Immune changes

The transplant-tolerant monkeys demonstrated a normal response to an environmental bacterial antigen (streptolysin O), suggesting they were immunocompetent rather than immunosuppressed and, therefore, that genuine tolerance had developed. However, the treated monkeys also showed significant immune-system changes compared with controls. Despite a phenotypically normal T-cell population, their long-term antibody response to a previously unmet antigen was much weaker, suggesting limited T-cell amplification. A mean 22-fold increase in plasma levels of interleukin-10 (IL-10) and a sixfold increase in IL-4 was also observed, and was sustained for at least 12 months. 'The cytokine changes indicate that tolerance induction by this novel strategy results in immune deviation from Type I to Type II immunity,' says lead author, Judith Thomas. 'Sustained IL-10 and IL-4 production in the presence of the graft suggests an active process, possibly due to a regulatory T-cell population that contributes to the stability of this tolerance.'

Type 1 diabetes in humans is an autoimmune disease, a condition that is not present in the STZ model. There is a risk, therefore, that transplanted islet cells might also be killed by autoimmunity. However, co-administration of IT and DSG has been shown to reduce the population of memory T-cells[3], suggesting that this might also control recurring autoimmunity. This would be highly significant because it could lead to new treatments for multiple sclerosis, rheumatoid arthritis and other autoimmune diseases.

Human trials are currently being planned: 'We need to complete the testing of anti-human CD3 immunotoxin, which is similar, but not identical to anti-monkey CD3 immunotoxin,' says Thomas. Future research will be focused on further understanding the mechanism of transplant tolerance to facilitate its safe and effective translation to clinical therapy.

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Electrifying new treatment for epilepsy

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Researchers believe that mild electric fields could control epilepsy, after results showing that seizure-like activity can be inhibited by applying these fields to brain cells *in vitro*[1].

Researchers at the Krasnow Institute for Advanced Study at George Mason University (Fairfax, VA, USA) say that using such electric fields to modulate neuronal activity offers the opportunity to minimize the use of invasive techniques such as medical and surgical treatments currently used in epilepsy.

Epileptic seizures can be defined as the paroxysmal discharge of cerebral neurones resulting in disorderly muscular activity and mental changes. 'It is thought that in epilepsy, small groups of neurons fire in a co-ordinated fashion, as opposed to the normal state of individual neurones firing infrequently,' explains Bruce Gluckman, Assistant Professor of Physics and Astronomy at the Krasnow Institute. 'But there is still a great deal to discover about the epileptic process. '

Current treatments

As many as one or two in 100 people have epilepsy, defined by the occurrence of more than one seizure. In one-third of these people with epilepsy, the symptoms can be well controlled using pharmacologically active agents; in another one-third the epilepsy can be reasonably controlled; and the final one-third of epileptic patients have pharmacologically intractable epilepsy. For the last group the principal treatment offered is surgical resection of the epileptic foci.

'With resection, there is always the potential hazard that the part of the brain you're cutting into is not going to function. There is almost no part of the brain that is not serving some useful function,' says Steven Schiff, the Krasnow Professor of Neurobiology. 'For example, when the temporal lobes are resected, there is some decrement in verbal memory if the left side is operated on, and spatial memory if the right side is operated on.'

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He adds that pharmacological therapies are also far from ideal because they influence every cell in the brain and have a tendency to affect cognition and produce a host of side effects.

Electrical alternatives

In 1927, William Rushton (Cambridge, UK) showed that electric fields can influence the threshold of excitability of neurons[2]. It is believed that electric fields redistribute the electrical charges in individual neurons, changing the likelihood that they will fire in response to stimulation by other neurons around them.

'In these neurons, the long dendrites act like antennae in the electric field, causing a slight polarization of the neuron. This shifts the transmembrane potential of the cell bodies either towards or further away from the threshold at which action potentials are initiated, stimulating the neurons to fire more or less readily, respectively,' says Gluckman.

Previously, Gluckman and Schiff showed that DC electric fields applied externally, *in vitro*, to brain tissue could modulate neuronal activity and could even transiently suppress seizure-like activity[3]. In the current study, the team altered the salt balance in the fluid surrounding transverse and longitudinal hippocampal slices of rat brain to produce the excessive excitation that is characteristic of epilepsy. They measured the onset of firing using one set of electrical probes and applied carefully tailored electric fields using another set, thus producing a feedback system that inhibited the group firing. The team observed the successful suppression of seizure-like behaviour in 20 of 30 seizing slices and maintained control for up to 16 min. Lack of suppression was thought to be a result of the elimination of dendrites during slice preparation and inaccurate positioning of the probes.

'The importance of the inclusion of feedback is that we want to build a device for use in patients that produces the least amount of interaction when not needed,' says Gluckman.

Although there is no evidence of functional damage caused by electric-field stimulation, a proper safety evaluation of the technology will require histological evaluation of tissue after exposure to electric-field modulation and feedback control for extended periods of time. One major question remains: will brain cells in the living organism respond to electrical fields in the same way that cells do in a laboratory culture?

Future studies

Present research is being directed at working out how to translate the results of this *in vitro* research to the intact brain using animal models. Currently, the team are working on a prototype device that could be used in clinical trials. The idea is that non-polarizing electrodes could be implanted into the intraventricular, subdural or epidural spaces of the brain, and located close to the epileptic foci.

'The first clinical use is likely to be in patients before undergoing resection surgery. The major advantage here is that if there are complications in the brain tissue they will occur in areas of the brain that are to be removed,' says Schiff. Studies will also need to be performed in the presence of other pharmacological compounds. 'It's possible that certain classes of drug will have a synergistic effect with this electrical approach, whereas others might react badly,' says Schiff.

'The idea of switching off seizures before they can develop fully is very exciting,' says John Jeffries from the Division of Neuroscience at the University of Birmingham, UK. 'Gluckman and Schiff have a radical approach, which, if it works, could be a very effective method for seizure control with minimal side effects. However, many problems remain; it could be hard to get the electrodes in the right place within the epileptic tissue in human patients. This will remain much more difficult than prescribing pills, so surgery is likely to be available at a limited number of centres. That said, I will be very interested to see how this develops.'

As well as developing a device to shut off seizures the team hope to use the technology to modulate network behaviour and to start to understand the dynamics of the epileptic brain. Researchers believe that the method could also be extended to suppress other pathological neuronal activities in conditions such as Parkinson's disease.

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