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SPECIAL ARTICLE

Oxidative stress in perinatal asphyxia and hypoxic-ischaemic encephalopathy☆

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Abstract Birth asphyxia is one of the principal causes of early neonatal death. In survivors it may evolve to hypoxic-ischaemic encephalopathy and major long-term neurological morbidity. Prolonged and intense asphyxia will lead to energy exhaustion in tissues exclusively dependent on aerobic metabolism, such as the central nervous system. Energy deficit leads to ATP-dependent pumps blockage, with the subsequent loss of neuronal transmembrane potential. The most sensitive areas of the brain will die due to necrosis. In more resistant areas, neuronal hyper-excitability, massive entrance of ionic calcium, activation of NO-synthase, free radical generation, and alteration in mitochondrial metabolism will lead to a secondary energy

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[1] Appendix A lists the co-researchers in the clinical trial.

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failure and programmed neuronal death by means of the activation of the caspase pathways. A third phase has recently been described that includes persistent inflammation and epigenetic changes that would lead to a blockage of oligodendrocyte maturation, alteration of neurogenesis, axonal maturation, and synaptogenesis. In this scenario, oxidative stress plays a critical role causing direct damage to the central nervous system and activating metabolic cascades leading to apoptosis and inflammation. Moderate whole body hypothermia to preserve energy stores and to reduce the formation of oxygen reactive species attenuates the mechanisms that lead to the amplification of cerebral damage upon resuscitation. The combination of hypothermia with coadjuvant therapies may contribute to improve the prognosis.
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PALABRAS CLAVE
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Estrés oxidativo en la asfixia perinatal y la encefalopatía hipóxico-isquémica

Resumen La asfixia intraparto es una de las causas más frecuentes de muerte neonatal precoz pero también puede, en los supervivientes, evolucionar a una encefalopatía hipóxico-isquémica responsable de una elevada morbilidad neurológica. La presencia de episodios de hipoxia-isquemia prolongados conduce a un rápido agotamiento energético en los tejidos exclusivamente dependientes del metabolismo aeróbico, como el sistema nervioso central. El déficit energético conlleva una paralización de las bombas ATP-dependientes y subsiguiente pérdida del potencial neuronal transmembrana. La población neuronal de las regiones más sensibles del SNC mueren por necrosis, mientras que en otras áreas se produce una hiperexcitabilidad neuronal con entrada masiva de calcio iónico, activación de NO-sintasa, generación de radicales libres que alteran el funcionamiento mitocondrial, provocando un fallo energético secundario y muerte neuronal por apoptosis. Recientemente se ha propuesto una tercera fase en la que factores como la inflamación persistente y los cambios epigenéticos causarían un bloqueo de la maduración de los oligodendrocitos, alteración de la neurogénesis, del crecimiento axonal y de la sinaptogénesis. En este contexto, el estrés oxidativo va a tener un papel protagonista como responsable tanto en causar daño directo al SNC como en activar cascadas metabólicas conducentes a la apoptosis e inflamación. La hipotermia moderada precoz, al preservar las reservas energéticas y disminuir la formación de especies reactivas de oxígeno, atenuará el daño cerebral posreanimación. La combinación de la hipotermia con terapias coadyuvantes para modular el estrés oxidativo podría contribuir a mejorar el pronóstico.
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Introduction

So-called oxy-regulator tissues, such as the central nervous system (CNS) and myocardium, require high amounts of energy to maintain membrane potentials and therefore depend on aerobic metabolism, which generates energy much more efficiently than anaerobic metabolism.[1] In the CNS, the transmission of action potentials involves ATP-dependent ion pumps, which use a large amount of energy. Furthermore, the CNS cannot store energy in forms that can be mobilised rapidly, such as phosphocreatine or glycogen, and therefore depends on a continuous supply of glucose and oxygen. In consequence, oxygen and glucose deprivation lead to a rapid depletion of energy stores and cell death in a matter of minutes.[2–4]

Intrapartum asphyxia is characterised by periods of hypoxia/ischaemia during labour that, depending on severity, may result in death or cause hypoxic-ischaemic encephalopathy (HIE). The mortality due to HIE is of 1 to 8 deaths per 1000 live births in developed countries and can be as high as 26 deaths per 1000 live births in developing countries. The main challenge for neonatologists is to reduce the morbidity and mortality associated with HIE, since despite the widespread use of hypothermia, as many as 45% of these patients still die today, while a high percentage of survivors develop significant disabilities.[5]

The purpose of this review article is to describe the biochemical basis of oxidative metabolism as well as the adjuvant therapies that may help control the production of free radicals and improve the outcomes of hypothermia.

Oxidative metabolism[2,6–9]

Aerobic metabolism and oxidative phosphorylation (Fig. 1)

In multicellular organisms, oxygen must be available for mitochondrial oxidative phosphorylation to produce the energy required to sustain life. Substrates such as glucose,

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