The Blood-Brain Barrier in Normal and Pathological Conditions

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ABSTRACT

The blood-brain barrier (BBB) consists of a specialised endothelium which effectively prevents free exchange between the blood and the brain but selectively allows the transport of nutrients and maintains homeostasis in the central nervous system. Despite decades of research, many aspects of the BBB are still obscure. The current study investigated the BBB in normal and pathological conditions induced by intravascular and extravascular insults. Intravascular insult was induced by the administration of Clostridium perfringens (Cl p) type D epsilon prototoxin. Extravascular insult was induced by an impact acceleration model for closed head injury to induce traumatic brain injury (TBI). The integrity of the BBB was examined ultrastructurally and by its ability to exclude endogenous and exogenous tracers. The expression of two BBB specific proteins, the endothelial barrier antigen (EBA) and the glucose transporter 1 (GLUT1), was studied.

The normal BBB was impermeable to macromolecules (serum albumin and horseradish peroxidase (HRP)) and small molecules (ionic lanthanum). Ultrastructurally the cerebral endothelium was non-fenestrated and had a low density of cytoplasmic vesicles. Tight junctions sealed the interendothelial cleft and effectively prevented the passage of tracers. Endothelial cells (ECs) at the BBB strongly expressed EBA and GLUT1.

Breakdown of the BBB was observed in both the Cl p prototoxin and the TBI models. Leakage of tracers indicated the development of vasogenic brain oedema. Undulation of EC luminal membrane and increased cytoplasmic vesicles appeared
to be a common response to vascular injury in the two models. The alteration of tight junctions occurred mainly in traumatic brain injury.

A reduction in EBA immunoreactivity in brain vessels correlated with the disruption of the BBB in both models and appeared to be a sensitive indicator of the compromised BBB. The function of EBA at the BBB was further studied by \textit{in vivo} immunological targeting of this antigen. Intravenous injection of anti-EBA led to rapid opening of the BBB and the intravenously injected anti-EBA was bound to ECs, suggesting the formation of antigen-antibody complexes \textit{in vivo}.

GLUT1 expression showed dissimilar results in the two models. \textit{Clp} prototoxin injection did not affect the expression of GLUT1, while TBI evidently reduced GLUT1 immunoreactivity. It appears that TBI has a profound effect on the cerebral glucose metabolism.

This study increased our understanding of the pathobiology of the BBB. Targeting BBB-specific proteins may provide a useful tool for future research into the function of the BBB.