

## Cerebral Angiogenesis: A Realistic Therapy for Ischemic Disease?

David A. Greenberg

### Abstract

Angiogenesis, the sprouting of new capillaries from existing blood vessels, accompanies clinical and experimental stroke and is focused particularly in the salvageable ischemic border zone. As this endogenous angiogenic response correlates positively with clinical prognosis, a more complete understanding of the underlying molecular mechanisms and timing of these events may help in the design of novel therapies for vascular regeneration after stroke. In this review we discuss endogenous protective mechanisms, including angiogenesis and vasculogenesis, and underlying molecular mechanisms. We also consider the feasibility of angiogenic therapy for stroke and its optimal timing.

**Key words** Angiogenesis, Arteriogenesis, Collaterals, Endothelial progenitor cells, Ischemia, Stroke, Thrombolytics, Vasculogenesis, Vascular endothelial growth factor

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### 1 Introduction

Angiogenesis, the sprouting of new capillaries from existing blood vessels, typically in response to hypoxia, is an integral feature of physiological (e.g., development) and pathological (e.g., cancer) processes [1]. Angiogenesis also accompanies clinical [2] and experimental [3] stroke, wherein the expression of angiogenic factors is induced within hours and new capillaries are formed within days of the onset of ischemia [3, 4]. Although angiogenesis in this setting is focused in the salvageable ischemic border zone and correlates with prognosis [5], the precise relationship between angiogenesis and outcome from stroke is uncertain. Unsettled in particular are whether this relationship is causal and, if so, what mechanisms are responsible.

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## 2 Endogenous Mechanisms of Improving Blood Flow to Ischemic Brain Tissue

Several scenarios have the potential for improving blood flow to ischemic brain tissue. Immediately upon the establishment of a pressure differential between normally perfused and occluded arteries, flow occurs through preexisting collateral channels, such as the leptomeningeal anastomoses connecting the anterior, middle, and posterior cerebral arteries [6]. These collaterals may then enlarge over time to support increased flow through a process termed arteriogenesis which, like the initiation of collateral flow, is pressure—rather than hypoxia—driven [7]. Collateral blood flow to ischemic brain regions is associated with reduced stroke risk [8] and improved outcome [9], and also with a better response to thrombolytic therapy [10], perhaps due to enhanced access of thrombolytics to the target thrombus through collateral channels. Because the onset of collateral flow is virtually instantaneous in ischemia, it is easy to imagine how this process could salvage tissue and prevent or reduce neurological deficits.

Vasculogenesis, defined as the *de novo* generation of blood vessels from progenitor cells, is usually associated with development, but may also occur postnatally [11]. Endothelial progenitor cells in blood-forming or local tissues appear to be mobilized by ischemia and may contribute, directly or indirectly, to vessel repair and growth following stroke [12]. Some studies suggest that this process might help promote a more favorable clinical outcome [13]. However, vasculogenesis is unlikely to occur quickly enough to prevent tissue damage from acute cerebral ischemia.

The role of spontaneous or therapeutically induced angiogenesis in recovery from stroke is also unclear, partly because of the delay involved in constructing new, functional vessels. Moreover, demonstrating a functional benefit of angiogenesis would require that angiogenesis be selectively ablated or stimulated, and the consequences observed, but such selectivity is difficult to achieve. For example, angiogenic stimuli like hypoxia, growth factors, and cell transplants can trigger additional, potentially protective or restorative processes, such as neurogenesis, gliogenesis, and trophic effects.

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## 3 Potential Mechanisms of Angiogenic Protection Following Ischemic Stroke

At least three potential mechanisms have been invoked as possible bases for the salutary effects of angiogenesis in stroke [14]. One possibility is that angiogenesis protects against the acute effects of cerebral ischemia by enhancing cell survival, but this is difficult to reconcile with the observation that ischemic cell death proceeds much more rapidly than angiogenesis. On the other hand, angiogenic

factors induced by brain ischemia have acute cytoprotective effects that are evident well before the appearance of new vessels [15], so in this sense angiogenesis could be viewed as acutely protective. Another way in which angiogenesis might afford protection from ischemia is in the setting of recurrent transient ischemic attacks. Thus, ischemia-induced angiogenesis might contribute to ischemic preconditioning leading to ischemic tolerance, as proposed for exercise-induced tolerance [16].

Another theory, the clean-up hypothesis [17, 18], posits that angiogenesis contributes to recovery from stroke by providing macrophages with access to necrotic brain tissue and thereby facilitating its removal. Supportive evidence includes the transiency of many vessels induced by ischemia and their extension into the ischemic core.

Finally, angiogenesis may be an important factor in the regeneration of brain tissue after stroke. First, any regenerated tissue presumably requires a new vascular supply. Second, angiogenesis is thought to provide a niche for the proliferation of new neurons (neurogenesis) and their migration to sites of ischemic brain injury [19]. Third, as noted in relation to acute neuroprotection, signaling by angiogenic factors may have non-angiogenic effects that promote recovery. For example, vascular endothelial growth factor (VEGF-A) [20] and its principal angiogenesis-related receptor (VEGFR-2) [21] are induced at remote sites of brain plasticity after experimental stroke in primates.

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## 4 Potential Clinical Use of Angiogenic Therapy

Is cerebral angiogenesis a realistic therapy for ischemic disease? Probably not, in the sense that angiogenesis is unlikely to be inducible quickly enough at the onset of ischemia to protect brain cells from acute ischemic death. However, if the definition of angiogenic therapy is extended to include treatment with drugs or cells that are angiogenic but also have other (e.g., neuroprotective or neuroregenerative) effects, then preclinical studies suggest that this approach may be effective [22, 23]. Purely angiogenic treatments could also be effective if administered preemptively, such as for recurrent transient ischemic attacks, where cerebral ischemia can be anticipated for at least several days before its occurrence. This presupposes that the cause of ischemia in a particular situation is amenable to correction by an increase in capillary flow, which may or may not be the case. Selective therapeutic enhancement of angiogenesis might also contribute to brain repair after stroke, if this involves processes, like neurogenesis, that depend on a vascular niche, or if regenerating tissue outgrows the existing blood supply. In each instance, an underlying assumption is that postischemic induction of angiogenesis by endogenous factors is not already optimal.

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