How neurotoxic glutamate is released in stroke

I report experiments on the early events causing brain damage during stroke.

Nerve cells in the brain send information to one another by releasing chemicals called neurotransmitters. These act on receptor proteins in a nearby cell, altering the voltage across its membrane. To allow rapid information processing, the neurotransmitter is removed afterwards by a kind of vacuum cleaner, which normally sucks the transmitter from outside the cell to inside the cell where it cannot act on receptors. We have found that in stroke, however, these ‘vacuum cleaners’ run backwards. They blow out a neurotransmitter called glutamate, which is known to overexcite the nerve cells and trigger their death, leading to mental and physical handicap.

To discover this, we did experiments on slices of brain tissue, and used the nerve cells’ own receptors for glutamate to detect the release of glutamate during a simulated stroke. We then used drugs to block different possible mechanisms of glutamate release (there are many!). Only the drug which blocked operation of the glutamate ‘vacuum cleaner’ prevented the release of glutamate during stroke.

To understand why the ‘vacuum cleaners’ run backwards in stroke, it is necessary to understand how they are powered. From experiments in which their operation is recorded as an electric current, we know that they get their energy from the movement of ions such as sodium, protons and potassium across the membrane. During stroke there is a change of concentration of these ions inside and outside the cells, and it is this change that switches the direction of operation of the ‘vacuum cleaners’.

Experiments like these are giving us a better understanding of the molecular operation of the neurotransmitter ‘vacuum cleaners’ and of the events in the first few minutes of stroke. In the future, this may open the way to modulate the activity of the ‘vacuum cleaners’ therapeutically, either to prevent the destructive consequences of stroke, or to alter brain function in other mental diseases.

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Regulation of autoimmunity by the molecular adaptor Cbl-b

Signalling thresholds of cell surface receptors determine immunity or tolerance to self-molecules. The molecular mechanisms that maintain T and B lymphocyte immunotolerance in vivo are still poorly understood. Members of the Cbl/Sli family of molecular adaptors function downstream of growth factor and antigen receptors. Gene-targeted mice lacking the adaptor Cbl-b develop spontaneous autoimmunity characterised by autoantibody production, infiltration of activated T and B lymphocytes into multiple organs, and parenchymal damage. In vitro, Cbl-b deficient lymphocytes are hyperresponsive to antigen receptor stimulation. Cbl-b is thus a key regulator of activation thresholds in mature lymphocytes and of immunologic tolerance and autoimmunity.

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Female sterility by invalidation of the mouse gene encoding the tetraspanin CD9

The CD9 antigen belongs to the tetraspanins’ superfamily of surface proteins. Mice with an inactivation of the CD9 gene do not have obvious abnormalities. However, two groups have just shown that the females homozygote for the deletion presented a severe reduction of fertility. Although sperm migrate normally towards the oviduct, the oocytes are not fertilized. Moreover, multiple sperm frequently occupy the perivitelline space. The oocyte block in metaphase of meiosis II in unmated mice indicates a normal maturation. The development of normal embryos after intracytoplasmic injection of spermatozoids (ICSI) in the oocytes of mouse CD9 also goes in the direction of a defect of fusion rather than of an anomaly of maturation. This observation suggested a defect of fusion of the sperm with the oocyte, which was confirmed by a dye transfer test (the oocytes are marked by Hoechst 33342, a vital dye of the ADN, and in the event of fusion, the DNA of the sperm is coloured). It was shown that the oocytes of wild mice strongly express the CD9 antigen and that anti-mouse