Apoptosis vs. necrosis: Role of Ca^{2+} and energy failure

Neuronal cell death mediated by excessive stimulation of NMDA receptors has been implicated in many neurologic disorders. In spite of a substantial experimental database and ready application of thermodynamic formalism to cell death (Maddox, Nature 355:201, 1992), quantitative theories of excitotoxicity are yet to be presented. Cell death represents a process of transition from non-equilibrium to equilibrium state with respect to the surrounding. In response to an excitotoxic NMDA stimulus (e.g., 200 μM), the relaxation time of a spherical cell (e.g., 20 μm in diameter) can be calculated to be on the order of 10 min. in accord with experimental data. Resilience, i.e., the time it takes to reestablish the resting state following removal of NMDA, is ~1 min. in the absence of constraints on energy levels. However, this prediction is inconsistent with the experimental data because it does not take into account intracellular Ca^{2+} buffering. If we assume that mitochondria represent the predominant Ca^{2+} buffer in neurons and that this places certain constraints on ATP utilization (Nicholls and Akerman, Biochimica et Biophysica Acta 683:57, 1982), we can calculate the minimum concentration of NMDA necessary to induce necrosis (passive cell death causing osmotic lysis because of energy failure) rather than apoptosis (an active form of cell death requiring energy production): necrosis would begin to intervene at [NMDA] > 500 μM (for tens of minutes). Formally stated, $dN/dt = r(R-N)(T-N)(E-N)$, where $N = [Ca2+]_i$ intracellular calcium concentration following a toxic NMDA stimulus, and R, T, and E are resting, threshold for necrosis, and extracellular $[Ca^{2+}]_e$, respectively, and r is a proportionality constant. This formalism is consistent with previous experimental data (e.g., Bonfoco et al., PNAS 92:7162, 1995; Ankarcrona et al., Neuron 15:961, 1995) and may serve to guide future efforts at novel therapeutics.