Inhibiting endostatin expression could reduce secondary injury following TBI

After traumatic brain injury (TBI), secondary tissue deterioration caused by hypoperfusion can enlarge the area of damage caused by the initial trauma. Endostatin inhibits angiogenesis, so its role in angiogenic remodeling following TBI is of considerable interest.

Using immunohistochemistry, Deininger *et al.* compared the spatial and temporal distribution of endostatin/collagen XVIII$^+$ cells in the brains of 18 patients with TBI and 7 neuropathologically unaltered control patients. In control brain samples, very few endostatin/collagen XVIII$^+$ cells were observed. In the brains of patients with TBI who survived longer than 48 h following injury, however, a time-dependent increase in endostatin/collagen XVIII$^+$ cells was noted. Following 14 days of survival, massive accumulation of endostatin/collagen XVIII$^+$ cells was observed in and around the areas of tissue damage. Double-labeling experiments revealed the frequent co-location of inducible nitric oxide synthase with endostatin/collagen XVIII$^+$ cells and also confirmed that the majority of endostatin/collagen XVIII$^+$ cells were of macrophage/microglial identity.

In vitro experiments using mouse N9 microglial cells revealed an important role for hypoxia in the induction of endostatin/collagen XVIII release; challenge by reactive oxygen intermediates had a lesser effect. Both of these types of cellular stress are involved in secondary tissue deterioration following TBI. Further *in vitro* experiments demonstrated the ability of two nitric oxide synthase inhibitors, aminoguanidine and L-NAME, to inhibit the induction of endostatin/collagen XVIII$^+$ following challenge by reactive oxygen species. These results indicate the potential of pharmacological inhibition of nitric oxide synthase for altering endostatin release following TBI.

Original article Deininger MH *et al.* (2006) Endostatin/collagen XVIII accumulates in patients with traumatic brain injury. *J Neurotrauma* **23:** 1103–1110

Intravenous flumazenil in Parkinson's disease

Researchers from Baylor College of Medicine in Houston, TX, previously showed in an open-label trial that a 0.5 mg intravenous dose of the non-selective γ-aminobutyric (GABA) antagonist flumazenil was well tolerated and improved motor symptoms in patients with Parkinson's disease (PD). They have now replicated the results in a placebo-controlled, crossover trial, using a higher 1 mg dose.

In this study, eight subjects were initially randomized to receive flumazenil and eight to receive placebo. Finger-tapping tests were performed at baseline and for 90 min following infusion, at 15 min intervals. Following a 90 min washout, the medications were reversed. Change in tapping speed from baseline was significantly improved in subjects who received flumazenil compared with those who received placebo ($P<0.0001$); improvement was seen at every time point ($P<0.01$) except 15 min following infusion. Although Unified Parkinson's Disease Rating Scale (UPDRS) score improved more in the flumazenil group (particularly for bradykinesia and rigidity), this finding was not significant. Half of the subjects reported light-headedness, dizziness or wooziness on flumazenil, but the drug was generally well tolerated.

Proposed explanations for flumazenil's effect include normalizing of thalamic and pedunculopontine nucleus activity, improving output from the basal ganglia, and direct activation of the cortex. The authors acknowledge that intravenous flumazenil is unlikely to become a practical therapy for PD, but its proposed mechanisms of action warrant further investigation and indicate that GABA antagonists could be a novel potential treatment class for this condition.

Original article Ondo WG and Silay YS (2006) Intravenous flumazenil for Parkinson's disease: a single dose, double blind, placebo controlled, cross-over trial. *Mov Disord* [doi: 10.1002/mds.21022]

Diagnosis of AD by SPECT and cognitive testing

Patients with mild cognitive impairment (MCI) are more likely than unaffected individuals to develop Alzheimer's disease (AD), a condition associated with reduced blood flow in the parietal lobe. To investigate the link between cerebral perfusion and dementia, Huang *et al.* used single-photon emission computed tomography (SPECT) to observe regional cerebral blood flow in 39 patients with MCI and 20