Neuropharmacology 134 (2018) 280–292

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The cerebral collateral circulation: Relevance to pathophysiology and treatment of stroke

Myron D. Ginsberg

Department of Neurology, University of Miami Miller School of Medicine, Clinical Research Center, Room 1331, 1120 NW 14th Street, Miami, FL 33136, USA

ARTICLE INFO

Article history:
Received 30 June 2017
Received in revised form
28 July 2017
Accepted 6 August 2017
Available online 9 August 2017

Keywords:
Collateral circulation
Acute ischemic stroke
Cerebral ischemia
Thrombolysis
Endovascular intervention
Reperfusion
Therapy
Neuroimaging
Inhaled nitric oxide
Albumin

ABSTRACT

The brain's collateral circulation consists of arterial anastomotic channels capable of providing nutrient perfusion to brain regions whose normal sources of flow have become compromised, as occurs in acute ischemic stroke. Modern CT-based neuroimaging is capable of providing detailed information as to collateral extent and sufficiency and is complemented by magnetic resonance-based methods. In the present era of standard-of-care IV thrombolysis for acute ischemic stroke, and following the recent therapeutic successes of randomized clinical trials of acute endovascular intervention, the sufficiency of the collateral circulation has been convincingly established as a key factor influencing the likelihood of successful reperfusion and favorable clinical outcome. This article reviews the features of the brain's collateral circulation; methods for its evaluation in the acute clinical setting; the relevance of collateral circulation to prognosis in acute ischemic stroke; the specific insights into the collateral circulation learned from recent trials of endovascular intervention; and the major influence of genetic factors. Finally, we emphasize the need to develop therapeutic approaches to augment collateral perfusion as an adjunctive strategy to be employed along with, or prior to, thrombolysis and endovascular interventions, and we highlight the possible potential of inhaled nitric oxide, albumin, and other approaches.

This article is part of the Special Issue entitled 'Cerebral Ischemia'.

Contents

E-mail address: mginsberg@med.miami.edu.

https://doi.org/10.1016/j.neuropharm.2017.08.003
0028-3908/

Abbreviations

ALB	(High-dose) albumin
ASL	Arterial spin labeling
ASITN/SIR	American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology
ASPECTS	Alberta Stroke Program Early CT Score
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CI	Confidence interval
CTA	Computed tomographic angiography
CTP	Computed tomographic perfusion
DWI	Diffusion-weighted imaging; ED Emergency Department
eNOS	Endothelial nitric oxide synthase
FLAIR	Fluid-attenuated inversion recovery
iNO	Inhaled nitric oxide
IV	Intravenous
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRP	Magnetic resonance perfusion
MTT	Mean transit time
mTICI	Modified Treatment in Cerebral Ischemia (scale)
NO	Nitric oxide
OR	Odds ratio
sICH	Symptomatic intracerebral hemorrhage
Tmax	Time of maximal intensity
TNF-alpha	Tissue necrosis factor - alpha
TOF	Time-of-flight
tPA	Tissue-type plasminogen activator
VEGF	Vascular endothelial growth factor

1. Introduction

The collateral circulation of the brain may be defined as the artery-to-artery anastomotic pathways that are capable, when needed, of supplying nutrient perfusion to a brain region whose primary source of blood flow has been reduced or compromised by disease. While the anatomic features of the brain's collateral vascular pathways were described long ago, the potential importance of these channels has become fully apparent only recently as randomized clinical trials of therapies to restore perfusion in patients with acute ischemic stroke via intravenous thrombolysis and endovascular interventions have established that successful reperfusion is closely tied to collateral status. In addition, basic investigations in genetically varied mouse strains have characterized the major genetic determinants of collateral development; and a variety of pharmacological and non-pharmacological approaches have been explored for enhancing collateral perfusion as a potential adjunctive therapeutic modality for acute ischemic stroke.

2. Characteristics of the brain's collateral circulation

Three anatomic components of the cerebral collateral circulation may be distinguished. The first is the circle of Willis — the anastomotic arterial circle at the base of the brain that interconnects its anterior (internal carotid-middle cerebral-anterior cerebral arteries) and posterior (vertebrobasilar) arterial supplies. Substantial variability exists in the size and degree of completeness of the circle in normal subjects. In one study, the anterior portion was complete in only 68% of patients, the posterior portion in 47%, and the entire circle in only 36% (Hartkamp et al., 1999). In another large survey of patients with noncardiac ischemic strokes, MR angiography (MRA) revealed a complete circle of Willis (type I) in only 25% of cases; an incomplete anterior half (type II) in 57%; an incomplete posterior half (type III) in 3%; and incomplete anterior and posterior portions (type IV) in 15% (Zhou et al., 2016) (Fig. 1). Stroke severity on admission and discharge were lowest in type I compared to types II and IV, and a complete (type I) circle was a significant predictor of favorably recovery. A sophisticated mathematical modeling study has shown that the communicating arteries of the circle of Willis become more important in providing collateral flow under conditions of common carotid artery (rather than MCA) occlusion (Ryu et al., 2015).

The brain's secondary collateral pathways consist of intracranial leptomeningeal anastomoses between the distal segments of the anterior, middle, and posterior cerebral arteries as well as between the posterior cerebral and major cerebellar arteries; and anastomoses between branches of the *external* carotid artery (e.g., facial, maxillary, middle meningeal and occipital arteries) and those of the internal carotid artery (e.g., ophthalmic artery) (Liebeskind, 2003; Ginsberg, 2016).

Early angiographic and blood-flow studies in patients with small, deep infarcts that spared the overlying cortex first identified the latter zone as lying within the *ischemic penumbra* — a non-infarcted but functionally suppressed region of delayed arterial filling and diminished cerebral perfusion supplied by collateral channels (Olsen et al., 1983). (The concept of the ischemic penumbra is fully reviewed in this issue and elsewhere (Hakim, 1987; Hossmann, 1994; Heiss, 2011; Ginsberg, 2016)). Laboratory studies in animals with arterial occlusion have shown that collaterally perfused tissue is especially vulnerable to hypoperfusion during induced hypotension (Muhonen et al., 1992) and that the pace of metabolic deterioration of collaterally perfused ischemic tissue is inversely related to the amount of residual blood flow (Sakoh et al., 2000). Studies using laser speckle contrast imaging and other methods to characterize the spatiotemporal features of collateral perfusion have shown it to be highly dynamic following vascular occlusion, with the immediate appearance of collaterals in zones of sub-critical perfusion (Wang et al., 2012b), probably triggered by pressure gradients between arterial fields (Romero et al., 2009); the variable persistence of collaterals over time (Wang et al., 2012b); and the cessation of collateral flow after spontaneous reperfusion (Armitage et al., 2010). Small cortical arterioles (diameter 50–250 μm) appear to be the vessels primarily responsible for modulating vascular resistance (Meyer and Denny-Brown, 1957).

3. Methods to evaluate the collateral circulation

3.1. Digital subtraction angiography

Among available methods for visualizing the brain's collateral circulation, conventional *digital subtraction angiography* is regarded as the reference standard in that it provides direct, high-resolution, time-resolved images of the arterial, capillary, and venous phases of the cerebral circulation in the course of angiographic contrast injection of a major feeding artery (e.g., common carotid, vertebrobasilar) (Bang et al., 2015; Raymond and Schaefer, 2017). Its disadvantages, however, are that it is invasive and time-consuming