SCIENTIFIC COMMENTARY

Calcium dysregulation in Parkinson’s disease

The major motor features by which Parkinson’s disease is diagnosed are mainly the consequence of degeneration of dopaminergic neurons in the substantia nigra pars compacta. This observation was the basis upon which dopamine replacement therapy became the cornerstone of symptomatic treatment. But as our understanding of the clinical phenotype, pathology and pathogenesis of Parkinson’s disease has improved, it has become clear that non-dopaminergic neuronal loss and synuclein-related pathology extend far outside the substantia nigra pars compacta, and even involve the autonomic plexuses of the gut and endocrine system. Non-dopaminergic neuronal loss in Parkinson’s disease is associated with a considerable clinical burden that increases with disease progression and becomes the predominant determinant of quality of life, and the requirements and costs for long-term care in these patients (Chaudhuri et al., 2006). The features that do not depend on loss of dopaminergic neurons are often referred to as non-motor, although dopamine replacement can improve more than the motor symptoms of Parkinson’s disease (Chaudhuri and Schapira, 2009). Therefore a major unmet need in Parkinson’s disease is the development of treatments that can delay or prevent progression of the neurodegenerative process that affects both dopaminergic and non-dopaminergic neurons.

The pathogenesis of Parkinson’s disease has been informed by a number of related and interdependent fields of research: pathology, biochemistry, physiology and genetics. Each provides separate insights into the molecular pathogenesis of the disease, but when the individual evidence is convergent on common pathways to neurodegeneration, the relevance of these data becomes particularly compelling. Mitochondrial dysfunction, oxidative stress, protein aggregation and inflammation each play a role in the pathogenesis of Parkinson’s disease. Additional data support the interaction of these systems not only between each other but also with important cellular functions such as lysosomal-mediated degradation. Evidence also supports the concept that synuclein pathology spreads by templating. The role of calcium regulation in Parkinson’s disease has been of interest for some time and is another example of a topic that cuts across several of the established pathways that lead to neurodegeneration. The paper by Hurley and colleagues in this issue of Brain (page 2077) makes a further significant contribution to our understanding by emphasizing that calcium dysregulation also participates in this process.

Calcium is crucial to normal cell physiology and the function of excitable cells. The calcium ion gradient across cells is maintained by the active extrusion of Ca\(^{2+}\) to the extracellular space by the plasma membrane Ca\(^{2+}\)-ATPase pump and the Na\(^{+}\)/Ca\(^{2+}\) exchanger, or sequestration into intracellular organelle stores by the sarco-endoplasmic reticulum ATPase pump. The pumping of calcium requires substantially more energy than exchange of sodium or potassium (Surmeier and Schumacker, 2013). Voltage-gated calcium (Ca\(_V\)) channels regulate neuronal electrical activity and modulate neurotransmitter release inter alia by either influx of Ca\(^{2+}\) into cells following membrane depolarization or release from intracellular stores. Voltage-gated calcium channels have three main subtypes: Ca\(_V\)1 or L-type; Ca\(_V\)2; and Ca\(_V\)3 (Hurley and Dexter, 2012). The Ca\(_V\)1 and Ca\(_V\)2 channel isoforms activate at a high depolarization voltage and produce long-lasting calcium currents, while Ca\(_V\)3 channels open at a lower depolarization voltage and produce transient Ca\(^{2+}\) currents. Although messenger RNA expression and western blot data showing the distribution of calcium channels in rodent brain have become available, the results have sometimes been conflicting. Most importantly, until the publication of this paper by Hurley and colleagues, very little was known about the distribution of the calcium channels in human brain, particularly in Parkinson’s disease.

Dopaminergic neurons in the substantia nigra pars compacta have distinct neurophysiological properties (Surmeier, 2007). Substantia nigra pars compacta dopamine neurons are autonomously active and generate continuous low frequency activity in the absence of synaptic input that is dependent on L-type Ca\(^{2+}\) channels. These neurons have a pore-forming Ca\(_V\)1.3 subunit, low affinity for dihydropyridines and open at hyperpolarized membrane potentials than Ca\(_V\)1.2 channels. There is evidence that, over time, nigral dopaminergic neurons develop an increasing reliance on L-type calcium Ca\(_V\)1.3 channels to maintain their autonomous activity and this comes at a significant bio-energetic cost. The need to maintain calcium homeostasis includes coordination of endoplasmic reticulum pumps and the uptake of calcium into mitochondria. The Ca\(_V\)1.3 channels generate mitochondrial-mediated oxidative stress during autonomous activity which in turn induces mitochondrial uncoupling as a protective mechanism (Guzman et al., 2010). The lysosome has also recently been identified as an important participant in intracellular calcium shuttling (Kilpatrick et al., 2013).

In control brain, neither the expression of Ca\(_V\)1 subtypes nor the distribution of calcium binding proteins associates with regions prone to neurodegeneration in Parkinson’s disease. In adult...
substantia nigra pars compacta, there is a clear dominance of CaV1.2 expression and this predominantly occurs in tyrosine hydroxylase-positive cells. In the substantia nigra pars compacta of patients with Parkinson’s disease, fewer neurons express CaV1 channels, but the total expression of CaV1.2 remains stable and that of CaV1.3 increases indicating a greater density of channels in each surviving cell. Overall, there are regional differences in the expression of CaV1 subtypes in normal brain and these alter significantly in Parkinson’s disease. In Parkinson’s disease, increased CaV1 subtype expression precedes disease pathology in specific areas, e.g. cortex, and there is a change in the ratio of CaV1.2 to CaV1.3 in favour of a greater use of CaV1.3 channels. As noted above, this imposes a greater bio-energetic burden on these neurons and renders them susceptible to excitotoxicity and/or oxidative stress.

However, the pattern of neurons using CaV1 subtypes in control brain does not reflect neuronal vulnerability in Parkinson’s disease. Nor does the relative neuronal use of CaV1.3 compared to CaV1.2 correlate with neuronal vulnerability; the substantia nigra pars compacta has one of the lowest CaV1.3 to CaV1.2 ratios, yet this area undergoes marked neurodegeneration in Parkinson’s disease. Nevertheless, the changed expression of voltage-gated calcium channel subtypes in areas of the Parkinson’s disease brain, such as the substantia nigra pars compacta, is of particular interest. Could this change in expression reflect a compensatory mechanism or alternatively a pre-existing phenotype rendering the patient susceptible to the development of Parkinson’s disease? If so, measurement of CaV1.2 and CaV1.3 expression in lymphocytes might serve as a biomarker for susceptibility to the disease. A drug-induced effect seems less likely given that changes in the expression of voltage-gated calcium channels occur into the late stages of the disease often despite years of therapy.

There is increasing evidence that dysregulation of intracellular calcium homeostasis plays an important role in the pathogenesis of Parkinson’s disease. The calcium pathway intersects with mitochondrial function and oxidative stress both of which are involved in the pathogenesis of Parkinson’s disease. More recently it has become apparent that calcium regulation also interacts with endoplasmic reticulum function and the unfolded protein response (Mattson, 2012; Schapira, 2012; Selvaraj et al., 2012; Davey and Bolanos, 2013). The lysosome is now identified as an important component in calcium homeostasis and lysosomal dysfunction is believed to play a role in Parkinson’s disease (Tofaris, 2012). Dopamine metabolism will exacerbate the calcium-mediated increase in oxidative stress and render substantia nigra pars compacta neurons increasingly vulnerable to damage.

What is particularly appealing about the calcium hypothesis in Parkinson’s disease is that it may represent a suitable target for therapeutic intervention designed to retard progress of the disease. Epidemiological data support the concept that dihydropyridine calcium channel blockers may reduce the risk of developing Parkinson’s disease (Pasternak et al., 2012). To date, there are no potent or selective inhibitors of CaV1.3 channels, but modified pyrimidine-2,4,6-triones have recently been identified as potential candidates in high-throughput screens (Kang et al., 2012). What is appealing about the strategy of targeting calcium channels is that the benefit may well extend beyond the dopaminergic neurons, and therefore address the non-dopaminergic deficits that cause so many problems in the later stages of the disease (Goldberg et al., 2012). This hypothesis is supported by the data now reported in this issue of Brain (Hurley et al., 2013). The process leading to practical application of such drugs and their translation through clinical trial to medical practice is, of course, complex and challenging.

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References