Neonatal Organ Damage due to Ischemia Reperfusion

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Ischemia or hypoxia results in cell death and tissue damage as a function of time and severity of the insult. Restoration of blood flow or oxygen delivery is necessary for organ survival, but it is also critical because damage may be amplified during this period. For example, if the superior mesenteric artery of a cat is clamped for 3 h and then reperfused for 1 h, mucosal damage is more severe than after 4 h of ischemia without reperfusion [1]. If reperfusion is carried out with deoxygenated blood, no further damage occurs beyond that observed after 3 h of ischemia. This study shows that restoration of oxygen supply is more detrimental than restoration of circulation and suggests a role for reactive oxygen metabolites (ROM) in the pathogenesis. Other studies have supported the basic concept and the role of ROM [2].

Bradycardia and hypotension are essential features of perinatal asphyxia. It thus represents global ischemia, which is followed by reperfusion upon resuscitation. In the context of reperfusion injury, the two important sources of ROM are xanthine oxidoreductase (XOR) and granulocytes. XOR catalyzes the last two steps of purine catabolism in man, oxidation of hypoxanthine to xanthine and on to uric acid [3]. Under physiological conditions, it exists mainly as dehydrogenase, uses NAD⁺ as the electron acceptor, and generates no ROM. In ischemic tissue xanthine dehydrogenase can be converted into xanthine oxidase (XO), which utilizes molecular oxygen and produces O[•] and HO[•]. Also during ischemia, ATP is catabolized and hypoxanthine accumulates. During reperfusion O₂ is introduced and the stage is set for production of ROM. Evidence for the role of XOR in reperfusion injury is mainly indirect, based on prevention of organ damage in animal models with XOR inhibitors (allopurinol, oxipurinol, tungsten). Hundreds of such studies have been reported that are relevant to reperfusion damage of the heart, intestine, kidney, liver, lung, and brain. In normal adults, XOR activity is high in liver and intestine, low in kidney and undetectable in other organs. This is in accordance with our findings of immunoreactive XOR in fetal and neonatal organs [4]. XOR activity decreases in human intestine but increases in liver during fetal development. In ischemic organs, the conversion of xanthine dehydrogenase to XO was thought to occur within minutes, but the time scale has turned out to be too slow to account for the burst of radical production and the rapid onset of postischemic damage [3]. However, a minimum of 10-15% of total XOR activity is always in the XO form, which may be sufficient to account for the damage. Immunolocalization studies have shown XOR mainly in capillary endothelial cells [5]. Thus, even if in whole tissue homogenates enzyme activity is unmeasurably low, XOR may be relevant,

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since capillary damage and increased permeability are important in the pathogenesis of reperfusion injury.

In ischemic and reperfused tissue, neutrophils adhere to the endothelium, extravasate through the vessel wall, and accumulate in the interstitium [6]. They are activated by inflammatory mediators released during ischemia and produce mainly superoxide. The role of neutrophils is supported by attenuation of reperfusion damage to the heart and intestine by granulocyte depletion [7]. Similar protection is obtained by blocking neutrophil adhesion to the endothelium with antibodies to either neutrophil or endothelial cell adhesion molecules [7].

The brain is the most important but not the only organ at risk for damage after perinatal asphyxia. By analogy with animal studies on intestinal and renal ischemic injury, and human studies on renal transplantation, the type of injury sustained is determined by the severity and duration of ischemia [8]. After short-term ischemia, reperfusion is the main cause and apoptosis the main mechanism of organ damage, but direct ischemic injury and cell necrosis become dominant as a function

of ischemia time. In between there is, at least in theory, a 'therapeutic window' for potential intervention [8].

Both indirect and direct electron paramagnetic resonance measurements have indicated that ROM are formed in the first minutes of reperfusion after cerebral ischemia [9]. Some of these may arise in brain parenchyma, since increased amounts are recovered by micro-dialysis from the striatum. However, the main site of their generation appears to be the endothelial cell. Reduction of their formation by oxipurinol [9] implicates XO as one source, and a similar effect of indomethacin suggests prostanoïd synthesis as another. Free radicals are probably the cause of endothelial damage, increased permeability, and brain edema following asphyxia.

Current hypotheses ascribe neuronal death after hypoxia-ischemia to excitotoxicity, triggered by synaptic release of glutamate and followed by influx of Ca^{2+} through NMDA receptor-associated channels. ROM may be directly involved in glutamate release and/or clearance, and superoxide production has been demonstrated after exposure of cultured cerebellar granule cells to NMDA [10].

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Extended Abstracts

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