Anti-Adhesion Molecule Monoclonal Antibodies
Therapeutic Potential in Ischaemic Stroke

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Summary

Leucocytes appear to potentiate stroke injury by clogging the microcirculation and infiltrating into the brain where they release free radicals and other substances that are toxic to neurons. Through the use of specific monoclonal antibodies directed against leucocyte adhesion receptors, both the microcirculation obstruction and the leucocyte infiltration can be decreased. Experimental studies have found reduced stroke damage through the use of antibodies that bind to either the CD18 leucocyte adhesion receptor or the corresponding endothelial cell receptor, intercellular adhesion molecule-1 (ICAM-1). These studies have shown the most benefit when anti-adhesion monoclonal antibodies are used in experimental models in which reperfusion follows an initial period of ischaemia. Based on these encouraging experimental results, a clinical trial using an anti-ICAM-1 adhesion agent has just been completed, with final results expected soon.

The appearance of leucocytes in CNS ischaemic tissue has previously been considered to represent a pathophysiological response to existing injury. However, recent evidence suggests that leucocytes may also be directly involved in the pathogenesis and extension of CNS ischaemic injury.1,2 Two proposed mechanisms of leucocyte involvement in ischaemia are: (i) direct microvascular occlusion after endothelial and basement membrane adhesion;3,4 and (ii) transendothelial migration of leucocytes with secondary CNS tissue infiltration and neuronal cytotoxic injury.5 Initial adhesion of leucocytes to microvascular endothelium is essential for initiation of either of these mechanisms.

The primary leucocyte-endothelial interaction ('rolling') is mediated by selectins involving P-selectin on the surface of the endothelial cells and L-selectin on leucocytes.5 Upon activation of leucocytes, firm adherence of leucocytes to the endothelial lining ('sticking') is mediated by a leucocyte membrane glycoprotein receptor complex termed CD18 (or β2-integrin) and its endothelial ligand, intercellular adhesion molecule-1 (ICAM-1).6,7 [see fig. 1]. We previously demonstrated that CD18/ICAM-1-mediated neutrophil adhesion increases following clinical and experimental stroke.8,9

Leucocyte infiltration into the brain has been shown to occur rapidly following a stroke. In experimental focal CNS ischaemia, granulocyte infiltration occurs as early as 4 hours and peaks at 24 hours after stroke, with marked infiltration seen in reperfusion stroke models.10-12 Early leucocyte infiltration has also been observed in clinical stroke.13 Previous studies have also found evidence of early granulocyte plugging of the cerebral micro-
circulation within 1 hour following brain ischaemia. This leucocyte capillary plugging may also be the major mechanism of the ‘no-reflow phenomenon’. This phenomenon, first described in the CNS by Ames et al., is defined as the incomplete restoration of normal blood flow following a period of ischaemia. Areas of parenchyma that might be viable when blood flow returns to the large vessels are not adequately reperfused and ultimately die.

The role of leucocyte adhesion and infiltration in potentiating CNS ischaemia is supported by the results of older experimental studies in which systemic leucocyte depletion was produced using either antiserum, cyclophosphamide or chlormethine (mechlorethamine) and then subjecting the animals to CNS ischaemia. These studies showed that leucocyte depletion:

- improved blood flow in an embolic stroke model;
- reduced infarct size in a model of thromboembolism;
- improved blood flow in a forebrain ischaemia model.