

Inflammation and Cell Death in Parkinson's Disease

Parkinson's disease (PD) is characterised by a slow and progressive degeneration of dopaminergic (DA) neurons in the substantia nigra (SN). This neuronal degeneration leads to the loss of DA terminals in the striatum but also in other basal ganglia and cortical brain regions.^{1,2} Non-DA neurons located in various regions of the central nervous system also degenerate in PD.³ The origin of this neuronal degeneration is unknown and may involve several molecular and cellular events, including oxidative stress, accumulation of altered proteins, excitotoxicity, proapoptotic mechanisms and mitochondrial dysfunction.⁴

In addition, it has been suggested that a glial reaction and inflammatory processes may also participate in the cascade of events leading to neuronal degeneration. In 1988, McGeer and coworkers observed a strong astroglial and microglial reaction in the substantia nigra (SN) of PD patients.⁵ Also, they reported a small number of CD8-positive T lymphocytes in the vicinity of degenerating neurons in the SN of a PD patients. In line with this, an increased density of glial cells expressing pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α) and interleukin-1 β was observed in the SN of PD patients, as well as an increased density of interferon- γ -positive cells compatible with the presence of lymphocytes.⁶ However, until recently, it was unclear whether these inflammatory changes merely reflected a consequence of DA neuronal cell death or if this process was a self-sustaining, feed-forward loop contributing to ongoing cell demise in the SN (Figure).

Strong support for the latter hypothesis came from the study of young drug addicts who developed a parkinsonian syndrome after 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP) intoxication. In a paper on the postmortem neuropathological examination of three subjects with MPTP-induced parkinsonism, gliosis and clustering of microglial cells around DA neurons were detected despite survival times ranging from 3 to 16 years.⁷ These findings not only indicated ongoing nerve

cell loss after a time-limited insult, but also suggested that activated microglial cells may perpetuate neuronal degeneration. Reactive microglial cells have also been detected in the brain of MPTP-intoxicated monkeys.⁸⁻¹⁰ Interestingly, as in humans, a microglial reaction was observed long after the last MPTP injection (up to one year), suggesting that MPTP had triggered an ongoing inflammatory process in which microglial cells may play an instrumental role.

In living PD patients, two recent studies have analysed the degeneration of the nigrostriatal DA system by PET imaging of pre-synaptic dopamine transporter using a specific ligand and 11C-PK11195 (1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3 isoquinoline carboxamide) imaging for activated microglial cell detection.^{11,12} The findings were somewhat contradictory, either showing increased microglia in the midbrain¹¹ or in non-DA CNS regions¹² in PD patients compared to controls. Important methodological issues may account for these anatomical discrepancies; in any case, it is important to note that microglial activation in PD brains seemed to be present in early disease stages in both studies, thus potentially driving the disease via cytokine release. Also, the presence of microglial activation outside the midbrain supports the notion of PD as a multisystem disorder which may be linked to chronic inflammation in various CNS regions, as suggested by recent postmortem data.¹³

Epidemiological studies also suggest a role of inflammatory processes in susceptibility to PD, given that the use of non-steroidal anti-inflammatory drugs, in particular ibuprofen, seems to lower the risk of PD.^{14,15} Whereas these data only provide very indirect evidence for neuroinflammation as a pathogenic factor in PD, they nevertheless add weight to the pressing debate whether glial activation and release of pro-inflammatory cytokines may represent a therapeutic target in PD.

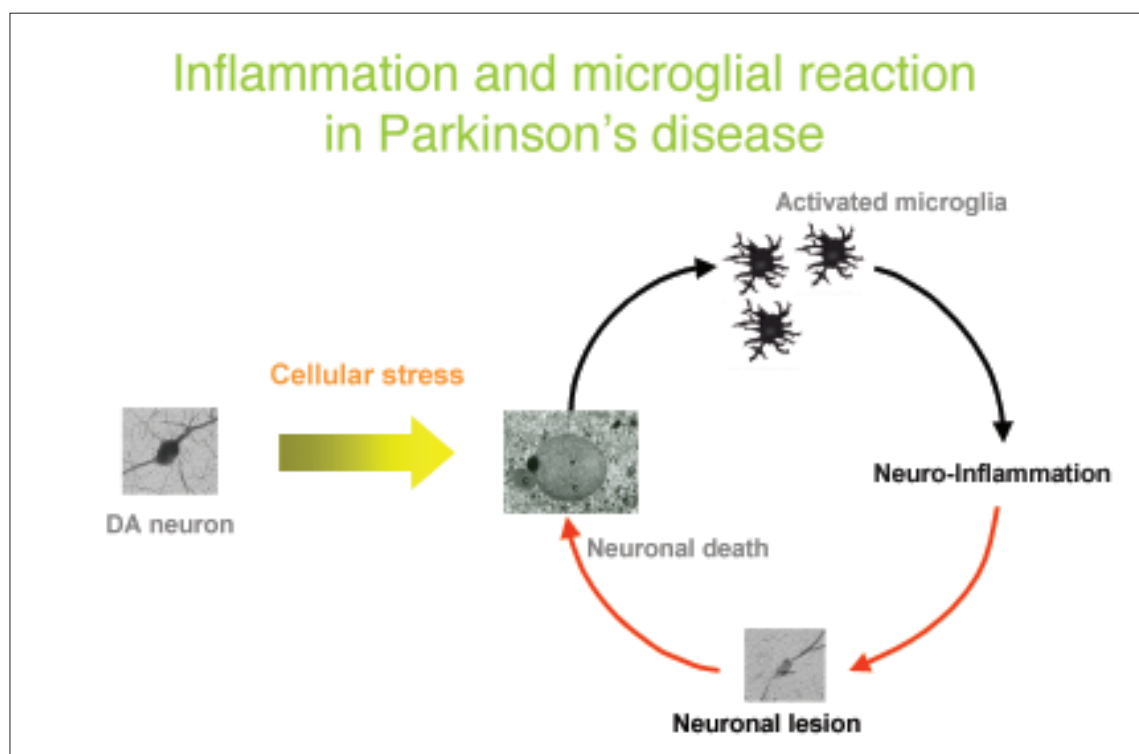
Transgenic mice models have offered some clues in this regard. It has been shown that interferon- γ , inter-



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leukin-1 β and TNF- α can induce the expression of the inducible form of nitric oxide synthase (iNOS) via the expression and activation of the low affinity receptor CD23.⁶ Accordingly, iNOS knockout animals are more resistant to MPTP toxicity than their wild-type counterparts.^{16,17} Moreover, mice deleted for cyclooxygenase-2, the rate-limiting enzyme in prostaglandin E2 synthesis, are relatively preserved against MPTP.^{18,19}

Translated into pharmacological interventions in animal models of PD, peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists, a member of the nuclear receptor super-family that has been shown to inhibit inflammatory processes, protect against MPTP toxicity in mice²⁰⁻²² and monkeys.²³ Other anti-inflammatory drugs such as minocycline have also been shown to protect DA neurons against MPTP intoxication by different groups, but other groups of investiga-

tors have reported a detrimental effect of this compound.²⁴ However, a preliminary clinical study investigating minocycline in PD patients has suggested a small but significant neuro-protective effect of this compound over placebo during a one year course.²⁵ Inhibitors of COX-2 have also produced controversial results in PD animal models.²⁶ Yet, such variable results are very likely explained by the pharmacological profile and the specificity of the drugs used (salicylate, aspirin, meloxicam, indomethacin, paracetamol, diclofenac, ibuprofen, etc.).

To date, it remains unclear how glial cells are and remain activated in PD. One possibility involves cell necrosis and subsequent leakage of intracellular contents into the extracellular space, for instance of alpha-synuclein, a major constituent of Lewy bodies.²⁷ A humoral immune response triggering microglial activation has also been recently proposed.²⁸ Finally,

suffering neurons may send distress signals related to increased oxidative stress to neighbouring microglial cells, thus generating a vicious circle resulting in apoptotic DA cell death.²⁹ These signals may be conveyed directly between neurons and microglia, or be relayed by astrocytes.³⁰

In conclusion, the available data obtained both in animals and humans strongly suggest that (i) inflammation and glial reaction is a chronic process occurring in the SN (and possibly other brain regions) of PD patients, (ii) that this process is not only a consequence of neuronal death but actively contributes to sustained DA cell demise and (iii) that targeting these deleterious processes may represent a worthwhile therapeutic target in PD. At the present stage, it is however likely that inhibiting neuroinflammatory processes in PD will only achieve partial protection and that more upstream pathways must also be targeted.

Inflammatory changes in the substantia nigra of Parkinson's disease patients do not only reflect a consequence of dopaminergic neuronal death but are a self-sustaining process, ie. a feed-forward loop contributing to ongoing cell demise

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