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Review article

Expanding the concept of neuroprotection for acute ischemic stroke: The pivotal roles of reperfusion and the collateral circulation

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ABSTRACT

This review surveys the efforts taken to achieve clinically efficacious protection of the ischemic brain and underscores the necessity of expanding our purview to include the essential role of cerebral perfusion and the collateral circulation. We consider the development of quantitative strategies to measure cerebral perfusion at the regional and local levels and the application of these methods to elucidate flow-related thresholds of ischemic viability and to characterize the ischemic penumbra. We stress that the modern concept of neuroprotection must consider perfusion, the necessary substrate upon which ischemic brain survival depends. We survey the major mechanistic approaches to neuroprotection and review clinical neuroprotection trials, focusing on those phase 3 multicenter clinical trials for acute ischemic stroke that have been completed or terminated. We review the evolution of thrombolytic therapies; consider the lessons learned from the initial, negative multicenter trials of endovascular therapy; and emphasize the highly successful positive trials that have finally established a clinical role for endovascular clot removal. As these studies point to the brain's collateral circulation as key to successful reperfusion, we next review the anatomy and pathophysiology of collateral perfusion as it relates to ischemic infarction, as well as the molecular and genetic influences on collateral development. We discuss the current MR and CT-based diagnostic methods for assessing the collateral circulation and the prognostic significance of collaterals in ischemic stroke, and we consider past and possible future therapeutic directions.

Contents

Abbreviations: ALB, high-dose albumin therapy; CBF, cerebral blood flow; rCBF, regional cerebral blood flow; lCBF, local cerebral blood flow; CBV, cerebral blood volume; CI, confidence interval; CT, computed tomography; CTA, computed tomographic angiography; CTP, computed tomographic perfusion; DSMB, Data Safety and Monitoring Board; DWI, diffusion-weighted magnetic resonance imaging; EEG, electroencephalogram; eNOS, endothelial nitric oxide synthase; IA, intra-arterial; ICH, intracerebral hemorrhage; ICA, internal carotid artery; MCA, middle cerebral artery; MR(I), magnetic resonance (imaging); mRS, modified Rankin Scale score; mTICI, modified Treatment in Cerebral Ischemia scale; MTT, mean transit time; NIHSS, National Institutes of Health Stroke Scale score; NO, nitric oxide; iNO, inhaled nitric oxide; OR, odds ratio; PET, positron emission tomography; tPA, recombinant tissue plasminogen activator, alteplase.

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"Thought arising from factual experience may be a bridle or a spur." Winston Churchill, *Closing the Ring*

1. Introduction

The overall intent of this article is to provide a comprehensive review of the scientific efforts that have been undertaken to achieve clinically efficacious protection of the ischemic brain. Our key point of emphasis is that cerebral perfusion plays a central role in attaining this goal. Thus, we begin by considering the development of quantitative strategies to measure cerebral perfusion at the regional and local levels and the application of these methods to elucidate flow-related thresholds of ischemic viability as a function of the severity and duration of ischemia. From these considerations, the ischemic penumbra and its sensitivity to small decrements in cerebral perfusion emerge as concepts central to the pathophysiology of ischemic neuroprotection. Accordingly, we underscore that the modern concept of neuroprotection must necessarily incorporate a consideration of cerebral perfusion, which constitutes the obligatory substrate upon which ischemic brain survival depends. In surveying the major mechanistic approaches to neuroprotection that have been subjected to clinical investigation, we comprehensively review the multitude of completed or terminated phase 3 clinical trials for acute ischemic stroke, emphasizing those whose results appear to be the most instructive (citicoline, uric acid, NXY-059, high-dose albumin, and magnesium sulfate). We next review the evolution of thrombolytic therapies by considering the lessons learned from the initial, negative multicenter trials of endovascular therapy and how they pointed to the role of the collateral circulation in influencing outcome. We then describe the remarkable advance in the therapy of acute ischemic stroke provided by the five highly successful positive clinical trials published in 2015 that, together, definitely established a role for endovascular clot removal. As these studies point to the key role of the brain's collateral circulation in achieving successful reperfusion, we provide a detailed review of the anatomy and pathophysiology of collateral perfusion as it relates to ischemic infarction, as well as the molecular and genetic influences on collateral development. We discuss the current MR and CT-based diagnostic methods for assessing the collateral circulation and the prognostic significance of collaterals in ischemic stroke, pointing to the possible therapeutic benefit of collateral augmentation; and we stress the need to define the time course of collateral enhancement in relation to therapeutic benefit or harm. Finally, we consider past and possible future therapeutic directions.

2. Historical background

2.1. The evolving awareness of the relevance of regional cerebral perfusion to the consequences of ischemic stroke

The modern era of cerebral blood flow (CBF) measurement dates from the pioneering studies of Kety and Schmidt in the mid-1940s, who established a quantitative technique for determining whole-brain CBF and oxygen consumption by utilizing the inert diffusible gas, nitrous oxide, and applying the Fick principle (which had been established decades earlier to measure cardiac output (Fick, 1870; Kety and Schmidt, 1948b)). This method was soon applied to characterize CBF in physiological states as well as in a variety of clinical conditions (for example, (Kety et al., 1948; Kety and Schmidt, 1948a)). Subsequently, methods were developed by which blood flow to distinct (albeit often ill-defined) brain regions could be quantified in humans by the external monitoring of the cerebral clearance curves of administered radiotracers (*regional* cerebral blood flow, rCBF) (Lassen et al., 1963; Ingvar and Lassen, 1965). In experimental animals, the development of autoradiographic methods enabled the precise determination of CBF at a single time-point within multiple anatomically distinct tissue loci (*local* cerebral blood flow, lCBF) via the direct assay of radiotracer concentrations within discrete brain structures (Landau et al., 1955; Sakurada et al., 1978). Analogously, Sokoloff and colleagues developed and validated a sophisticated and powerful autoradiographic strategy for quantifying local cerebral glucose utilization in the brain (Sokoloff et al., 1977). Finally, with the advent of positron emission tomography, "in vivo autoradiography" became possible in humans: regional brain blood flow, oxygen consumption and glucose utilization could now be studied in the living brain (Phelps et al., 1982; Raichle, 1998).

Enabled by the above methodological innovations, clinical investigators in the late 1960s and early 1970s had the tools needed to begin to explore regional CBF alterations in human conditions such as hypertension, stroke, and carotid endarterectomy (Meyer et al., 1967, 1970; Boysen, 1971). At the same time, experimentalists conducted related studies in animals with focal ischemic stroke. The early studies of Crowell, Morawetz and colleagues are particularly instructive in this regard: In unanesthetized monkeys