PERSPECTIVE

A different view on the pathophysiology of Parkinson's disease: a descendent neurochemical hypothesis?

It has been already shown that Parkinson's disease (PD) is characterized by a prominent degeneration in substantia nigra (SN) neurons. Growing evidence suggests that there is a latent period of PD associated with slight non-motor findings such as olfactory dysfunction (Dickson et al., 2018). However, the potential biomarker role of olfactory dysfunction in PD has been a topic of great interest in the last years (Raskin et al., 1990; Dickson et al., 2018). The classical hypothesis of Braak suggests that PD begins as a synucleinopathy in the lower brainstem or in the olfactory bulb (OB) that progresses rostrally to the SN and amygdala to cause parkinsonism at a later stage of the disease (Burke et al., 2008). However, Braak's hypothesis should be cautiously interpreted since this scheme is not based on the distribution of neuronal cell loss, but on the distribution of the accumulation of abnormal α-synuclein aggregates which leaves unanswered how it relates to the progression of neurochemical changes.

The patterns of synucleinopathy described by Braak are often not observed in clinical practice and there is no relationship between Braak's stage and the clinical severity of PD (Burke et al., 2008). For instance, the deposition of synuclein protein described by Braak is often not observed, particularly in special type of dementia syndromes (*i.e.*, Lewy body dementia). In line with this, numerous postmortem studies in humans have shown that there was severe synucleinopathy in asymptomatic aged individuals while many individuals with initial Braak's stage had clinically advanced PD (Burke et al., 2008; Rietdijk et al., 2017). The Braak's initial studies have also been criticized because of the potential for selection bias resulting from exclusion of cases with alpha synuclein pathology in higher brain regions and the inclusion of non-representative samples in the preclinical PD group. Another reason to question the Braak's hypothesis is that many of these brains with synuclein pathology in the upper midbrain do not exert a lower brainstem synucleinopathy. However there are multiple sites for the generation of Lewy Body rather than a spread from lower to higher brain regions. Taken together these findings contradict with the Braak scheme proposing that synuclein pathology in the lower brainstem is the initial pathophysiological step for the later appearance of PD (Burke et al., 2008; Rietdijk et al., 2017). Moreover, there is limited clinical and pathophysiological information on the pre-clinical PD group in Braak's studies and the causal relationship between the amygdala synuclein pathology and the neurofibrillary Alzheimer changes has not been confirmed yet. Accordingly, a very limited number of PD patients exhibited amygdala synuclein pathology (Rietdijk et al., 2017). Although the Braak scheme assumes that Lewy pathology reliably detects PD-related neuronal dysfunction, from a pathophysiological point of view, studies have suggested that synuclein pathology may not be associated with PD-related dysfunction. Moreover, abnormal synuclein accumulation does not guarantee the cellular dysfunction, and it is unknown if there is a direct link between the Braak's stage and neuronal loss in the lower brain stem. These findings suggest that the presence of synuclein immunostaining cannot be interpreted as strong evidence for the neuronal cell dysfunction. Conversely, the absence of abnormal immunostaining for synuclein in neurons cannot prove that there is no PD-related neuronal dysfunction. These findings were also suggested with clinical studies showing that Lewy pathology is not a reliable indicator of PD cellular dysfunction in patients with specific PD-causing mutations (such as leucine-rich repeat kinase 2) (Burke et al., 2008; Rietdijk et al., 2017). Therefore, the Braak hypothesis describing that the location of synuclein accumulation is characterized with the initial stages of Parkinson's Disease does not seem not reasonable.

Although Braak and his colleagues did not reveal a relationship between Braak stage and the clinical scores, their hypothesis indicated that the toxic oligomeric variety of α-synuclein is able to spread cellularly from the enteric and olfactory system to the higher brain regions where it can provoke a vicious circle of neuroinflammation (Burke et al., 2008). Despite these pieces of evidence suggesting that there is a caudo-rostral pattern of progression in PD, it is notable that there is also an early dysfunction in executive functions (*i.e.*, attention, planning) which is associated with olfactory dysfunction before appareent Parkinsonian symptoms (Raskin et al., 1990; Dickson et al., 2018). Menwhile, volumetric brain studies suggested that brain regions related to olfactory dysfunction are closely associated with cognitive dysfunction (Raskin et al., 1990; Dickson et al., 2018). Also in drug-naive PD patients, olfactory dysfunction has been linked with impaired visuospatial and executive function (Raskin et al., 1990; Dickson et al., 2018). On the other hand, the olfaction process has been shown to require serious memory and other higher-order cortical interactions. These findings together suggested that there could be a close interaction between the cognitive dysfunction and impaired olfaction in the latent phase of the disease. The assumption that both the central and peripheric degeneration might be interconnected in a quasi-simultaneous fashion rather than an algorithm having a linear sequence of degenerative events. The hypothetic problem here could be to detect a neurochemical link between the centrally degenerated dopaminergic neurons and the pathophysiological changes in the OB. For instance, immunostaining studies have already shown that muscarinic acetylcholine receptors were expressed in OB dopaminergic neurons suggesting that local cholinergic network might exert a regulatory role through connecting into the dopaminergic circuit (Psia et al., 1999; Davila et al., 2003; Pignatelli et al., 2008; Mundinano et al., 2013). These findings together suggested that there is an interactive link between the dopaminergic and cholinergic systems in OB. Interestingly, recent studies indicated that olfactory dysfunction is related to an increased dopaminergic transmission (D2 receptor activation) in the OB that is responsible for impaired olfaction caused by the depression of synaptic transmission between the olfactory receptor neurons and mitral cells. Hence, compensatory decreased cholinergic transmission might also play a critical role in impaired olfaction process suggesting that the increased dopamine in the OB might be increased secondary to the impaired dopaminergic neurotransmission in the brain (Huisman et al., 2004). In contrast to Braak's hypothesis suggesting that α-synuclein deposition first occurs in olfactory structures before the SN and amygdala, it could be possible that the decreased dopaminergic transmission might first occur in the SN due to the simultaneous accumulation of α-synuclein (**Figure 1**). This might suggest that there is a multicentric disease process from the onset that could lead to an increased dopaminergic transmission in the glomeruli of the OB. This hypothesis neither excludes the co-localization of PD pathology in the OB and SN, nor the mechanistic link among the olfactory nerve layer, glomeruli of the OB, dendrites of mitral and tufted cells and the cortical nucleus of the amygdala. As mentioned previously, recent studies suggested that false case selection might have biased the results in favour of "early" medullar pathology in Braak's scheme while prospective autopsy studies confirmed that the proposed staging scheme does not fit well for normal people with widespread Lewy pathology (Burke et al., 2008; Rietdijk et al., 2017). In contrast to the classical ascen-

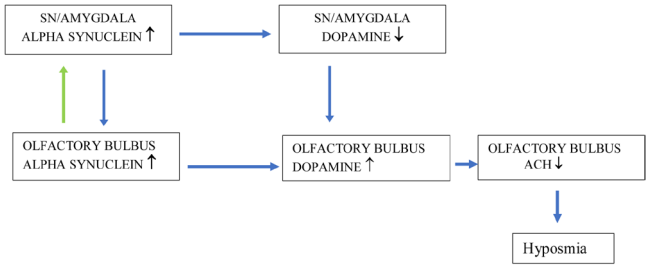

Figure 1 Neurochemical interaction between the ascendant and descendent pathways in Parkinson's disease.
The new hypothesis (blue lines) proposes a neurochemical interaction between the ascendant and descendent pathways in Parkinson's disease, while Braak's scheme (green line) suggested an ascendant neuropathophysiology in Parkinson's disease.

dent scheme of Braak, here we offered a different perspective which might suggest that α-synuclein accumulation in neuronal perikarya may be the tip of the iceberg implying that there could be an interactive process between the descendent neurochemical pathway and the ascendent α-synuclein pathology during the neurodegenerative process. Notably, it is well-known from the relevant scientific literature that α-synuclein, besides other proteins, maintains its central role in the molecular pathology of the PD. To the best of our knowledge, there is no clinical study in PD patients which evaluated the bi-directional link between the enteric nervous system and OB. Here, it should be mentioned that a recent axonal tracing study indicated that dopamine depletion in the substantia nigra led to an impaired olfactory function which was reversed with dopamine receptor agonist rotigotine. Beyond suggesting that dopamine ablation in the SN might evoke the degeneration in the olfactory system through centrfugal axonal projections into the olfactory bulb, these study indicated that there is a direct axonal dopaminergic projection from the SN to the OB (Höglinger et al., 2015) which modulates the perception of odorants through dopaminergic transmission. In this respect, there are ongoing controlled clinical trials evaluating the role of dopaminergic therapy in early PD patients with hyposmia. Furthermore, it has been suggested that point mutations and/or high copy numbers of the α-synuclein lead to the degeneration of dopaminergic neurons in the SN which is a critical area characterized with high dopamine turnover (Ozansoy et al., 2013). However, it is easy to recognize that dopamine auto-oxidation plays an important role in the degeneration of dopaminergic neurons through the generation of reactive-quinone species, hydrogen peroxide and other reactive oxygen species. These findings are interesting in the light of the latest studies showing that oxidized dopamine metabolites augment the neurodegeneration *via* maintaining the kinetic stability of the α-synuclein oligomers in the SN (Ozansoy et al., 2013).

Although existing studies have suggested that the cortical nucleus of the amygdala, SN and olfactory bulb (*i.e.*, mitral and tufted cells) present with Lewy body deposition in a time-dependent manner, it should be noted that this is only a hypothesis based on the projections from the olfactory bulb to the SN and cortical amygdala, that neglect the possibility of a bidirectional interaction among the amygdala, SN and bulbus olfactorius. Interestingly, a very recent study suggested that there are also corticofugal projections from the amygdala to the OB which modulate the mitral cell responses in the OB (Oboti et al., 2018)). As mentioned above, a new dopaminergic nigrio-olfactory pathway has been defined (Höglinger et al., 2015). Considering all of these findings it is justifiable that there could be reverse neurochemical interaction between brain and OB. In this respect, the late detection of motor symptoms of PD in compared to when identifying the olfactory dysfunction very shortly after the glomerular dopaminergic impairment would be responsible for a false interpretation of the neurodegenerative changes in PD.

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