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Fetal hypoxia insults and patterns of brain injury: Insights from animal models

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Synopsis

The outcome of perinatal hypoxia-ischemia is highly variable, with only a very broad relationship to the 'severity' of oxygen debt as shown by peripheral base deficit and the risk of damage. The present review examines the pathophysiology of asphyxial injury. We dissect the multiple factors that modify the risk of injury, including the depth ('severity'), duration, and repetition of the insult, the maturity, and condition of the fetus, pre-existing hypoxia, and exposure to pyrexia and infection/inflammation.

Introduction

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 colleagues 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

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(stage II) hypoxic–ischemic encephalopathy develop handicap. However, even those who do not develop cerebral palsy have increased risk of learning and more subtle neurological problems in later childhood (8). This strongly infers that much of the variation in outcome is related to the immediate insult period.

This chapter 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 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 (i.e. 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, i.e. 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. Technically, asphyxia is defined as the combination of impaired respiratory gas exchange (i.e. hypoxia and hypercapnia)

accompanied by the development of metabolic acidosis. To understand much of the apparent variation in outcome it is critical to keep in mind that this definition tells us much about things that can be measured relatively easily (blood gases and systemic acidosis) and essentially nothing about blood pressure or perfusion of the brain.

Cerebral injury: an ‘evolving’ process

The seminal concept to emerge from both experimental and clinical studies is that brain cell death does not necessarily occur during hypoxia-ischemia (the ‘primary’ phase of injury), but rather that the injurious event may precipitate a cascade of biochemical processes leading to delayed cell death hours or even days afterwards (the ‘secondary’ phase). Experimental studies have demonstrated the existence of both a primary phase of energy failure during hypoxia-ischemia, a ‘latent’ phase during which oxidative metabolism normalizes, followed by secondary failure of oxidative metabolism in piglets (14), immature rats (15), and the fetal sheep (16). Consistent with these studies, although some newborn infants exposed to profound asphyxia show no initial recovery of oxidative metabolism after birth and typically have very severe brain injury and high mortality (17), in many other cases infants show initial, transient recovery of cerebral oxidative metabolism followed by a secondary deterioration, with cerebral energy failure from 6 to 15 hours after birth (17,18). The severity of secondary energy failure correlates closely with the severity of neurodevelopmental outcome at 1 and 4 years of age (18). Critically, for hypoxia associated with labor insults, experimental studies show that a single ‘sub-threshold’ insult that causes either minor or no neural injury can lead to a phase of increased vulnerability to further insults in a similar window of around 6 or more hours (19–21).

Mild to moderate hypoxia is not injurious

The fetus can fully adapt to mild to moderate reductions in oxygen tension without injury, from normal values of greater than 20mmHg down to 10 to 12mmHg (22,23). The late gestation fetal sheep fetus shows an initial transient, moderate bradycardia followed by tachycardia and an increase in blood pressure, typically accompanied by a minor initial increase in circulating lactate (22,23). There is a rapid peripheral vasoconstriction reducing blood flow to peripheral organs such as the gut, lungs, skin and muscle, in favor of the brain, heart and adrenal gland (23). Thanks to this increased blood flow to the brain that helps to restore oxygen delivery, greater oxygen extraction, and a switch to lower frequency EEG states with approximately a 20% reduction in oxygen consumption (24), brain oxygen consumption is maintained at normal values. If the hypoxia is sustained, the fetus can fully adapt essentially indefinitely shown by normalization of heart rate and blood pressure and the return of normal sleep state cycling, although redistribution of blood flow is maintained (25,26), resulting in reduced somatic growth.

Asphyxia, hypotension and hypoxic-ischemic brain injury

Asphyxia by definition involves both hypoxia and hypercapnia with metabolic acidosis. It is important to appreciate that experimental studies of asphyxia have typically involved a greater depth of hypoxia than is possible using maternal inhalational hypoxia. Brief, total clamping of the uterine artery or umbilical cord leads to a rapid reduction of fetal oxygenation within a few minutes (27–29). In contrast, gradual partial occlusion induces a slow fetal metabolic deterioration without the initial fetal cardiovascular responses of bradycardia and hypertension; this is a function of the speed and relative depth of hypoxia that was attained (30). During profound asphyxia, corresponding with a severe reduction of uterine blood flow to 25% or less and a fetal arterial oxygen content of less than 1 mmol/L, the fetus responds very differently than during mild to moderate hypoxia. Typically, we can distinguish two phases: an initial, rapid chemoreflex-mediated period of compensation (31–34), followed by progressive

hypoxic-decompensation, ultimately terminated by profound systemic hypotension with cerebral hypoperfusion (Fig. 1)(28,29,35).

Term and preterm fetuses alike respond to asphyxia in a qualitatively similar manner, albeit the preterm fetuses can survive for much longer without injury (35–37). A wide range of studies suggest that it is the period of hypotension during severe asphyxia that is associated with cerebral injury across paradigms, likely because of the close relationship between maintenance of fetal blood pressure during severe asphyxia and changes in brain perfusion (carotid blood flow (CaBF)) as shown in Figure 1. In these fetuses, MAP initially rose with intense peripheral vasoconstriction; at this time CaBF was maintained at around baseline values, but with profound suppression of EEG activity (13,35). Microsphere studies have shown that although total brain flow did not change, within the brain blood flow is diverted away from the cerebrum and increased in the brain stem (38). As umbilical cord occlusion was continued MAP eventually fell. The key mediators include impaired cardiac function secondary to of hypoxia, acidosis, depletion of myocardial glycogen and cardiomyocyte injury (39) and loss of the initial peripheral vasoconstriction (35,40). Once MAP fell below baseline, carotid blood flow fell in parallel, consistent with the known relatively narrow low range of autoregulation of cerebrovasculature in the fetus (27), and there is loss of redistribution of flow within the brain (38).

In the near-term fetus neural injury has been commonly reported in areas such as the parasagittal cortex, the dorsal horn of the hippocampus, and the cerebellar neocortex after a range of insults including pure ischemia (41), prolonged single complete umbilical cord occlusion (28), and prolonged partial asphyxia (30,42,43) and repeated brief cord occlusion (e.g. as illustrated in the bottom panel of Fig. 2) (44). These areas are ‘watershed’ zones within the borders between major cerebral arteries, where perfusion pressure is least, and in both adults and children lesions in these areas are typically seen after systemic hypotension (45).

There are some data suggesting that limited, or localized white or gray matter injury may occur even when significant hypotension is not seen (30,43), particularly when hypoxia is very prolonged (46). Clearly it remains possible that regional hypoperfusion may have occurred or that perfusion was insufficient for particular, highly metabolically active regions. Nevertheless, the magnitude of damage reported after insults without hypotension is modest (46) and there is a strong correlation between either the depth or duration of hypotension and the amount of neuronal loss within individual studies of acute asphyxia (42–44,47) (e.g. Fig. 3). This is also seen between similar asphyxial paradigms causing severe fetal acidosis which have been manipulated to either cause fetal hypotension (42) or not (30). In fetal lambs exposed to prolonged severe partial asphyxia induced by partial occlusion of the uterine artery neuronal loss occurred only in fetuses in whom one or more episodes of acute hypotension occurred (42). In contrast, in a similar study where an equally ‘severe’ insult was induced gradually and titrated to maintain normal or elevated blood pressure throughout the insult no neuronal loss was seen except in the cerebellum (30).

Basal ganglia injury: cardiovascular collapse and repeated insults?

Although the watershed-type injuries described above are a commonly recognized clinical MRI pattern, basal ganglia and thalamic damage is widely recognized. It is typically associated with more severe or “sentinel” events at birth (48), and with more severe neurodevelopmental disability (49). Although the basal ganglia seem to be relatively mildly affected in the experimental settings mentioned above, the clinical association with more severe acute events at birth (49,50) raises the possibility that it may be a function of more severe cardiovascular collapse. Blood to the brain during the initial adaptation to asphyxia is not distributed evenly, but rather reduced to the cortex and increased in the basal ganglia/thalamus and brainstem

(38). This suggests that in part the apparent sparing of the basal ganglia and other critical deep nuclei during many insults reflects this greater residual perfusion, and that it must fail during profound hypotension which would expose the deep nuclei to overt ischemia (51).

Another contributing factor is suggested by the experimental association between relatively repeated but prolonged episodes of asphyxia selective neuronal damage to the striatal nuclei (putamen and caudate nucleus, Fig. 2, top) (21,44,52). Further, whereas a single 30 minute period of cerebral ischemia leads to predominantly parasagittal cortical neuronal loss, with only moderate injury to the dorsolateral striatum, when the insult was divided into three episodes of 10 minutes of ischemia, a greater proportion of striatal injury was seen relative to cortical neuronal loss (Fig. 4) (19). Intriguingly, significant striatal involvement was also seen after prolonged partial asphyxia in which distinct episodes of bradycardia and hypotension occurred (42).

The striatum is not in a watershed zone but rather within the territory of the middle cerebral artery. Thus it is likely that the pathogenesis of striatal involvement in the near-term fetus is related to the precise timing of the relatively prolonged episodes of asphyxia and not to more severe local hypoperfusion. The mechanism is unclear, however, the relatively greater striatal predominance with greater spacing between insults (19) suggests that it is in part a consequence of the evolving neural dysfunction and sensitivity triggered by noninjurious single insults, and thus speculatively, with slower recovery of this period of sensitivity to further insults in the basal ganglia than the cortex. Further, we should note that the inhibitory striatal neurons were primarily damaged by repeated ischemia (21), raising the possibility that this enhanced injury is related in part to abnormal excitatory inputs to these neurons.

Pre-existing metabolic status, and chronic hypoxia

While the original studies of factors influencing the degree and distribution of brain injury, primarily by Myers (53), focused on metabolic status, the issue remains controversial. There is evidence, for example, that hyperglycemia during hypoxia-ischemia reduces damage in the infant rat whereas it was associated with greater damage in adult rats (54,55), but had no effect in the piglet (56). These differences may reflect species specific maturational differences in the activity of cerebral glucose transporters (55). The most common metabolic disturbance to the fetus is intrauterine growth retardation (IUGR) associated with placental dysfunction. Although clinically IUGR is usually associated with a greater risk of brain injury, recent studies have suggested that the risk of encephalopathy has fallen markedly over time (6). One interpretation of this finding is that the apparently increased sensitivity to injury is mostly due to reduced aerobic reserves, leading to early onset of systemic compromise during labor.

Consistent with this hypothesis, chronically hypoxic fetuses from multiple pregnancies developed much more severe, progressive metabolic acidosis than previously normoxic fetuses during brief (1 minute) umbilical cord occlusions repeated every 5 minutes ($\text{pH } 7.07 \pm 0.14$ vs 7.34 ± 0.07) and hypotension (a nadir of 24 ± 2 mmHg vs 45.5 ± 3 mmHg after 4 hours of repeated occlusion) (57). The fetuses with pre-existing hypoxia were smaller on average, and had lower blood glucose values and higher PaCO_2 values. Similarly, in normally grown fetuses, 5 days of induced chronic hypoxemia was associated with increased striatal damage after acute exposure to repeated umbilical cord occlusion for 5 minutes every 30 minutes for a total of four occlusions (52). Together, these data support the clinical concept that fetuses with chronic placental insufficiency are vulnerable even to relatively infrequent periods of additional hypoxia in early labor.

Less obvious adverse intrauterine events may also modify fetal responses to hypoxia. There is considerable interest on the effects of stimuli such as maternal undernutrition and steroid exposure, particularly at critical times in pregnancy, not only on the fetal responses to

challenges to its environment such as hypoxia, but also on risks for adverse health outcomes in adult life (58). Intriguingly, mild maternal undernutrition that does not alter fetal growth may still affect development of the fetal hypothalamic-pituitary-adrenal function, with reduced pituitary and adrenal responsiveness to moderate hypoxia (59). There is some evidence that exposure to glucocorticoids may also detrimentally alter the responses to hypoxia (60).

Brain maturity

The effect of maturation on sensitivity to injury is of great importance, for two reasons. First, in recent years improvements in obstetric and pediatric management have resulted in significantly increased survival of preterm infants from 24 weeks of gestation, with continuing very high rates of physical disabilities and long-term learning, cognitive and behavioral problems (61). Second, many infants may sustain neural injuries well before birth, including a significant number of infants with cerebral palsy (62). The characteristic patterns of cerebral injury in the preterm fetus differ from those seen at term or after birth, with preferential injury of subcortical structures and white matter.

Their high rate of disability intuitively suggests that premature infants are more vulnerable to hypoxic damage than at term. Recent experimental studies now show that in fact the premature fetus is *less* vulnerable to a given duration of asphyxia than at term, and further that tolerance to hypoxia-ischemia falls with postnatal age (36). For example, the premature sheep fetus at 90 days gestation (term is 147 days), prior to the onset of cortical myelination, can tolerate extended periods of up to 20 minutes of umbilical cord occlusion without neuronal loss (37, 63). The very prolonged cardiac survival during profound asphyxia (up to 30 minutes, Fig. 1 (35)) corresponds with the peak in cardiac glycogen levels that occurs near mid-gestation in the sheep and other species including man (64).

Interestingly, while the preterm fetal response to mild to moderate hypoxia appears to be different to that seen at term (65), the overall pattern of cardiovascular and cerebrovascular response during severe asphyxia was very similar to that seen in more mature fetuses, with sustained bradycardia, accompanied by circulatory centralization, initial hypertension, then a progressive fall in pressure (35,66–68). As also reported in the term fetus, there was no increase in blood flow to the brain during this initial phase, and again this was due to a significant increase in vascular resistance rather than to hypotension. Compared with the term fetus 0.6 and 0.7 gestation fetuses showed significantly slower suppression of EEG activity at the start of umbilical cord occlusion (35,68). Speculatively, this delay is indicative of the relative anaerobic tolerance of the preterm brain. As shown in Figure 1, as in the term fetus, once blood pressure begins to fall blood flow to the brain falls in parallel (35). The fall in pressure is partly a function of continuing fall in fetal heart and thus of combined ventricular output (35) and partly the loss of redistribution of blood flow with a rise in femoral blood flow (FBF). Similar responses are also seen in the kidney and gut (66,67).

In the latter half of maximum survivable interval of asphyxia in the preterm fetus there is progressive failure of combined ventricular output, with a fall in both central and peripheral perfusion, both associated with falling blood pressure. This phase is much less likely to be seen for any significant duration in the term fetus as cardiac glycogen stores are depleted more quickly at term (64). Thus, at 0.6 gestation the majority of fetuses survived up to 30 minutes of complete umbilical cord occlusion (68). In contrast, term fetuses are unable to survive such prolonged periods of sustained hypotension, and typically will recover spontaneously from up to a maximum of 10–12 minutes of cord occlusion, whereas after a 15 minute period of complete occlusion the majority of fetuses either died or required active resuscitation with adrenaline after release of occlusion (28,29,35). Thus, as a consequence of this extended survival during severe asphyxia, the premature fetus is exposed to extremely prolonged and

profound hypotension and hypoperfusion. At 0.6 gestation, for example, no injury occurs after 20 minutes of complete umbilical cord occlusion even though hypotension is already present as shown in Figure 1 (63), but severe subcortical injury occurs if the occlusion is continued for 30 minutes (37). It may be speculated that during this final 10 minutes of asphyxia there is a catastrophic failure of redistribution of blood flow within the fetal brain which places previously protected areas of the brain such as the brainstem at risk of injury (53), consistent with clinical observations (50).

Temperature and hypoxia-ischemia

Brain temperature during and after hypoxia-ischemia potently modulates outcome. Whereas hypothermia during experimental cerebral ischemia is consistently associated with potent, dose-related, long-lasting neuroprotection (69), hyperthermia of even 1 to 2 °C extends and markedly worsens damage, and promotes pan-necrosis (70,71). The impact of cerebral cooling or warming the brain by only a few degrees is disproportionate to the known changes in brain metabolism (approximately a 5% change in oxidative metabolism per °C (72)), suggesting that changes in temperature modulate the secondary factors that mediate or increase ischemic injury. Mechanisms that are likely to be involved in the worsening of ischemic injury by hyperthermia include greater release of oxygen free radicals and excitatory neurotransmitters such as glutamate, enhanced toxicity of glutamate on neurons, increased dysfunction of the blood brain barrier, and accelerated cytoskeletal proteolysis (69).

These data logically lead to the concept that although mild pyrexia during labor might not necessarily be harmful in most cases, in those fetuses also exposed to an acute hypoxic-ischemic event it would be expected to accelerate and worsen the development of encephalopathy. Case control and case series studies strongly suggest that maternal pyrexia is indeed associated with an approximately four fold increase in risk for unexplained cerebral palsy, or newborn encephalopathy (73).

Clearly, this association could potentially be mediated by maternal infection or by the fetal inflammatory reaction. However, maternal pyrexia was a major component of the operational definition of chorio-amnionitis in all of these studies, and in several studies pyrexia was either considered sufficient for diagnosis even in isolation, or was the only criterion (73). Consistent with the hypothesis that pyrexia can have a direct adverse effect, in a case control study of 38 term infants with early onset neonatal seizures, in whom sepsis or meningitis were excluded, and 152 controls, intrapartum fever was associated with a comparable 3.4-fold increase in the risk of unexplained neonatal seizures in a multifactorial analysis (74).

In newborn rodents recent studies suggest intriguingly that exposure to mild infection or inflammation can sensitize the brain, so that short or milder periods of hypoxia-ischaemia, which do not normally injure the developing brain, can trigger severe damage (75–77). The effect is complex and time dependent. A low dose of LPS given either shortly (four or six hours) or well before (72 hours or more) hypoxia in rat pups was associated with *increased* injury ('sensitization') (76,78). In contrast, when given at an intermediate time (24 hours) before hypoxia-ischemia, LPS actually *reduced* injury ('tolerance') (78). In mice, fetal exposure to endotoxin affected the responses to hypoxia-ischemia even in adulthood, with both reduced and increased injury, in different regions (75). Thus given that profound asphyxia or septic shock causing acute injury around the time of birth are only seen in a minority of preterm infants, these data raise the intriguing possibility that sensitization by infection/inflammation may compromise the fetus such that even normally non injurious periods of hypoxia can be transformed into a damaging event.

Final conclusions

The experimental studies reviewed above, and clinical experience (5), strongly suggest that there is, and can be, no close, intrinsic pathophysiological relationship between the severity of metabolic acidosis, and fetal compromise. Peripheral acidosis is primarily a consequence of peripheral vasoconstriction, and reflects peripheral oxygen debt which occurs during redistribution of combined ventricular output. Thus severe acidosis may accompany both successful protection of the brain, and catastrophic failure (44). Conversely, brief but intense insults such as complete cord occlusion may cause brain injury in association with comparatively modest acidosis (13). In contrast, we now know that there are very strong relationships both within and between paradigms between the development and severity of fetal blood pressure and impairment of cerebral perfusion, and the development of subsequent cerebral injury. The impact of hypotension is directly related to both its depth and cumulative duration in relationship to the brains' metabolic requirements given its developmental stage.

How this hypoxia-ischemia triggers different patterns of injury is not fully understood, but key factors include profound hypotension and the pattern of the insult. The link between profound hypotension/hypoperfusion during asphyxia and subcortical damage in the preterm fetus likely reflects compromise of the initial intracerebral redistribution of blood flow from the forebrain to the subcortical areas. Of particular interest to clinicians, it is striking that repeated, relatively prolonged episodes of asphyxia or ischemia (5 to 10 minutes) are associated with selective basal ganglia damage, and that the proportion of basal ganglia damage relative to cortical injury increases as the interval between insults is increased. This relationship emphasizes the importance of interaction between even relatively benign, non-injurious individual periods of hypoxia-ischemia in labor that can lead to regionally specific, compounding damage.

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Figure 1.

Changes in fetal heart rate (FHR, bpm, top panel), mean arterial pressure (MAP, mmHg, second panel), femoral blood flow (FBF, ml/min, third panel) and carotid blood flow (CaBF, ml/min, bottom panel) in 0.6 (▽), 0.7 (●) and 0.85 gestation (*) fetuses during complete umbilical cord occlusion. FHR, MAP, FBF and CaBF data represent one minute averages and are expressed as percentage of baseline. The period of umbilical cord occlusion for each group is indicated by the rectangles. Data are mean $\pm$ SE. Data modified from Wassink et al (35).

Figure 2.

The distribution of neuronal loss assessed after 3 days recovery from two different paradigms of repeated prenatal asphyxia in near-term fetal sheep. The top panel shows the effect of five minute episodes of umbilical cord occlusion, repeated four times, at intervals of 30 minutes. There is marked neuronal loss in the putamen and caudate nucleus, which are nuclei of the striatum. The bottom panel shows the effects of brief umbilical cord occlusions repeated at frequencies consistent with established labor, either 1 minute every 2.5 minutes or 2 minutes 5 minutes. Occlusions were terminated after a variable time, when the fetal blood pressure fell below 20 mmHg for two successive occlusions. This insult led to damage in the watershed regions of the parasagittal cortex and cerebellum with sparing of the striatum. CA 1/2 and the

dentate gyrus are regions of the hippocampus. Data are mean $\pm$ SD and derived from de Haan et al (44,47).

Figure 3.

The relationship between hypotension and neuronal damage. The severity of fetal systemic hypotension during asphyxia induced by partial common uterine artery occlusion is closely related to the degree of neuronal loss and risk of death in the near-term fetal sheep (mean arterial pressure (MAP) (42).

Figure 4.

The effects of different intervals between periods of cerebral ischemia insults on the distribution of cerebral damage the near-term fetal sheep. Cerebral ischemia induced by bilateral occlusion of the carotid arteries was applied either for 10 minutes, repeated three times at intervals of either 1 or 5 hours, or for a single continuous episode of 30 minutes. The divided insults were associated with a preponderance of damage in the striatum, whereas a single episode of 30 minutes of carotid occlusion was associated with severe cortical neuronal loss. When the interval was increased to 5 hours, cortical damage was nearly completely abolished, but there was still substantial neuronal loss in the striatum. Data derived from Mallard et al (19).