and, finally, some overarching comments and perspectives for future research.

Contents

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1. Introduction

More than 100 neurochemicals that are known to serve as neurotransmitters have been identified in the human brain, but only few of these have a demonstrable relationship with high-level cognitive and memory processes (Augustine, 2004; Robbins and Arnsten, 2009). Of these transmitters, especially the small-molecule neuromodulators, such as biogenic amines, are an important key part. Overall, norepinephrine (NE), dopamine (DA) and serotonin (5-hydroxytryptamine; 5-HT) are produced in relatively small-sized cell bodies in the locus coeruleus (LC), substantia nigra (SN)/ventral tegmental area (VTA) and raphe nuclei (RN), respectively, with diffusely ascending projections via long axons to virtually all parts of the brain and spinal cord. Remarkably, the LC, one of the smallest nuclei, has the most extensively branched axons and has a major role in behavioral arousal, focused attention, accurate sensory perception, task performance, stress response, and context-dependent memory consolidation and retrieval. The LC-NE system may also orchestrate pain modulation, motor control, energy homeostasis, and, control of local blood flow (sympathetic and autonomic nervous system) (Benarroch, 2009). Moreover, a dysregulated LC-NE system is implicated in many pathological and psychiatric conditions, and, like the other monoamine pathways, is part of the 'ascending monoaminergic hypothesis' of dementia (Trillo et al., 2013). Latter hypothesis stems from the selective vulnerability of brainstem nuclei, and particularly monoaminergic cell groups (Parvizi et al., 2001), in neurodegenerative disease, such as Alzheimer's (AD) and Parkinson's disease (PD) (Buddhala et al., 2015; Del Tredici and Braak, 2013), leading to extensive 5-HT, DA and NE alterations across the brain. Furthermore it has been evidenced that these alterations strongly relate to the patient's behavioral profile and may even be dementia subtype-specific (Vermeiren et al., 2014, 2015, 2016).

PD is a progressive and debilitating disorder that currently affects an approximate 2% of the world's population aged 65 or older, with a general prevalence of 113 per 100,000 in the age category of 50–59 up to 2953 per 100,000 in the age group of 80 + years in Europa/North America/Australia (Pringsheim et al., 2014). Hallmark features include motor symptoms (e.g. bradykinesia, tremor, rigidity, postural instability, freezing) accompanied with autonomic dysfunction, neurobehavioral abnormalitites (mood and cognition), sensory difficulties, and, sleep disorders (i.e. non-motor symptoms) (Jankovic, 2008). The defining histopathological aspect of PD and related disorders, including dementia with Lewy bodies (DLB) and PD dementia (PDD), is the accumulation of misfolded α-synuclein (α-syn) into Lewy neurites (LN) and Lewy bodies (LB). Deposited α-syn aggregates can be found in multiple subcortical nuclei, including the SN, LC, nucleus basalis of Meynert (nbM), as well as RN and various cortical regions (Spillantini et al., 1998). For almost six decades, the motor symptoms of PD and related disorders have mainly been attributed to Lewy pathology (LP) in the pars compacta of the SN, causing significant loss of dopaminergic neurons (Vazey and Aston-Jones, 2012). Accordingly, the relative success of DA replacement strategies solely targeting the motor impairment further emphasizes the contemporary lack of validated treatments for the spectrum of non-motor problems specified above. In this respect, the marked reduction of NE throughout PD brain remains largely neglected in much of current research, notwithstanding firm evidence that LP in the LC occurs much earlier and even to greater extent than in the SN (Del Tredici et al., 2002; German et al., 1992; Rommelfanger and Weinshenker, 2007). Furthermore, LC neuronal loss may be one of the primary pathological events of PD etiology, since norepinephrinergic neurons directly innervate the SN, facilitating burst firing, and, additional LC lesioning causes even more severe dopaminergic cell loss and supplementary motor manifestations, as shown in PD animal models (Benarroch, 2009). In fact, NE has profound effects on brain inflammation, oxidative stress (O'Donnell et al., 2012), and possesses neuroprotective properties that may even delay dementia onset as hypothesized by Rommelfanger and Weinshenker (2007).

By and large, dysregulation of the LC-NE system constitutes an important pharmacological target for the (symptomatic) treatment of PD, and, LC cell loss represents a crucial turning point in PD progression. Hereafter, we will discuss all relevant neurochemical research, starting with the functional organization of the LC-NE system.

2. Functional organization of the LC-NE system

NE is synthesized starting from its precursors L-phenylalanine and L-tyrosine. Initially, L-tyrosine is converted into L-dihydroxyphenylalanine (L-DOPA; levodopa) by tyrosine hydroxylase (TH), after which L-DOPA is converted into DA by DOPA decarboxylase, and, finally, this intermediate compound is transformed into NE by the action of DA β-hydroxylase. This final step takes place within synaptic vesicles to which DA is transported by means of the vesicular monoamine transporter. The rate-limiting enzyme of this multi-enzyme pathway is TH. Inactivation of NE occurs by the presynaptic reuptake via a selective NE transporter, followed by metabolism into 3,4-dihydroxyphenylglycol by monoamine oxidase, and, accordingly, into 3-methoxy-4-hydroxyphenylglycol (MHPG) by means of catechol-*o*-methyltransferase (Kuhar et al., 2006). Interestingly, MHPG passes the blood-brain as well as the blood-cerebrospinal fluid (CSF) barrier (Sharma et al., 1994). Consequently, MHPG constitutes a good index of central (Chase et al., 1973) and peripheral (Kessler et al., 1976) NE activity and metabolism. It is estimated that approximately 30–50% of MHPG derived in the brain is excreted via urine (Kuhar et al., 2006). Released NE acts locally at nearby synapses or distally as a paracrine hormone. This catecholamine binds to G-protein coupled receptors,