Neurobiology

Glia and the blood–brain barrier

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SINCE the classic dye experiments of Ehrlich[1] in 1885 it has been known that many substances injected into the blood have limited entry into the mammalian brain. Rival theories to explain this effect were a restricted extracellular space in the brain, or a barrier at the blood–brain interface. The proposed barrier was also variously attributed to the endothelium, the basement membrane or the end-feet of glial cells (astrocytes), which together form the brain microvessel wall. It was not until 1969, when Brightman and Reese[2] showed that the electron microscope tracer horseradish peroxidase was blocked at the level of endothelial tight junctions when injected into the blood or into the brain, that the debate was resolved. On page 253 of this issue[3], R. C. Janzer and M. C. Raff provide clear evidence that the blood–brain barrier is induced by astrocytes. This result not only provides another function for astrocytes, but also could help to explain the breakdown of the blood–brain barrier that occurs in some pathologies of the brain[4]. However, comparison of the barrier layer in different animal groups suggests that the induction story will not be straightforward.

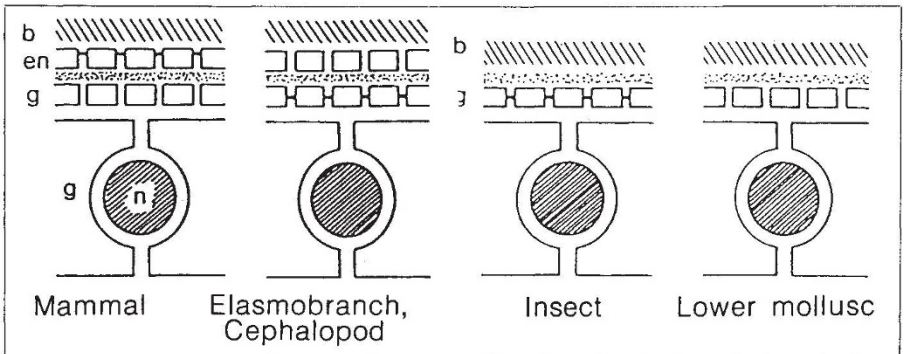
The role of perivascular glial cells has been tantalizingly difficult to establish. The well-ordered 'pavement' of glial end-feet on the endothelial wall suggested that these cells in some way influenced blood–brain exchange. There were doubts that the endothelial layer could account for the observed rate of bicarbonate transport at the barrier, and transport by the glial end-feet was suggested[5]. Orthogonal assemblies of particles are clustered on the endothelium-facing but not on the lateral membranes of astrocytes, indicating that the cells are polarized[6]. The functions of the assemblies remain obscure, although it is possible they are involved in ion transport. Neurons release potassium ions when they are active. Astrocytes have a high density of potassium channels on their end-feet[7], providing a possible route for the 'siphoning' of potassium away from active neurons, so helping to maintain a stable neural environment.

Even before the location of the mammalian blood–brain barrier was known with certainty, Oldendorf[8] in 1967 proposed that the barrier could be maintained by the influence of astrocytes on endothelial cells. Svendgaard *et al.*[9] provided the first experimental evidence that brain tissue induces blood vessels to form a tight barrier by showing that two specific properties of the blood–brain barrier involving neurotransmitters, an enzymic trapping mechanism for L-DOPA and a barrier for catecholamines, develop in brain fragments transplanted into the anterior chamber of the eye but not in iris fragments grafted into the brain. That is, the donor tissue and not the ingrowing vessels from the host control the vessel wall function. Stewart and Wiley[10] were able to confirm this result in elegant grafting experiments between chick and quail embryos, where they unequivocally demonstrated the origin of vascular elements from host tissue.

Janzer and Raff's new work clearly shows an inductive effect by astrocytes, both in the rat and the chick, where invading host blood vessels become relatively impermeable to albumin within an exogenous astrocytic mass. The use of primary cultures of identified type 1 astrocytes is a significant advance on earlier work. The next step will be to establish to what extent these induced barriers mimic the normal blood–brain barrier, for instance in impermeability to ions and presence of carrier mechanisms. Monolayers of brain endothelial cells seem to be capable of forming junctions tight to horseradish peroxidase even when cultured without astrocytes, but these junctions are still of relatively low resistance[11].

What is the nature of the inducing signal that Janzer and Raff demonstrate? Is it a diffusible substance, or an effect communicated by cell contact? The presence of tight junctions in blood vessels at the brain surface that lack an astrocytic sheath[12] suggests the inducer is diffusible and is secreted into the interstitial fluid and cerebrospinal fluid of the brain. Is it produced by isolated astrocytes, or by astrocytes only in the presence of endothelial cells? The model systems introduced by Janzer and Raff will be extremely useful for elucidation of the biochemistry of the interaction.

Some intriguing questions remain. Many invertebrate groups have no blood–brain barrier. Insects, cephalopods and some arachnids do have a barrier, but it is glial, not endothelial[13,14] (see figure). What is the inducing signal here, and how is the need for a barrier and its location decided? Even in mammalian brain, the barrier isolating parts of the nervous system from blood is not always at the endothelial layer — for instance it is found instead at the level of ependymal derivatives in the choroid plexus and over neurosecretory zones, and tight junctions between parenchymal glia may contribute to the isolation of neurosecretory regions from the rest of the brain[14]. Are these barriers induced by a different signal, or have the endothelial cells here lost their sensitivity to the inducer? Among vertebrates, one anomalous group, elasmobranch fish, has its blood–brain barrier at the level of perivascular glial cells, although groups presumed close to the ancestral elasmobranch have an endothelial barrier[15]. What happened to the inducing signal or endothelial sensitivity in elasmobranch evolution? It seems certain that the induction of blood–brain barrier properties will turn out to be a complex and fascinating story. □



Blood–brain interface of different animal groups. Location of barrier layers is shown by bars connecting adjacent cells. b, Blood; en, endothelium; g, glia; n, neuron (modified from ref. 14).

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