Why hypothermia in neonatal hypoxic ischemic encephalopathy?

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The incidence of asphyxiated full-term infants is still high in both high income and developing countries. In up to 80 percent of infants, moderate to severe birth asphyxia results in long-term neurological sequelae. Many years of experimental work and a limited data on hypoxic-ischemic neonates have supported the hypothesis that hypothermia after the primary insult induces permanent neuroprotection. In this mini overview, we attempt to update pediatricians in this aspect and raise the following: Will the future treatment include hypothermia along with the conventional and or other promising drugs affecting different aspects of the hypoxia-ischemia?

Key words: brain cooling, neonatal hypoxic-ischemic encephalopathy, hypothermia.

Introduction

Hypoxic injury, in the fetal and newborn brain results in long term sequelea as mental retardation, epilepsy, cerebral palsy and learning disabilities as well as neonatal morbidity and mortality[1]. The origin and timing of injury often are less clear in the clinical settings than observed in animal models. This is why the potential future therapies are in their premature stage; are not put into reality before indepth understanding of the underlying mechanisms. Previous experimental and clinical data showed that hypoxic ischemic injury is a continuing process. There are two phases; first the primary energy failure during which the cerebral metabolism may initially recover but deteriorates in a latent secondary phase after 6-15 hours later[2,3]. It is very ikely that the prominent damage occurs in this secondary phase. In infants with hypoxic ischemic encephalopathy (HIE), a clear cut correlation between the secondary energy failure and neurodevelopmental outcome at 1 and 4 years of age exists[4]. Recent studies hav eled to the idea that modifying yhe post-ischemic cerebral temperature can effectively modulate encephalopathic process occuring both in the primary and secondary phases of cerebral injury[5]. Thus the idea of the neuroprotective effects of cerebral hypothermia during or after cerebral ischemia or asphyxia alone or in combination with other therapy modalities have gained enormous attention.

This review will primarily and briefly focuses on the main factors why this encouriging ttherapy could be promising for the hypoxia susceptible developing brain.

Why is the Developing Brain Prone to Hypoxia

In terms of neonatal brain the developmental status, the interplay of anatomic, structural and functional maturational processes and the response of the potential mechanisms to hypoxia of the cellular components determines the final winner in HIE (Fig. 1).

Brain is rich in polyunsaturated fatty acids that is highly susceptible to oxidative reactions[6]. Previous studies showed that the rate of lipid peroxidation as measured by thiobarbituric acid reactive substances (TBA) was higher in term brain than preterm probably due to the presence of this higher level of polyunsaturated fatty acids[7]. When the brain homogenates of normoxic and hypoxic term fetuses were compared; the TBA reactive substances in the hypoxic group were 3 times, the lipid peroxidation were 5 time shigher than the normoxic controls[8]. T hus during the developmental period a comparable amount of lipid peroxidation occurs in the term babies making them more prone to hypoxia than the pretem. This is one of the reasons why HIE is mostly seen in term neonates.

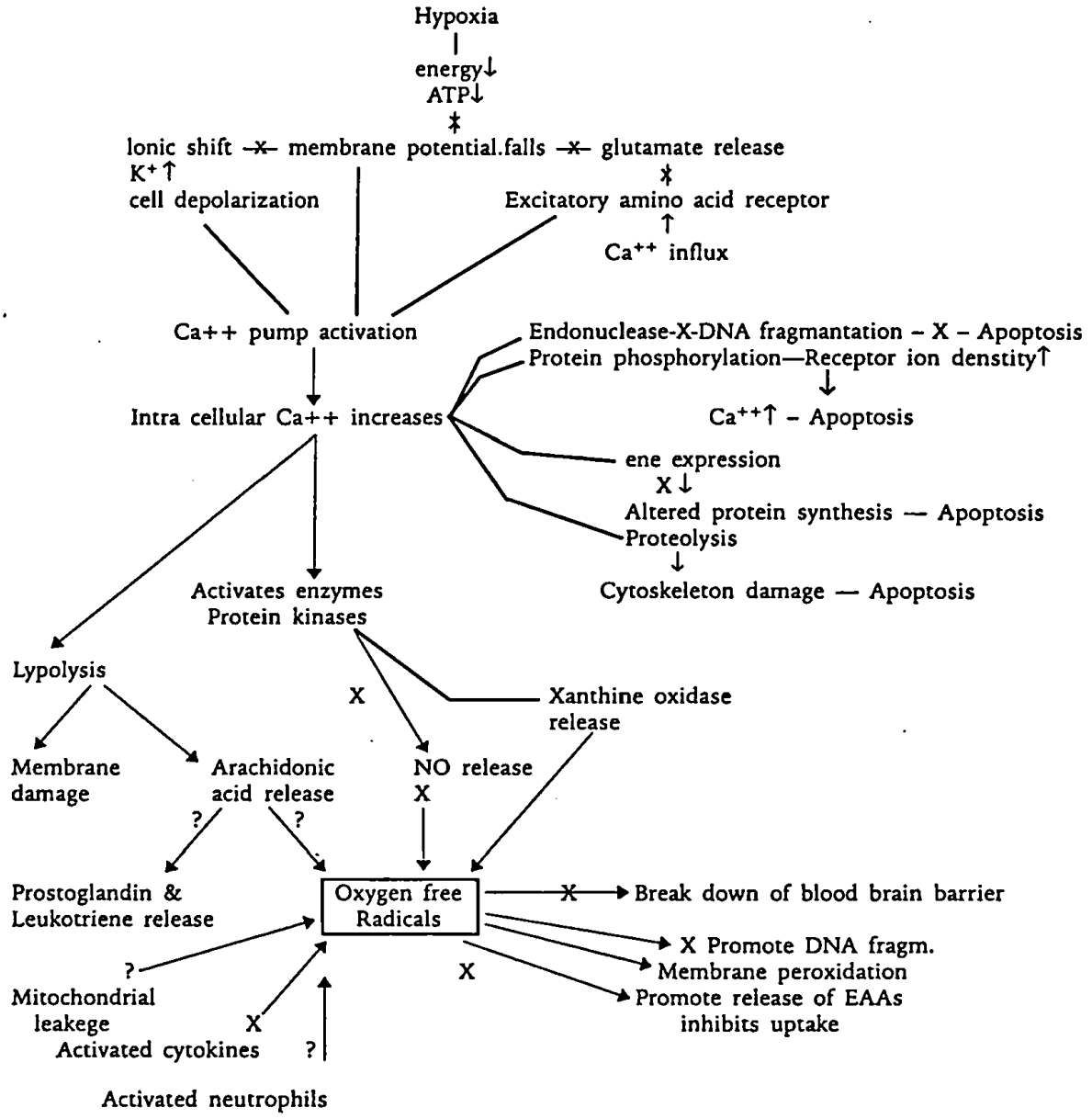

Fig. 1. Where hypothermia definitely (X) and indefinitely (?) interferes in HIE.

Excitatory amino acids is important in neuronal damage in hypoxia and ischemia[8]. As well the N-methyl-D aspartate (NMDA) glutamate receptor plays a pivotal role in the maturational process[9]. The density of glutamate receptors in areas of active development exeeds that in the mature brain The immature glutamate receptor has an increased agonist binding[10], an enhanced response to glycine[11], weaker magnesium blockade and less dependence on membrane depolarisation[11]. Thus ion channel opening is increased and a greater influx of calcium is seen. Mishra et al; showed that an increase in number and activation of NMDA receptor by glutamate and glycine during brain development could probably increase the vulnerability of the fetal brain to NMDA induced excitotocicity near term. This indicates that, the sensitivity of the developing brain to hypoxic injury via NMDA receptor augments with brain maturation. Furthermore hpoxia modifies the NMDA receptor-ion channel complex[12].

In addition during hypoxia the increased concentrations of free fatty acids, by impairing the mitochondrial function decrease its calcium buffering capacity[13]. An increased peroxidation of brain cell membrane lipids during hypoxia in the newborn piglets has been reported[14]. During hypoxia; due to the increased intra cellular calcium, activation of cyclooxygenase, lipooxygenase pathways, nitric oxide sythase occurs, and additionally conversion of xanthine dehydrogenase to xanthine oxidase results in free radical generation. In a study concerning neonatal hypoxic-

ischemic brain damage; the asphyxiated neonates had higher malondialdehyde levels and prostoglandin activity than the controls[15].

How Cooling is Effective

As explained above luckly,most of the main pathophysiologic mechanisms operating in asphyxiated neonates, are more or less effected by hypothermia. Cooling can either be systemic; total body, selective cerebral or both.Hypothermia produces a stepwise increase in cerebral metabolism of about 5-7% for each degree of temperature reduction[16]. Reduces the depletion of high energy phophates thus delays neuronal depolarization that seems toinitiate both apoptotic and necrotic cell death[17]. It also reduces the release of excitotoxins. By intraischemic hypothermia, the delayed neuronal depolarization was shown to reduce the accumulation of excitotoxic neurotransmitters[16]. Post depolarization decrease of release is also reported[18].

Hypothermia also decreases nitric oxide release. In newborn pilets; hypothermia starting immediately after hypoxic-ischemia had reduced NO efflux in the brain along with reduced levels of excitatory amino acids[19]. Cooling during the reperfusion period, by reducing oxygen metabolism hypothermia supresses oxygen free radical bursts abd lipid peroxidation[20]. Hypothermia extends secondary hypoperfusion. Cooling started at 1.5 and 5.5 hr after ischemia was shown to prevent later development of hyperperfusion during secondary phase and improved neuronal outcome[21]. It prevents intracelluler ion and water entery and final osmotic cell swelling even if the ATP dependent Na+/K+pump is inhibited, and prevents secondary cytotoxic oedema[21]. Hypothermia was suggested to prevent delayed cell degeneration via apoptotic mechanism in the cerebral cortex of the piglet withput effecting necrotic cell death[22]. In another study, they showed that the hypothermia had delayed rather than preventing apoptosis in cell cukture systems[23]. Further more, in the newborn rat hippocampus, hypothermia induced reduced apoptotic and necrotic cell death was reported[24*]. It also decreases inflammatory second messangers. IL1β receptor antagonists were proved to be protective in the 7 day old rat model of hypoxia and hypothermia supresses post traumatic release of IL1β in the adult rat[25].

As seen with most of its action mechanisms, hypothermia may be a promising neuroprotective method in hypoxic ischemic injury.

Brief or Prolonged Hypothermia

Hypothermia could be brief or prolonged in duration. The brief hypothermia due to the data in the literature suggests modest neuroprotection in the neonatal rat and piglet[26,16]. Thus brief cooling could be highly effective after relatively mild insults and the protection seems to be decreased if brief hypothermia is delayed, such as; from 15 to 45 minutes after the primary insult[27,28]. When prolonged hypothermia is applied; it was seen that extended period of cooling ranging between 5 and 72 hr post asphyxia was more effective[29]. In unanaesthesided infant rats after amoderate hypoxia-ischemia, a mild cerebral hypothermia applied for 72 hours immediately after hypoxia had prevented the cortical infarction, while 6 hours of cooling had non significant results[29]. As well, in the anaesthtised hypoxia induced piglet, with bilateral carotid ligation 12 hours of mild hypothermia applied just after hypoxia had prevented energy failure and had reduced neuronal loss as indicated before[27]. However when the post ischemic initiation of hypothermia in the fetal sheep was delayed to 5.5 hour just before the secondary sizures a still existing but reduced neuroprotection in intensity had been observed[27]. Gluckmann et al, showed that a delay of 90 minutes in commencing moderate selective cerebral cooling, if continued until 72 hours after ischemia in the fetal sheep had prevented secondary cytotoxic oedema and had improved electroencephalographic recovery[30]. All these observations indicate that optimal benefit is obtained by extending the duration of post ischemic cooling periods bet up to 72 hours.

How Far Cooling

Optimal neuroprotection obtained varies between the animal models used. In the fetal sheep and dog the best result was seen when the temperature was below 34 °C. In the adult humans, whole body cooling to 33.5 °C for 24 hours had improved outcome without profound adverse effects[31].

Newborn Studies

Gunn et al; showed that selective head cooling with mild systemic hypothermia at 34.5-35 °C,in 12 term infants with HIE for 72 hr following

perinatal asphyxia were safe[32]. Ballın et al found no late adverse effects in infants at the age of 18 months who had received selective head cooling[33]. The normal neurodevelopmental outcome of these children reassured us about the safetiness of the method as well. Simbruner had recently retrospectively analysed the records of 21 asphyxiated newborns head-cooled for an avarege of 3.5 days to a temperature between 34-35 °C and found that 4 of 21 infants in the hypothermia and 5 of 15 in the comparison group had died. The advers effects seen during and after induced long term hypothermia in the surviving neonates were not significant. Lately, Asano et al had succesfully treated a case of very low birth weighted of 31 weeks' gestation with intracranial hemorrage and severe asphyxia due to a traffic accident with selective head cooling with minimal hypothermia[34].

Adverse Effects

The two human studies with neonates, as mentioned above; first by Gunn et al, where combined head and body cooling in 12 asphyxiated infants wre applied had no advers effects[32]. Due to the second report by Simbruer et al; 22 asphyxiated infant had mild selective head and systemic cooling for an avare of 3.5 days. Mild hypothermia had reduced their heart and respiratory rates by 13 and 16% respectively. No episodes of bradycardia and dysrhythmias and apnea were observed. They neither reported increased coagulopathy or pulmonary hemorrage and hematuria. Only hypoglycemia incidence was increased[35].

Comments

Taken together all these animal work and human studies, phase I trials in asphyxiated neonates; the take home message is; extending the duration of post asphyxiated moderate hypothermia starting within the first 6 hours and lasting for 72 hours will seem to be promising. Hypothermic treatment effects several of the mechanisms of damage operating in the vulnerable brain of the neonate with HIE. Combining it with the future's planned drugs acting on mechanismas of HIE will give the best results. This millenium's neonatal order sheet for the baby with HIE along with the forthcoming future interventions, (antiapoptotic drugs, some growth factors, free radical scavengers, etc.) will also have ICE CAP therapy for 3 days for selective head cooling. Starting at the possible earliest time post partum, may be at the delivery room if the baby has documented intra uterine fetal distress.

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