Acta Neurochir (2006) [Suppl] 96: 276–278
© Springer-Verlag 2006
Printed in Austria

Forebrain ischemia and the blood-cerebrospinal fluid barrier

S. R. Ennis[1] and **R. F. Keep**[1,2]

[1] Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA
[2] Department of Physiology, University of Michigan, Ann Arbor, Michigan, USA

Summary

Although the effects of cerebral ischemia on the blood-brain barrier have been extensively studied, the effects on the blood-cerebrospinal fluid barrier (BCSFB) at the choroid plexuses have received much less attention. This paper reviews evidence on the effects of cerebral ischemia on the choroid plexus, particularly focusing on the degree of blood flow reduction required to damage the lateral ventricle choroid plexuses during transient forebrain ischemia, and whether disruption of the BCSFB might affect nearby tissues.

Studies have shown that 2 common models of forebrain ischemia (4-vessel and 2-vessel with hypotension) cause damage to the lateral ventricle choroid plexus via necrosis and apoptosis. We have found that bilateral common carotid artery occlusion with hypotension causes an 87% reduction in lateral ventricle choroid plexus blood flow during ischemia and an approximate tripling of the permeability of the BCSFB to inulin after 6 hours of reperfusion. Interestingly, evidence suggests that this disruption of the BCSFB rather than disruption to the blood-brain barrier is the major cause of enhanced inulin entry into the hippocampus. The hippocampus undergoes selective delayed neuronal loss in that model of forebrain ischemia and the BCSFB disruption may participate in or modulate that delayed injury.

Keywords: Carotid artery occlusion; hypotension; stroke; choroid plexus.

Introduction

Two barrier systems serve as an interface between blood and brain. The blood-brain barrier (BBB), formed by cerebral endothelial cells and their linking tight junctions, and the blood-cerebrospinal fluid barrier (BCSFB), formed by the choroid plexus (CP) epithelial cells with their linking tight junctions and the arachnoid membrane. The effects of cerebral ischemia (focal or global) on the BBB have been extensively studied. Thus, ischemia causes BBB disruption with the extravasation of plasma proteins and vasogenic edema formation. In addition, ischemia triggers changes in the endothelium that result in the migration of leukocytes into the injured brain, contributing to inflammation and brain injury. The effects of cerebral ischemia on CP and BCSFB function has been much less studied [6], even though the early studies of Pulsinelli *et al.* [9] found that transient forebrain ischemia caused CP necrosis after 6 hours of reperfusion. This pattern of injury contrasts to nearby brain parenchyma where there is delayed cell death. We review the evidence of the effects of forebrain ischemia on the CP with a particular focus on what degree of CP ischemia is necessary to cause CP injury, and the effect of CP injury on tissues bordering the cerebrospinal fluid (CSF) system.

Forebrain ischemia-induced CP injury in rat

Pulsinelli *et al.* [9] first examined the effects of transient forebrain ischemia (bilateral carotid and vertebral artery occlusion, 4VO, with reperfusion of the carotid arteries after 10, 20, or 30 minutes) on lateral ventricle CP morphology in the rat. They found evidence of necrosis after 6 hours. Johanson *et al.* [5], using bilateral carotid occlusion (2VO) with hypotension in the rat, also found early damage to the epithelial brush border, organelles, and nucleus following reperfusion (and restoration of blood pressure) with rapid necrosis. Although there is evidence of necrosis in these models, Ferrand-Drake and Wieloch [3] have also reported evidence supporting CP apoptosis after 18–24 hours of reperfusion in the rat 2VO with hypotension model, and Kitagawa *et al.* [7] found evidence of apoptosis as a result of reperfusion after 5 minutes of 2VO in the gerbil.

We have examined the effects of ischemia on CP epithelial function by measuring CP glutamine transport, a sodium-dependent process which indirectly utilizes adenosine triphosphate. CP glutamine transport was reduced by 45% and 72% after 10 and 30 minutes of

Table 1. *Changes in blood flow during ischemia and the influx of [^3H] inulin during reperfusion in different regions of the brain [2]*

	Blood flow (ml/g/min)		Inulin K_i (μl/g/min)	
	Control	Ischemia	Control	Ischemia + reperfusion
CSF	–	–	0.15 ± 0.01	0.43 ± 0.10* (287%)
Choroid plexus	2.46 ± 0.22	0.33 ± 0.06*** (13%)	–	–
Anterior cortex	0.94 ± 0.08	0.07 ± 0.03*** (7%)	0.041 ± 0.002	0.077 ± 0.014* (188%)
Hippocampus	0.92 ± 0.05	0.19 ± 0.05*** (21%)	0.048 ± 0.002	0.16 ± 0.035** (333%)

Measurements of blood flow were made in control rats and animals subjected to 10 minutes of ischemia. Measurements of the influx rate constant (K_i) for inulin were made in control rats and animals subjected to 30 minutes of ischemia with 6 hours of reperfusion. Values are mean ± SE, n = 7–8 for the influx rate constants, and n = 4 for blood flows.
*, ** and *** indicate a difference from control at $p < 0.05$, $p < 0.01$, and $p < 0.001$ levels, respectively. Numbers in parentheses are the ischemia or ischemia with reperfusion values expressed as a % of control. *CSF* cerebrospinal fluid.

permanent 2VO with hypotension in the rat [2]. Although CP glutamine transport returned to control values if the brain was reperfused after 10 minutes of ischemia, there was a residual deficit following reperfusion after 30 minutes [2]. Dienel [1] also found a long-term derangement in CP calcium homeostasis after 30 minutes of 4VO with reperfusion in the rat.

CP blood flow during ischemia

The levels of CP blood flow required to induce injury have received little study. Ten minutes of 2VO with hypotension caused a marked reduction in blood flow to the lateral ventricle CPs in the rat (~87%; [2]). By contrast, in the brain parenchyma, there was a 93% reduction in the anterior cortex and a 79% reduction in the hippocampus (Table 1; [2]).

BCSFB disruption during reperfusion

The effects of CP injury on BCSFB function merit further investigation. Ikeda *et al.* [4] found increased blood to CSF calcium flux after 5 minutes of 2VO with reperfusion in the gerbil. In our studies, rats receiving 6 hours of reperfusion after 30 minutes of 2VO with hypotension showed a marked increase in the influx rate constant for [^{3}H] inulin entry into CSF (to ~300% of control; [2]). Those animals also showed a marked increase of entry into hippocampus and a more modest increase into anterior cortex (Table 1).

Discussion

A number of studies have now shown that the lateral ventricle CPs are damaged by forebrain ischemia (reviewed in greater detail in [6]), and a number of these papers have also shown a fairly rapid recovery in CP function following the ischemic event [6]. Although not the subject of this review, an understanding of those mechanisms may be important for understanding BBB as well as BCSFB function after a stroke.

Studies on the CP blood flows necessary to induce such injury have been few. We have found that 2VO occlusion with hypotension induces a very marked 87% reduction in lateral CP blood flow [2]. This model of ischemia has been shown to induce apoptosis and necrosis in the CP [6]. The percentage reduction in blood flow that induced CP injury is similar to that which is known to induce parenchymal damage. It should be noted, however, that because control CP blood flows are much higher than in other brain regions like cerebral cortex, the absolute blood flows (~33 ml/100 g/min) that induced CP injury would likely not induce injury in the brain parenchyma. Thus, in terms of absolute blood flows, the CP may actually be selectively vulnerable to ischemia. This is also suggested by the work of Pulsinelli *et al.* [9], who found that forebrain ischemia caused early CP injury but much later damage in the hippocampus.

The lateral ventricle CPs receive blood from both the anterior and posterior choroidal arteries. This raises the question of whether blood flows from both sources would have to be compromised (such as in a heart attack) to reach the flows necessary to cause CP injury. Recently, however, Liebeskind and Hurst [8] have reported infarction of a lateral CP following a posterior choroidal artery stroke in man.

Ischemic damage to the CP might affect parenchymal injury by a number of different mechanisms [6].

For example, the CP may produce growth factors that would normally protect periventricular tissues from ischemic damage [5]. Another mechanism by which CP damage might affect parenchymal damage is by allowing the entry of blood components into the CSF. For this to be relevant pathophysiologically, however, the entry of such compounds across the damaged BCSFB would have to be greater than across the BBB. Recent evidence from our laboratory suggests that this is the case for the hippocampus following 2VO with hypotension [2]. In that model, despite the hippocampus blood flows being less affected than those of the anterior cortex (a 79% reduction in flow vs. a 93% reduction), there was a greater uptake of inulin into hippocampus from blood than into the anterior cortex (Table 1). The likely cause of this disparity is not differences in the degree of BBB disruption within the 2 tissues, but rather differences in proximity to the CSF system. For the hippocampus, which has close proximity to the CSF system, tissue inulin entry closely followed that into CSF [2]. In contrast, for the anterior cortex, which is seldom influenced by CSF, there was no correlation between tissue inulin entry with that into CSF [2].

In conclusion, the CP may be selectively vulnerable to ischemia in terms of absolute blood flows required to induce ischemic damage. In addition, ischemia-induced disruption of the CP may impact tissues adjacent to the ventricular system and may be a major cause of increased entry of blood-borne solutes into those tissues.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (NS 34709 to RFK).

References

1. Dienel GA (1984) Regional accumulation of calcium in postischemic rat brain. J Neurochem 43: 913–925
2. Ennis SR, Keep RF (2005) The effects of cerebral ischemia on the rat choroid plexus. J Cereb Blood Flow Metab [in press]
3. Ferrand-Drake M, Wieloch T (1999) The time-course of DNA fragmentation in the choroid plexus and the CA1 region following transient global ischemia in the rat brain. The effect of intraischemic hypothermia. Neuroscience 93: 537–549
4. Ikeda J, Mies G, Nowak TS, Joo F, Klatzo I (1992) Evidence for increased calcium influx across the choroid plexus following brief ischemia of gerbil brain. Neurosci Lett 142: 257–259
5. Johanson CE, Palm DE, Primiano MJ, McMillan PN, Chan P, Knuckey NW, Stopa EG (2000) Choroid plexus recovery after transient forebrain ischemia: role of growth factors and other repair mechanisms. Cell Mol Neurobiol 20: 197–216
6. Keep RF, Xiang J, Ennis SR (2005) The blood-CSF barrier and cerebral ischemia. In: Zheng W, Chodobski A (eds) The blood-cerebrospinal fluid barrier. Taylor & Francis, Boca Raton, pp 245–260
7. Kitagawa H, Setoguchi Y, Fukuchi Y, Mitsumoto Y, Koga N, Mori T, Abe K (1998) DNA fragmentation and HSP72 gene expression by adenovirus-mediated gene transfer in postischemic gerbil hippocampus and ventricle. Metab Brain Dis 13: 211–223
8. Liebeskind DS, Hurst RW (2004) Infarction of the choroid plexus. AJNR Am J Neuroradiol 25: 289–290
9. Pulsinelli WA, Brierley JB, Plum F (1982) Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann Neurol 11: 491–498

Correspondence: Richard F. Keep, Department of Neurosurgery, University of Michigan, R5550 Kresge I, Ann Arbor, Michigan 48109-0532, USA. e-mail: rkeep@umich.edu