Diabetic retinopathy

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The aims of this problem is to develop a network model of retinal metabolism and then use it to investigate the impact of raised blood glucose and breakdown of the blood-retinal barrier on the network.

BACKGROUND AND MOTIVATION

Diabetic retinopathy, the commonest cause of blindness in people of working age is a direct consequence of raised blood glucose levels. Tight blood sugar control normally prevents development of this complication. This makes understanding retinal glucose metabolism of great clinical significance. The initiating feature of the disease is hyperglycaemia, but most of the clinical features relate to breakdown of the blood-retinal barrier, and, while there is good understanding of how this breakdown occurs, it is neither clear what role hyperglycaemia plays in the initial phases nor why breakdown of the blood-retinal barrier should lead to retinal damage.

The brain and retina handle glucose metabolism quite differently from other tissues, with shuttling of key metabolites between cell types (which is the reason for the existence of both the blood-retinal and blood-brain barriers). Glycolysis takes place in glia cells and the tricarboxylic acid (TCA) cycle takes place in neurones.

It is assumed that raised blood glucose leads to an accumulation of one or more intermediates within the network. This in turn provides hope that reduction of activity of one step in the pathway would result in restoration of the network to a more physiological state.

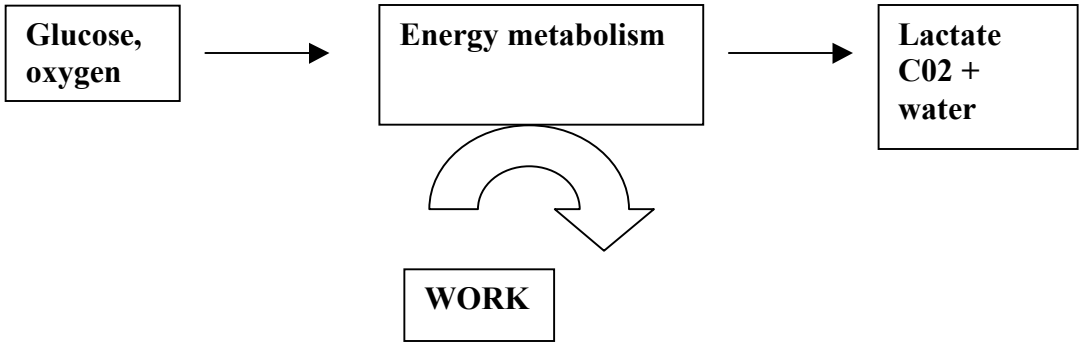
The late effect of diabetic retinopathy is breakdown of the blood-retinal barrier, which would tend to fix the concentrations of key metabolites in the extracellular space and thereby interfere with their shuttling between cell types. This again raises the issue of whether an appropriate inhibitor could restore the network under this condition to a more physiological state.

ADVANTAGES OF THE SYSTEM

Retinal metabolism may be particularly suited to a mathematical modelling approach for a number of reasons:-

1. The retina is a truly isolated system. The blood-retinal barrier makes the retina unresponsive to circulating hormones and it lacks an autonomic nervous system.
2. It uses one fuel: glucose.
3. It has two different work states corresponding to its functioning under light and dark.
4. It has a well-defined structure and is composed of just two major cellular components; neurones and glia.
5. There are good estimates of many system parameters.
6. The metabolic pathways are well-defined, modular networks, allowing the model to be constructed in stages.

   At the simplest level, the problem is:-



WORK DONE IN PREPARATION

In preparation:-

1. I have a list of the compartments of the key metabolic pathways and have constructed the stoichiometric matrix.
2. Have a table of the thermodynamic potentials of the compounds (corrected for pH7 and ionic strength). This means that the modelled reaction rates can be driven by the thermodynamic potentials and would allow whole pathways to be modelled as a single term allowing very considerable simplification.
3. List of key allosteric interactions
4. Estimates of the work terms for light and dark
5. Estimates of diffusion distances.