Brain Ischemia and Stroke

Synonyms

Brain damage; Cerebrovascular disease; Oxygen deprivation

Definition

Cerebral ischemia, which occurs during stroke, is insufficient blood flow to the brain and leads to loss of oxygen and glucose supply. This severely compromises cellular respiration, causing neuronal damage. Cells move towards cell death, which can be simplified as being apoptotic (controlled and "programmed") or necrotic (uncontrolled). Necroptopic cell death, which is a stereotypical necrotic death pathway, has also recently been characterized during stroke (Christofferson and Yuan 2010). In addition to being both a single-cell and multicell phenomenon, ischemic insult also involves transcriptional changes to regulatory networks of genes. Taken together, modeling the molecular and genetic aspects of ischemia is fundamental to understanding how to modulate neuroprotective elements in the case of stroke, which is the primary therapeutic approach in saving at-risk tissue. Computer-based cellular modeling can assist in understanding the molecular changes involved, the decision and control points for various cell fates, and the potential for recovery with partial damage as well as help define the scope of the genetic and regulatory network changes that occur.

Detailed Description

The mechanisms by which cells accumulate damage, signal damage to neighboring cells, and eventually die all remain unclear. The geometric complexity of neurons makes it difficult to elucidate single-cell diffusive mechanisms in the ischemic signaling cascade. Further complexity occurs due to difficulties in disconnecting effects at the cellular level from effects at the tissue level, as well as effects due the synaptic interconnectivity of the neurons, which can lead to network cascades in dying tissue. Compounding these difficulties is the fact that many signaling cascades are heavily interdependent on non-apoptotic, homeostatic mechanisms and have multiple nonlinear dependencies. The intricacies of signaling pathways that are potentially involved in cell death, both intracellular and intercellular, make it useful to study neuronal ischemia using multiscale modeling, which can describe the effects across subcellular and cellular levels.
Blood enters the brain via a complex arterial tree. When arteries or large arterioles are damaged through occlusion or rupture, blood supply is locally reduced, causing ischemic damage. The degree of damage is highly variable, depending on the extent and duration of the insult. Generally, we conceptualize two major separable regions: an ischemic core where blood flow is essentially zero and an ischemic penumbra where there is some residual blood flow. The ischemic penumbra is a region that is considered a target for rescue by appropriate treatment. At normal body temperature, full ischemia for 3-5 min is generally lethal to neurons. By contrast, occurrence of long-lasting damage in the penumbra may require several hours of ischemia. The cellular and molecular changes in these regions have markedly different presentations (Lipton 1999). Damage in the penumbra will be highly variable across multiple timescales. The duration of oxygen deprivation that triggers the ischemic cascade and the extent of damage will likely depend upon genetic and environmental factors in the individual and in the precise types of cells involved. In particular, it is hypothesized that larger cells, such as Purkinje cells and cortical pyramidal cells, may be particularly vulnerable.

Nutrient Delivery

Ultimately, all ischemia results from loss of substrates for the cell to generate adenosine triphosphate (ATP), its primary energy currency. Computer models of nutrient delivery at the level of blood and of extracellular tissue are therefore useful in providing the setting for effects on the individual cell. This nutrient modeling allows us to better define molecular differences in types of ischemia that will be produced. Simplified ischemia models at this level represent brain tissue as a set of voxels which exchange O_2, with influx and outflux of blood between the regions and oxygen consumption integrated at each simulation time-step (Hudetz et al. 1982). In a paper published in 2002, Duval et al. (2002) modeled 4 parameters: cerebral blood flow, rate of oxygen extraction from blood, metabolic rate of oxygen use by tissue, and the

apparent diffusion coefficient of water. A "survival delay" variable was also used to quantify the decay of tissue in the penumbra from functional to salvageable to necrotic. This modeling suggested that the penumbra could take on two major forms: ischemic and edematous. Ischemic penumbra tissue was metabolically altered and generally not salvageable, whereas the edematous penumbra tissue appeared to retain greater recovery potential. This model represented a first step towards clarifying how extracellular nutrient parameters might affect the generation of penumbral regions. Other models have included blood flow parameters in molecular models as a way of developing more robust models of cellular networks (Dronne et al. 2006).

Initiation of the Ischemic Cascade

After vascular damage, neuronal uptake of O_2 and glucose is reduced, leading to a sequence of metabolic and molecular changes. An early result of nutrient loss is a reduction in ATP. The biochemistry of energy production in brain tissue utilizes the same reactions that are used in other cells of the body. However, neurons are run at high metabolic states in order to maintain the electrochemical gradient that enables neurons to fire action potentials. They have additional ATP delivery challenges associated with the presence of long, thin processes with large surface to volume ratios. With disruption in ATP production, plasma membrane ionic gradients will begin to decay, preventing neuronal electrical function and allowing excitotoxic damage via calcium entry due to depolarized membrane potential.

Loss of ion homeostasis may precipitate the accumulation of reactive oxygen species and intracellular calcium dysregulation, both of which are primary "perpetrators" of cell death (Lipton 1999). Models of this process are similar to the early work done by Magnus and Keizer in pancreatic β-cells, another electrically excitable cell type (Keizer and Magnus 1989). This model demonstrated that increased glucose concentration could enhance burst spiking, generating elevated intracellular Ca^{++} and excitotoxicity. Later work by Magnus and Keizer focused on developing more robust models of mitochondrial Ca^{++} signaling (Magnus and Keizer 1998).

Similarly, in neuronal cells, loss of ATP due to poor blood flow triggers a cascade of reactions leading to apoptosis or necrosis. Four major mechanisms are recognized (Lipton 1999):

1. Influx of Ca^{++} ions through NMDA receptors and voltage-gated Ca^{++} channels.
2. Increased intracellular Na^{+} causes glutamate efflux, which also eventually leads to increased intracellular Ca^{++}.
3. Decreased ATP/ADP ratio producing a fall in intracellular pH.
4. Production of free radicals, particularly near mitochondrial membranes.

Ionic dysfunction is a hallmark of both necrotic and apoptotic cellular changes. This dysfunction is primarily manifest via abnormal Ca^{++} fluctuations within the cell. The generation of free radicals and inability to manage pH may also be tied to Ca^{++} dysregulation via Ca^{++} -binding control proteins such as calmodulin, calbindin, and calpain (Saftenku and Friel 2012). The products from these early reactions are heavily involved in the cell's final fate.

Due to the importance of Ca^{++} and Ca^{++} buffering in determining cell fate, much attention in ischemia research has focused on modeling this ion. Normally, there are very low resting levels of Ca^{++} in the neuron. This requires stochastic modeling, because small concentrations of ions cannot be identified as bulk units, which can be handled deterministically. Such a deterministic approach (e.g., rate laws) relies on the Law of Large Numbers; many aspects of Ca^{++} signaling do not obey this law. It has been suggested, in fact, that the cell uses chemistry as a computational tool and is able to harness stochastic Ca^{++} fluctuations to generate robust intracellular signaling networks. Ischemic cascades therefore involve stochastic events as well as deterministic events, and both involve considerable species diffusion through neurons and extracellular tissue space. Modeling allows us to explore Ca^{++} fluctuations and species diffusion at a very small-scale level.

Use of Boolean Networks in Ischemia Modeling

The changes in nutrients, in ATP, in Ca^{++}, etc. detailed above are only the beginning of a large array of interconnecting molecular changes. One way to make sense of such a complex and large network has been to use a Boolean Network (BN) formalism to model system dynamics. By conceptualizing the molecules in the signaling networks as having a

discrete set of states (ON/OFF or activated/repressed), interaction rules can be defined for a particular set of reactions. Mai et al. used BNs to model aspects of apoptosis (Mai and Liu 2009). They found downstream redundancies, feedback loops, points of control, and steps leading towards irreversible commitment to this endpoint. Although this approach simplifies reaction dynamics to a 0/1 decision, it can provide valuable information on system properties and points of modulation within the apoptotic pathway.

Therefore, the type of information that can be gleaned from a model depends very much on how the model is designed. One alternative to BN modeling is to use ordinary differential equation (ODE) kinetics to model Ca^{++} wave propagation and reactivity with a higher degree of precision. Within this context, one can also model Ca^{++} wave propagation and define parameters for wave oscillation interactions with other elements in the single cell. Such an approach, however, does not link Ca^{++} waves to network pathological processes within and without the cell. Recently, Kazemzadeh et al. used a combined Boolean and ODE approach to model network regulatory effects of apoptosis in a modified (c.f. "humanized") yeast model. Using databases to generate robust Boolean Networks that could then be solved at time-steps enabled them to calculate steady states of complex apoptotic networks and to test the effects of genetic knockouts and variable ischemic insults (Kazemzadeh et al. 2012). Another set of recent experiments by McDermott et al. were aimed at using BN formalism to study regulatory gene networks in response to ischemic insult. They modeled clusters of functionally related gene elements in steady state and then perturbed this system by using various types of preconditioning insults, including mild ischemia, and a later more serious ischemic insult. Results between the various initial states were compared, and the functional significance of genetic contribution to neuroprotection was analyzed by looking at the robustness of cluster response to preconditioning (McDermott et al. 2012). Most of the results from the computer model were confirmed by previously published experimental data. BN formalism is a reductionist view of network signaling, whereas simultaneous ODE solving at discrete time-steps gives a larger picture of intracellular signaling. Attempts to link these two modeling methods in studying apoptosis and ischemic cascades have been recently gaining popularity in computational neuroscience as well as systems biology (Bogda et al. 2013).

Future Considerations

Computer modeling affords several advantages in the study of ischemia. It allows us to accurately measure many reactants simultaneously in exceedingly complex environments. We can link top-down and bottom-up models of ischemia to create robust multicellular models. We have also begun to understand how genetic regulation and preconditioning effects may confer neuroprotection. And, importantly, we can identify control points for cascade modulation, which are appropriate targets for therapeutic intervention. Such research will likely provide proof of concept and system extrapolation for the development of new drugs to encourage recovery or enhance the duration of recoverability in the penumbra.

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