The blood–brain barrier in trauma, stroke and edema

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Abstract. Successful research on human disease mechanisms and adequate pharmacotherapy depends on the availability of consistent and relevant animal models. For complex pathologies e.g. stroke and cerebral trauma it is highly important that the experimental models as much as possible mimic the pathogenesis and that drugs are delivered at the right time and the right place. Thereby it is not sufficient to counteract solely the endpoint of a traumatic or ischemic process i.e. irreversible neuronal cell death, but also to interfere with changes in other brain constituents e.g. the glial and endothelial compartments. Both are structural components of the blood–brain barrier and play a key role in the development of secondary phenomena as edema formation. The course and structural aspects of edema formation will be discussed, based on experience with several animal models of brain ischemia and trauma. It is concluded that stroke and trauma therapy is not only a matter of neurons and that acute treatment should focus on prevention of brain swelling. © 2005 Elsevier B.V. All rights reserved.

Keywords: Blood–brain barrier; Neurotrauma; Stroke; Edema

1. Introduction

Successful pharmacotherapy starts with synthesis of potent molecular entities and ends with fulfilling particular clinical needs. Between medicinal chemistry and clinical practice, profound research has to be conducted to build knowledge on drug potency and its action mechanisms at molecular and cellular level. Since most clinical disease processes are rather complex, also rigorous characterisation of pathogenesis, safety and efficacy in appropriate animal models is required. To recognize and counteract problems that may arise in the neurosurgery clinic, we have been looking for answers in the laboratory of experimental neuropathology. Many years of experience with animal models of stroke and
neurotrauma [1–7] provided insight in specific morphologic mechanisms and revealed a strong similarity in neurodegenerative processes between stroke and trauma, especially with regard to dynamic progression and endpoint parameters. The therapeutic goal certainly is protection of neurons, but to our opinion this cannot be achieved without counteracting secondary phenomena such as edema formation which in conditions of stroke as well as trauma appear in the very acute phase. Thereby the integrity of the blood–brain barrier (BBB) may play a key role, not only with respect to drug access to critical areas but also in the regulation of uncontrolled swelling of brain tissue.

2. Characterisation of edema

Morbidity and mortality associated with head injury and stroke is largely a result of edema which has been classified as cytotoxic (or cellular) and vasogenic, depending upon whether or not vascular permeability is increased [8]. Since the edema fluid is derived from blood either by moving across an intact BBB so that proteins are excluded, or by moving through a disrupted BBB which cannot exclude proteins, all edema is in fact vasogenic. Therefore the terms ‘intact barrier’ and ‘open barrier’ edema have been proposed instead [9]. Progression of injury and response of the different brain constituents upon ischemic or traumatic aggression are multifactorial and behave in a rather unpredictable and variable way. Although the initial trigger in both diseases is different, during progression common phenomena such as edema formation, inflammatory reaction and retrograde/distant

![Diagram](image-url)

Fig. 1. Pathogenesis of cerebral edema and neuronal cell death after traumatic and ischemic challenge.
degeneration may occur (Fig. 1). As such BBB damage, brain swelling and ultimate pannecrotic infarction may occur in traumatic brain injury as well as in stroke.

Rather than being a disease, edema has to be regarded as a progressively developing secondary symptom originating at the level of the BBB. The latter is composed by the vascular endothelium, the basement membrane and an almost continuous layer of astrocytic endfeet. Instability of endothelial tight junctions, upregulation of pinocytotic vesicles in the endothelial membrane and destabilisation of basal membrane may contribute to extravasation of plasma proteins in ischemic or traumatic conditions where residual blood flow remains present. Astrocytes play an important role in maintaining the cerebral water balance, probably regulated by aquaporins that are abundantly expressed at the level of the blood–brain barrier, in particular the astrocytic endfeet located around blood vessels [10]. Astrocytes, however, have several additional roles in response to injury e.g. remodeling the extracellular matrix for wound healing, regulation of immunity and inflammation by cytokine secretion, promoting neuronal survival by secretion of neurotrophic factors, mobilisation of excitotoxic amino acids by secretion of transporter molecules and protection against neuronal cell death by activation of the antioxidant pathway [11]. Hence, preservation of astrocytic function can be regarded as a prerequisite for ultimate neuronal survival.

3. Edema in animal models of stroke and trauma

3.1. Stroke

In conditions of stroke, tissue swelling is located mainly in the penumbra region, where destabilisation of the BBB may lead to extravasation and progressive cellular edema [3,12]. From a functional or clinical point of view, the penumbra can be considered as the area at risk for the patient and the area of hope for therapy, since changes detected in this region are largely reversible. Functional deficit and neuronal loss are mainly dependent on duration of ischemia and amount of residual flow (circulatory window) and on the reaction of neurons and their immediate environment (cellular window). [For review we refer to appropriate chapters in Ref. [12]]. Two important cellular aspects deserve attention: selective neuronal necrosis vs. pannecrotic infarction and open vs. intact BBB.

After a short episode of moderate ischemia (e.g. 2-vessel occlusion) the BBB remains intact, edema is absent and selective neuronal necrosis develops with a considerable delay. After a long episode of severe ischemia, on the other hand (e.g. middle cerebral artery occlusion), the BBB is damaged, leading to extravasation, uncontrolled swelling of astrocytic endfeet and spongious pannecrotic infarction within a few hours. Neurons initially may remain structurally intact but depending on tissue pH, degree of hyper-excitation or lack of preconditioning stress, their dendrites can start swelling, thereby sparing the axons. The structural picture in such regions is very typical i.e. perivascular astrocytes are severely dilated and induce compression of small blood vessels (Fig. 2). From these pictures it is evident that microcirculation is considerably hampered. On the one hand, mechanical compression of microvessels should be beneficial since supply of edema substrate is reduced. Otherwise, in case of pre-existing ischemia, oxygen supply will be further reduced resulting in more BBB leaks, increased astrocytic swelling and concomitant dendritic swelling until complete necrosis of all tissue elements takes place.
3.2. Trauma

After traumatic brain injury, edema formation occurs as well and, in a similar way as in stroke, this may lead to pannecrotic degeneration. Extreme swelling in the rigid cranium can exert mechanical damage due to displacement of brain tissue. In addition, blood flow may become compromised due to increased intracranial pressure, leading to metabolic injury. Increased ICP is not necessarily caused by edema but may result from acute vasoparalysis and impaired autoregulation [4]. Thereby the stability of the blood–brain barrier may be compromised by an increase of transmural pressure and a blockade of venous outflow. Moreover, mechanical rupture of blood vessels may induce continuous extravasation or even severe hemorrhage. As in stroke, this induces progressive cellular swelling until flow ultimately ceases and pannecrotic infarction develops. Around the
hemorrhagic core, a penumbra is found that shows characteristics of an ischemic penumbra [3] (Fig. 3).

4. Brain protection

The majority of pharmacotherapeutic studies focus on neuroprotection. Undoubtedly, prevention of neurodegeneration or restoring of neuronal function must be the main goal of every treatment. However, it is questionable if this can be achieved simply by administering drugs that in vitro have proven to protect neurons from necrotic or apoptotic cell death. In situations of moderate trauma or moderate ischemia of short duration, only neurons will die and this occurs with a certain delay. Neuroprotective agents are the best choice, provided they reach the compromised territory, which is not evident in a situation where the BBB remained intact. Severe trauma with hemorrhage or severe prolonged ischemia, on the other hand, requires another approach. In the acute phase, when the barrier is still open, drugs have the best chance to arrive at the challenged site. They must primarily counteract extreme cellular swelling by sealing the BBB leaks and/or by regulating astrocytic water transporting systems to finally guarantee sufficient oxygenation. Subsequently, in the subacute phase neuroprotection deserves attention (Fig. 4).

5. Conclusions

The search for cerebroprotective drugs in stroke and neurotrauma till present has not been very successful. Not only is the pathogenesis extremely complex and far from understood, pharmacological research has also been over the years too much focused exclusively on neuroprotection. A lot of knowledge has been gathered about molecular and cellular processes and desired action mechanisms for new drugs have been limited to
those that play a role in rescue of neurons. However neurons are not the only actors when the brain is compromised. Their survival also depends on the reactivity of their immediate environment. There is sufficient evidence that a major function of microglial cells and astrocytes, respectively, is modulation of inflammatory response and maintenance of an optimal water balance. Cellular edema is the very first visible morphologic feature after ischemic or traumatic insult. Neurons die with a considerably delay. The BBB, which is situated in between the vascular compartment of fluid supply and the cellular compartment of fluid accumulation, may therefore be considered as a valid target for stroke and trauma therapy. Moreover, temporal destabilisation of this barrier can be beneficial because it may allow supply of larger molecular entities in the compromised region. Unraveling the timely progression of pathologic events in the different cellular constituents, is a prerequisite for future pharmacotherapeutic research.

References


Discussion

Scherrmann
When you say that pharmacotherapy is not effective, do you mean that it is because of a pharmacokinetic problem, because drugs are not crossing the BBB?

Verlooy
I would not go so far. I would not say what the reason is. I only say that none of the outcome measures, survival, the Glasgow Outcome Scale, things like that, have been
significantly altered by pharmacotherapy. That is what I mean. I do not know why. Probably, it may be because of the BBB.

_Scherrmann_
In the field of BBB in ischemia I remember a work showing that PGP is not working in the ischemic zone because of the depletion of ATP and, as you know, the ABC transporters are dependent on ATP.

_Verlooy_
I referred only to clinical trials in trauma. There have been clinical trials in ischemia where there has been some effect of drugs. Mostly neuroprotective drugs, calcium antagonists and so on.

_Stanimirovic_
I just wanted to comment that old age per se does mean that the blood–brain barrier is leaky. There is a bulk of literature showing that the BBB opening in ischemia is a function of the length of ischemia. Depending on what you consider an opening and what kind of size exclusion you are looking at, there is literature evidence that aging might cause the blood–brain barrier leakiness for smaller molecules, whereas stroke causes BBB disruption for proteins—and then brain oedema also accompanies these changes.

_Verlooy_
That is why I started my talk by saying that if I say opening of the blood–brain barrier is leakage of a tracer and pathological fluid, which is a very rude definition, of course, especially before this audience.

_Smith_
There have been a good number of neuroprotective agents that show very promising results in various animal models but later have had difficulty when they go to the clinic. You noted some of the problems that arise. What would you recommend, then, for the best index for scientists to use in animal models for the success of an agent?

_Verlooy_
As I mentioned, I think you should look at neurons because, of course, they remain the most important cells in the brain and nervous tissue, but we are sure that the role of microglia, the role of astrocytes, is underestimated. If you can do something about those cells, they might take care of the neurons, and maybe you should not direct all attention directly to one cell type. You have to look at the other cell types and give them some help so that they can rescue the neurons. It might be an easy way, just because until now the neuron protective agents have not been that successful.

_Tsuji_
I remember that before Dr Schinkel’s group developed MDR-1 knockout mice, we developed an ischemia model which completely depleted intracellular ATP level. At that time PGP was not working, but, during ischemia, there was no damage in the tight
junctons, because the sucrose transport was not changed during the 20 min of ischemia, but one day later, there was big damage. Then, during ischemia and after, we must consider the difference.

Verlooy
There are different types of ischemia and different time schedules where neurons are dying for days after the event. That is for sure. In that respect, you could think that you could salvage the neuron by giving neuroprotective agents.

Tsuji
I would like to comment that, with 30% depletion PGP is still working. One must completely depress the ATP to completely suppress PGP function.

De Boer
What do you think about the time window that is available to treat, for example, oedema?

Verlooy
We have been discussing that. In brain trauma there is a sudden event. Then, nobody exactly knows, there is a cascade of pathogenetic mechanisms that start, and of course it would be nice to have something that can be considered to be given to the patient at the site of the accident, at that time when he is taken in the ambulance, let us say. That would be the ideal thing, but we have to try and find out which of these different mechanisms is coming first, which is really the thing that starts the cascade and then to find products that can block this action and that you should administer almost on the spot. We have been thinking about that, but I have not found the solution yet!