The Neurosurgeon and the Blood-Brain Barrier. A Survey

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Summary

A survey is given on the history of the discovery of the blood-brain barrier, of its functions and of its clinical importance. Also attempts to circumvent or disrupt the barrier with the aim of introducing therapeutic or diagnostic agents into the brain tissue have been reported. Finally the possible negative effects of lasting barrier defects in transplanted foetal tissue are mentioned.

Keywords: Blood-brain barrier; survey.

The discovery of the blood-brain barrier, which is generally attributed to Goldmann5, fell within the early years of neurosurgery, when neurosurgeons tried to cope with a multitude of life-threatening complications, such as brain oedema, the relation of which to the blood-brain barrier was not yet recognized. The attitude of the neurosurgeon toward the barrier may since then be characterized as an affair of love and hate; love and the fear to cause it any harm, and hate when it frustrates our therapeutic efforts or behaves in an unexpected way.

It was not until the advent of electronmicroscopy in the 1950s, that several issues concerning the nature of brain oedema were solved, such as an inherent intracellular versus an extracellular localization. The inherent association of brain oedema with blood-brain barrier breakdown was elucidated by Klatzo, Piraux, and Laskowski in 195810, following their investigations using the new model for barrier disruption, namely a freezing injury to the cerebral cortex, introduced by Clasen et al.2. A better understanding of the pathogenesis of brain oedema was summarized in Klatzo’s11 classification of the types of brain oedema into vasogenic, consequent on blood-brain barrier disruption, and cytotoxic, resulting from interference with cellular metabolism.

Although the highly superior spatial resolution of the electron microscope could finally solve the question of intra- or extracellular location of the fluid accumulation in brain oedema, initially it also gave the erroneous image of the brain tissue lacking an adequate extracellular space2. It was Van Harreveld12 who showed on the basis of his measurements of tissue electrical impedance, correlated with electron microscopic observations of rapidly frozen tissue, that the central nervous system does possess extracellular space, and that the image observed in conventional electron micrographs is the product of an artifactual cell swelling induced by the procedure of histological fixation. As early as 1923 Grant demonstrated that brain tumours could be localized by the recording of electrical impedance of the tissue6, but it was not until the 1960s with the appearance of the studies of Van Harreveld and others, that tissue electrical impedance as a measure of tissue extracellular space could be used to identify tissue structures in stereotaxic procedures16,18, and that the decreased impedance observed in brain tumours was the manifestation of extracellular oedema in the tumour4a,14. Also other techniques such as the measurement of 35S-thiosulfate distribution to assess extracellular space, have demonstrated the relation of an enlarged extracellular space with the presence of vasogenic oedema15.

Studies on the various factors affecting vasogenic brain oedema have revealed the role of the blood-brain barrier. The use of hyperosmolar solutions to combat intracranial pressure elevation, introduced by Javid and Settlage9, appeared to be restricted by the barrier disruption in the lesion, as the hyperosmolar solute concentration in the blood, required for the dehydration, was readily transferred to the lesion through the leaky barrier, thus abolishing dehydration1. The barrier breakdown in vasogenic oedema also appeared to render the brain susceptible to isosmolar hyperhydration, since the barrier disruption made the brain tissue accessible to expansion of systemic sodium space1b.
In the early years of diagnostic cerebral investigation by angiography and pneumoencephalography mass lesions were as phantoms, whose presence could only be inferred from the displacements of vessels or ventricles they provoked; only exceptionally they manifested themselves as a blush on the angiogram. But since the introduction of radio-isotope scanning the tumours have revealed their presence on account of the barrier breakdown causing extravasation of the radioactive tracer. Although radio-isotope scanning is now largely abandoned because of the superior spatial resolution of computerized tomography and magnetic resonance imaging, the barrier disruption with its consequent contrast extravasation still constitutes a valuable landmark indicating the actual boundaries of the tumour amidst vast areas of oedema.

Increased awareness of the role of barrier breakdown in the production of vasogenic oedema, and of the vulnerability of barrier integrity to a multitude of events inherent in surgical manipulation, such as mechanical traumatisation, electrocautery, desiccation, and retractor compression, has resulted in the evolution of surgical discipline intended to minimize injury to the barrier, and thus avoid the risk of postoperative oedema.

However, barrier function which seems destined to provide the neural tissue with an optimal biochemical environment by the exclusion of external perturbing influences, to allow for the fine tuning of subtle intrinsic regulatory mechanisms, also appears to frustrate attempts at introducing therapeutic agents into the tissue. Studies on exchange processes between extracellular and cerebrospinal fluid have revealed the significance of the so-called sink-action of the cerebrospinal fluid (i.e., depletion of substances in the brain parenchyma by diffusion into the cerebrospinal fluid), which together with the action of the blood-brain in restricting the entry of extrinsic substances, may prevent the achievement of an adequate drug concentration in the cerebral tissue. In the management of neoplastic disease, Ommaya reservoirs connected to intraventricular catheters have been implanted to introduce drugs into the cerebrospinal fluid, thus circumventing the cumbersome presence of the barrier. Another approach, which goes against the neurosurgeon’s ingrained attitude toward preserving the barrier, constitutes the disruption of the barrier by infusion of hyperosmolar solutions into the carotid artery, to enable entry of the desired drug into the brain following its infusion. Although no manifest oedema was reported following the osmotic barrier disruption, shorter lasting modifications of the barrier have been attempted, e.g. by the infusion into the carotid of 1-0-alkyl-glycerols. Also recent efforts to apply monoclonal antibodies, which are directed against brain tumours, for specific diagnosis of the tumour by binding to MRI-contrast agents or radioisotopes, and for the treatment of the tumour by binding to cytotoxic agents, will strongly depend on the behaviour of the blood-brain barrier in allowing entry of the antibody.

Finally, in the recent efforts of implanting foetal tissue into the brain to replace degenerate structures, again the blood-brain barrier may be the spoil-sport, as lasting barrier defects have been observed in capillaries of the implants, conceivably allowing the entry of blood-borne substances, such as antibodies, which may have a detrimental effect upon the viability of the implant.

References

5. Goldmann EE (1913) Vitalfärbung am Zentralnervensystem. Abh Preuß Akad Wiss Phys Math, K 1 I: 169–175
6. Grant FC (1923) Localization of brain tumours by determination of the electrical resistance of the growth. JAMA 81: 2169–2171
13. Neuwelt EA, Specht HD, Barnett PA, Dahlgorg SA, Miley A,