Fetal Hypoxia Insults and Patterns of Brain Injury: Insights from Animal Models

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KEYWORDS

- Perinatal asphyxia • Hypoxic-ischemic encephalopathy
- Fetal sheep • Premature delivery • Neuronal loss
- Repeated hypoxia

Acute neonatal encephalopathy remains a significant cause of death and long-term disability.[1] Despite the highly adverse outcomes of moderate to severe encephalopathy around birth[2] the predictive value for cerebral palsy of abnormal fetal heart rate patterns is consistently weak.[3] Indeed, even measures of total oxygen debt such as base deficit (BD) or lactate show only a broad relationship with later encephalopathy. For example, profound acidosis (BD>18 mmol/L at 30 minutes of life) was associated with moderate to severe encephalopathy in nearly 80% of patients,[4] and no cases occur with mild BDs below approximately 10–12 mmol/L.[4,5] However, it is striking that Low and colleages found that less than half of babies born with cord blood BDs over 16 mmol/L (and pH <7.0) developed significant encephalopathy, and that encephalopathy still occurred, although at low frequency (10% of cases), in cases with moderate metabolic acidosis of between 12 and 16 mmol/L.[5] These data contrast with the presence of (very) non-reassuring fetal heart rate tracings and severe metabolic acidosis in those infants who do go on to develop neonatal encephalopathy.[2,6]

Early onset neonatal encephalopathy is important, because it is the key link between exposure to asphyxia and subsequent neurodevelopmental impairment.[7] Newborns with mild encephalopathy are completely normal to follow-up, while all of those with severe (stage III) encephalopathy die or have severe handicap. In contrast, only half of those with moderate (stage II) hypoxic–ischemic encephalopathy develop

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handicap. However, even those who do not develop cerebral palsy have increased risk of learning and more subtle neurologic problems in later childhood.[8] This strongly infers that much of the variation in outcome is related to the immediate insult period.

This article focuses on recent developments that help shed light on the factors that determine whether the brain is or is not damaged after apparently similar asphyxial insults. In part, this variation is simply because the fetus is spectacularly good at defending itself against such insults. Thus, it appears that injury occurs only in a very narrow window between intact survival and death. The fetus's ability to defend itself though is modified by multiple factors including the depth, duration, and repetition of the insult, the gestational age, sex and condition of the fetus, and its environment, and particularly pyrexia and exposure to sensitizing factors such as infection/inflammation.

Most of the studies discussed here were undertaken in chronically instrumented fetal sheep. The sheep is a highly precocial species, whose neural development around 0.8–0.85 of gestation approximates that of the term human.[9,10] Earlier gestations have also been studied; the 0.7 gestation fetus is broadly equivalent to the late preterm infant at 30 to 34 weeks, before the onset of cortical myelination, while at 0.6 gestation the sheep fetus is similar to the 26 to 28 week gestation human.

WHAT INITIATES NEURONAL INJURY?

It is useful to consider what is required to trigger injury of brain cells, independent of the fetus's cardiovascular defenses.[11] At the most fundamental level, injury requires a period of insufficient delivery of oxygen and substrates such as glucose (and in the fetus other aerobic substrates such as lactate) such that neurons (and glia) cannot maintain homeostasis. If oxygen is reduced but substrate delivery is effectively maintained (ie, pure or nearly pure hypoxia), the cells adapt in two ways. First, they can to some extent reduce non-obligatory energy consumption, initially switching to lower energy requiring states and then, as an insult becomes more severe, completely suppressing neuronal activity, at a threshold above that which causes neuronal depolarization.[12] This reduced activity is actively mediated by inhibitory neuromodulators such as adenosine.[13] Second, they can use anaerobic metabolism to support their production of high-energy metabolites for a time. The use of anaerobic metabolism is of course very inefficient since anaerobic glycolysis produces lactate and only 2 ATP, whereas aerobic glycolysis produces 38 ATP. Thus glucose reserves are rapidly consumed, and a metabolic acidosis develops due to accumulation of lactic acid, with local and systemic consequences such as impaired vascular tone and cardiac contractility.[11]

In contrast, under conditions of combined reduction of oxygen and substrate the neuron's options are much more limited, as not only is less oxygen available, but there is also much less glucose for anaerobic metabolism. This may occur during either pure ischemia (reduced tissue blood flow) and even more critically during conditions of hypoxia–ischemia, ie, both reduced oxygen content, and reduced total blood flow. Under these conditions depletion of high energy metabolites will occur much more rapidly and profoundly than during hypoxia alone, while at the same time there may actually be less metabolic acidosis both because there is much less glucose being delivered for metabolism to lactate, and because the insult is evolving more quickly. This is important, since the fetus is commonly exposed to hypoxia–ischemia due to hypoxic cardiac compromise.

These concepts help to explain the consistent observation discussed below that across multiple paradigms in the fetus most cerebral injury after acute insults occurs in association with hypotension and consequent tissue hypoperfusion or ischemia.