Traumatic brain injury

Apolipoprotein E4 and traumatic brain injury

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Apolipoprotein E plays a critical part in the maintenance, repair and growth of neurones, and seems to have an important part in the neural response to brain injury

Considerable variability exists in outcome after traumatic brain injury (TBI), which is only partly explained by premorbid factors and severity of injury. Genetic factors influencing the brain's susceptibility to injury, and its capacity for reorganisation, neuronal regrowth and repair are likely to play a part.

Apolipoprotein (Apo) E plays a critical part in the maintenance, repair and growth of neurones. The E4 isoform results in reduced growth and branching of neurites in vitro and seems to have an important part to play in the neural response to injury. In clinical genetic studies, the ApoE-ϵ4 allele is associated with attentional impairments and white matter abnormalities in normal controls; an increased risk of late-onset sporadic Alzheimer's disease; and adverse functional outcomes acutely, early and late after severe but not clearly after mild and moderate TBI; and also after haemorrhagic but not after ischaemic stroke, cardiac surgery, cardiopulmonary resuscitation and probably subarachnoid haemorrhage. It is not known whether ApoE4 acts by increasing neural susceptibility to the consequences of neurotoxic agents, such as amyloid β-peptides, or age, traumatic injury, oxidative stress, ischaemia and inflammation,[1] or by pre-injury effects on vascular wall pathology or blood-clotting mechanisms. Against the background of a large number of studies on the in vitro toxicity and clinical associations of ApoE4, this issue of the *Journal of Neurology, Neurosurgery & Psychiatry* includes two papers reporting further associations of ApoE in TBI—one with the neuropathological effects of TBI and the other with neuropsychological outcomes.

Smith *et al*[2] (***see page xx***) describe postmortem examination findings in a large series (n = 239) of fatally injured patients. They found a relationship between the ApoE-ϵ4 allele and the severity of contusions and ischaemic brain damage, but not with other pathological changes after TBI, including diffuse axonal injury, or with the risk of fatal outcome. They suggest that the mechanism(s) that may underlie greater contusional injury is (are) related to the involvement of ApoE either in blood vessel wall integrity and pre-injury predisposition to atherosclerosis and cerebral amyloid angiopathy, or in blood coagulation mechanisms. By contrast, they relate their finding of a trend ($p = 0.08$) associating ApoE-ϵ4 and the severity of ischaemic damage to the reduced excitotoxic protection and larger lesions seen in ApoE-ϵ4 compared with ApoE-ϵ3 animal models after ischaemia.

A further study by Ariza *et al*[3] reports the influence of ApoE polymorphisms on different aspects of cognitive function and behaviour 6–9 months after severe and moderate TBI. Earlier studies on neurosurgical cohorts of patients with TBI have reported significantly poorer global functional outcome in ApoE-ϵ4 carriers at 6 months, particularly in children and young adults,[4] and a trend ($p = 0.08$) towards poorer global outcome in the very long term after injury.[5] This study contributes to previous data that explore the impairments underlying these poorer global outcomes, and identifies greater problems in temporal and frontal cognitive functions and behavioural disturbances in ϵ4 carriers, despite no significant differences in acute measures of injury severity. The authors speculate that ApoE-ϵ4 carriers are less able to avoid secondary damage and repair damaged tissue after TBI.

The economic consequences of TBI rival that of stroke, and an enormous number of patients sustaining mild and moderate, as well as severe, TBI might benefit from simple medical treatment early after injury. Overall, the ApoE data in TBI continue to suggest that the ϵ4 allele modulates both the severity and nature of the acute consequences of injury and the processes of neural regrowth and repair involved in recovery; other genetic factors are also likely to play a part, including those controlling neurotrophic factors associated with synaptic plasticity and the response to training and rehabilitation.[6] The structural features of ApoE4 make this protein an excellent therapeutic target, and the patient's ApoE genotype may also influence symptomatic treatments, just as emerging data suggest that patients with Alzheimer's disease who lack the ApoE-ϵ4 allele respond better to some cholinesterase inhibitors.

Computational approaches are often used to screen a compound's possible effects by ''docking'' small molecules into the target macromolecule. Investigations of novel compounds that modulate ApoE4 are in their early stages, but include molecules that block ApoE4 binding and decrease β-peptide production.[7] Targeted strategies are based on in vitro and in vivo data: ApoE modulators include agents capable of converting ApoE4 into E3-like molecules (structure correctors) that inhibit the direct ApoE4 effect and the indirect effect of increased β-amyloid production. Other agents block ApoE4 proteolytic processing and the production of toxic fragments such as those of β-amyloids (protease inhibitors). These therapeutic agents are mainly aimed at treating Alzheimer's disease, but the evidence discussed highlights an overlap with TBI and suggests that the use of medical treatments in parallel with rehabilitation techniques might reduce its residual long-term effects.

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