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Reperfusion injury in brain stroke

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ABSTRACT

The occlusion of a cerebral artery by a thrombus accounts for about 80% of strokes. Reperfusion can save hypoperfused brain tissue from early cerebral blood flow restoration (CBF), thus limiting neurological impairment. The most successful treatments for stroke care have proven to be reperfusion techniques. One of the key drawbacks of these treatment methods is that early ischemic brain tissue reperfusion can lead to adverse effects, including blood-brain barrier breakdown, which can lead to cerebral oedema, haemorrhage of the brain, or both. Haemorrhages are especially devastating after reperfusion and are associated with exceptionally high morbidity and mortality. Fear of haemorrhage-related reperfusion greatly restricts the use of stroke therapies. Reperfusion injury, a mechanism that further damages brain cells, the ischemic arterial wall, and the microvasculature, is due to the deleterious effects of early restoration of cerebral blood flow following stroke. It seems clear that the brain will benefit from therapies to restore CBF to an ischemic region. The brain's reliance on normal CBF levels is underlined by the sensitivity of the brain to relatively short ischaemic cycles. Experimental and clinical data, however, suggests that tissue damage can be aggravated by organ reperfusion. [1] Studies have failed to prove that infarct size is increased by reperfusion. Reperfusion can aggravate the formation of oedema and lead to abnormal blood flow patterns and microvascular lesions within the reperfused areas.

Keywords
reperfusion injury,
brain stroke,
neurosurgery

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FOCAL CEREBRAL ISCHEMIA – REPERFUSION INJURY

It is characterized by a thick infarction center surrounded by a peripheral zone of penumbra-called potentially viable tissues. [2] This is a crucial region for the dissemination of ischemic lesions. Ischemia-reperfusion induces a cascade of molecular events that cause neuronal death that range from immediately to several days later in time. [3] Two different mechanisms of cell death are displayed by post-ischemic neurons: necrosis and apoptosis. During ischemia-reperfusion injury, several events occur, including Ca21-induced protease activation, glutamate toxicity, free radical development, receptor-mediated death signals, and altered pro-apoptotic and anti-apoptotic protein expression, eventually triggering the morphological result that can be either necrosis or apoptosis. [4] Apoptosis is spread predominantly in the penumbra. In focal or incomplete cerebral ischemia, propofol has

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been shown to be effective in preventing cerebral injury. [5] But the propofol therapeutic window was not well explored.

In focal cerebral ischemia, infarction in the reperfused brain can extend into the peripheral region, and the degree of this expansion may be due to the penumbra cell outcome. [5] The acute penumbra is evanescent and deteriorates steadily, ultimately subsuming within the ischaemic heart. [2] The co-existence of apoptosis and necrosis indicates the pathological result of focal cerebral ischemia-reperfusion damage.

Reperfusion-related brain injury and melatonin

Melatonin is an interesting compound that, among other tissues in mammals, is mainly synthesized in the pineal gland. In response to environmental light-dark cycles, its secretion, primarily at night, is regulated circadically by the suprachiasmatic nucleus, and has been associated with several significant physiological phenomena that have been attributed to the timing of pineal melatonin secretion. [6] In addition to its related physiological functions, it is recognized that melatonin performs direct and indirect antioxidant activities both at physiological and endogenous concentrations and at concentrations exceeding physiological levels by many orders of magnitude. It is understood that overproduction of free radicals during cerebral ischemia and reperfusion leads to functional dysfunction and neuronal death, among other pathophysiologic mechanisms. As a consequence, in view of its antioxidant activities compared to the detrimental cellular actions of free radicals, attention was given to melatonin as a neuroprotective medication against ischemia/reperfusion brain injury. The key causes of permanent brain injury and damage are focal cerebral ischemia induced by thromboembolic occlusion of the major cerebral artery, often the middle cerebral artery, as well as global cerebral ischemia caused by cardiac arrest, extreme hypotension, or significant hemorrhage, leading to temporary or permanent interruption or decrease of blood flow in particular brain structures or the entire brain. [8] As a consequence of its specific biochemical features, the brain is particularly susceptible to oxidative damage. [9] Chemical substrates for further increasing cellular changes, neuronal death and neurological deficits can also include reperfusion and reoxygenation of the ischaemic tissue, which must be restored within minutes in an attempt to avoid serious neurological damage and facilitate the survival of individuals. [10]

NLRP3 and ROS in reperfusion Injury of the brain

It is well known that the brain damage initially caused by ischemia can be aggravated by reperfusion, causing an I/R injury. [11] Inflammation and oxidative stress are involved in the pathogenesis of brain I/R among the different underlying mechanisms of stroke, and adequate inflammatory level control can play a critical role in the prevention and treatment of stroke. [12] The role of inflammasomes, especially NLRP3, in postischemic inflammation after stroke has been recognized in recent years. Since inflammation is triggered by the inflammasome, NLRP3 inflammasome modulation can regulate the inflammatory response. However, from a molecular point of view, a number of molecular signalling systems in the I/R brain can activate the NLRP3 inflammasome pathway and several mechanisms have not yet been completely identified. Specifically, this cytokine is produced by macrophages or microglial cells during central nervous system disease or after brain injury [14], and molecular mediators such as mitochondrial ROS and lysosomal protease cathepsin B are essential for the development of interleukin-1β by microglial cells [14].

Reperfusion Injury treatments

In the post-ischemic environment, many pharmacological agents often protect the brain when given. (S)-emopamil, a novel blocker of the calcium channel and antagonist of serotonin S2, reduces infarct size when administered after permanent and temporary occlusion of MCA. Blocking of amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors by the 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline (NBQX) blocker, a selective antagonist for the excitatory amino acid receptor subtype AMPA/kainate, has also been shown to protect both global and focal ischemia histopathologically. Most recently, when given after the first provocation, the non-competitive N-methyl-D-aspartate (NMDA) antagonist MK-801 protected the brain from the cumulative effects of repeated brief ischemic episodes. Ischemia-induced calcium ion treatment techniques and neurotransmitter disturbances are critical areas for ongoing study. In

the pathogenesis of reperfusion injury, several studies have implicated oxygen radicals. [13]

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