

CALCIUM HANDLING ASPECTS OF PARKINSON'S DISEASE PATHOGENESIS

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Computational approaches are significant in the analysis of events that are multi-factorial. Parkinson's Disease (PD) is the cumulative result of system malfunctioning that leads to severe degeneration in the Substantia nigra (SN), a locus in the mid-brain. Traditional approaches tend to focus on isolated sub-components of the pathogenic pathways. However, such an approach may be inadequate to describe the pathogenesis.

SN neurons function on an expensive energy budget, due to a high level of arborization and pacemaking activity. Pacemaking involves the L-type calcium channel, and could impose long-term accumulation of calcium within SN organelles. We analyse the role of calcium handling within the SN neuron by a mathematical model based on the pacemaking activity.

Simulations suggest, calcium can accumulate within the mitochondria over time and this may be reduced by blocking the L-type calcium channel. Excessive mitochondrial calcium accumulation would trigger a cascade of events that leads to a positive feedback loop which would prove fatal to SN neurons. Lewy Bodies (LB) that are generally considered a consequence of these events could intensify the proceedings by pilfering calbindin, a protein responsible for calcium buffering, during its aggregation. Increased mortality among SN neurons with low expression of calbindin [1] and a synergistic association of calbindin and alpha-synuclein genes [2] support this hypothesis. This model may be incorporated into a larger framework of SN energy metabolism[3].

[1] P. Damier et al. *Brain*, 122(8):1437-1448, 1999.

[2] Ikuko Mizuta, *Human Genetics*, 124:89-94(6), August 2008.

[3] Cloutier et al, *J Comput Neurosci*, 2009, DOI 10.1007/s10827-009-0152-8