Mechanisms of Ischemic Brain Injury

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Introduction
Stroke remains the third leading cause of death and the leading cause of long-term disability in the United States. Approximately 80% of all strokes are ischemic and there are limited therapies approved for the treatment of acute ischemic stroke. Understanding the mechanisms of ischemic brain damage is necessary for the development of innovative treatment strategies. In this review, we discuss the hemodynamic and molecular mechanisms of ischemic brain damage and the potential therapeutic strategies, including reperfusion and primary and secondary neuroprotection, and strategies for recovery of function, such as neural plasticity and stem cell transplantation. The effective treatment of ischemic stroke is likely to result from a combination of therapeutic modalities aimed at different mechanisms of ischemic brain damage and delivered at specific times after acute cerebral ischemia.

Regional Cerebral Blood Flow and Cerebral Metabolism in Cerebral Ischemia
Ischemic core and ischemic penumbra
Cerebral ischemia due to occlusion of a major cerebral artery results in immediate decrease of regional cerebral blood flow (rCBF) to the territory supplied by that artery. The flow reduction is not homogenous throughout the ischemic territory but is maximal at its center, and this region is called the ischemic core. The region surrounding the ischemic core, in which the decrease in rCBF is less severe, is called the ischemic penumbra. Collateral blood flow from adjacent nonischemic areas account for the relative maintenance of rCBF in the ischemic penumbra [4]. Using positron emission tomography (PET) studies, the ischemic core can be defined as the region of severe ischemia (< 7 mL/100 g/min), and the ischemic penumbra can be defined as the region of moderate ischemia (7–17 mL/100 g/min) [5].

Mechanisms of ischemic brain damage are generally triggered when the severity and duration of ischemia are adequate to cause ischemic depolarization of the neuronal plasma membrane [3]. Ischemic depolarization usually occurs when the rCBF is less than 10 mL/100 g per minute [6]. Experimental studies have shown that reperfusion of the core within 1 hour of focal ischemia onset can result in neuronal salvage [7]. On the other hand, PET studies have shown that ischemic penumbra can be detected up to 24 hours after stroke onset, suggesting the theoretic benefit of reperfusion up to 24 hours, although the expected benefit decreases substantially after 3 hours [5].

Strategies for reperfusion
The duration of ischemia is clearly a critical determinant of subsequent brain damage [5,7]. Reperfusion therapy is aimed at improving rCBF to the ischemic region, thus limiting the size of the acute infarction. Therefore, early reperfusion is the first and foremost therapeutic goal in acute stroke therapy.

Intravenous thrombolytic therapy
Thrombolysis can re-establish rCBF by dissolving intraluminal clots and recanalizing acutely occluded arteries. The National Institute of Neurological Disorders and Stroke rt-PA (alteplase) Stroke Study, a multicenter, randomized, double-blinded, placebo-controlled study in 624 patients, showed that selected acute stroke patients who received IV rt-PA within 3 hours of symptom onset had a significant clinical improvement at 3 months [8••]. The US Food and Drug Administration approved IV rt-PA in June 1996 [2].

Mechanisms of Ischemic Brain Damage and Potential Therapeutic Strategies
In this review, we discuss the various hemodynamic and molecular mechanisms of ischemic brain damage, along with potential therapeutic strategies. A schematic representation of the various mechanisms of ischemic brain damage is shown in Figure 1.
Intra-arterial thrombolytic therapy

Majority of patients with acute ischemic stroke present to the hospital after 3 hours of symptom onset. Intra-arterial (IA) thrombolysis may serve as an alternative or adjunct to IV rt-PA and has the theoretic advantage of delivering the drug directly to the clot and thereby minimizing potential systemic complications [2]. The Prolyse in Acute Cerebral Thromboembolism II study [9•] was a randomized, controlled, multicenter, open-label clinical trial of 180 patients with blinded follow-up that evaluated the efficacy of IA recombinant pro-urokinase (r-proUK) in patients with acute ischemic stroke of less than 6 hours duration caused by middle cerebral artery occlusion and showed that treatment with IA r-proUK significantly improved clinical outcome at 90 days. However, the limitations include an increased risk of symptomatic intracranial hemorrhage, and failure of arterial recanalization in around one third of the patients. Newer third-generation thrombolytics such as tenecteplase and reteplase have longer half lives, greater penetration into the thrombus matrix, and could potentially improve recanalization rates [10].

Intra-arterial mechanical clot disruption or removal

Intravenous and IA thrombolytic therapies tend to be limited by 3- and 6-hour time windows, respectively. In addition,