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A biophysical model for cytotoxic edema

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We present a dynamical biophysical model to explain cytotoxic edema in conditions of low energy supply, as observed in cerebral ischemia. Our model contains Hodgkin-Huxley type ion currents, a recently discovered voltage-gated chloride flux through the ion exchanger SLC26A11, KCl cotransporters and ATP-dependent pumps. The model predicts changes in ion gradients and cell swelling under various conditions. We theoretically substantiate experimental observations of chloride influx generating cytotoxic edema, while sodium entry alone does not. We further show that a tipping point exists, where cell volume rapidly increases as a function of reduced activity of the Na⁺/K⁺ pump, and a Gibbs-Donnan-like equilibrium state is reached, that precludes return to physiological conditions even when pump strength returns to baseline. However, when voltage-gated sodium channels are temporarily blocked, cell swelling reverses with normalisation of the membrane potential, yielding a potential therapeutic strategy to reduce cytotoxic edema after cerebral ischemia.