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Why do premature newborn infants display elevated blood adenosine levels?

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ABSTRACT

Our preliminary data show high levels of adenosine in the blood of very low birth weight (VLBW) infants, positively correlating to their prematurity (i.e. body weight class). This prompted us to look for a mechanism promoting such impressive adenosine increase. We hypothesized a correlation with oxygen challenge. In fact, it is recognized that either oxygen lack or its excess contribute to the pathogenesis of the injuries of prematurity, such as retinopathy (ROP) and periventricular white matter lesions (PWMI). The optimal concentration of oxygen for resuscitation of VLBW infants is currently under revision.

We propose that the elevated adenosine blood concentrations of VLBW infants recognizes two sources. The first could be its activity-dependent release from unmyelinated brain axons. Adenosine in this respect would be an end-product of the hypometabolic VLBW newborn unmyelinated axon intensely firing in response to the environmental stimuli consequent to premature birth. Adenosine would be eventually found in the blood due to blood–brain barrier immaturity. In fact, adenosine is the primary activity-dependent signal promoting differentiation of premyelinating oligodendrocyte progenitor cells (OPC) into myelinating cells in the Central Nervous System, while inhibiting their proliferation and inhibiting synaptic function.

The second, would be the ecto-cellular ATP synthesized by the endothelial cell plasmalemma exposed to ambient oxygen concentrations due to premature breathing, especially in lung. ATP would be rapidly transformed into adenosine by the ectonucleotidase activities such as NTPDase I (CD39), and NT5E (CD73). An ectopic extra-mitochondrial aerobic ATP synthetic ability was reported in many cell plasma-membranes, among which endothelial cells.

The potential implications of the cited hypotheses for the neonatology area would be great. The amount of oxygen administration for reviving of newborns would find a molecular basis for its assessment. VLBW infants may be regarded as those in which premature exposure to ambient oxygen concentrations and oxidative stress causes a premature functioning of the extra-mitochondrial oxidative phosphorylation primarily in axons and endothelium. Adenosine may become a biomarker of prematurity risk, whose implications further studies may assess.

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Background

Most very low birth weight (VLBW) infants now survive [1] but some 10% of these will sustain neurological injuries leading to persistent disabilities. Morbidity of survivors among VLBW infants includes retinopathy of prematurity (ROP), necrotizing enterocolitis of newborn (NEC), broncho-pulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and periventricular white-matter injury (PWMI) [2]. The latter is the most common cause of brain injury in preterm infants and the leading cause of chronic neurological disability [3]. Lesions are a continuum from focal cystic necrotic to noncystic injuries, the latter now emerging as the predominant lesions. Since the 1960s unique VLBW infant white

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matter lesions have been described, consisting of coagulative necrosis known as periventricular leukomalacia (PVL). Recently, association of PVL with inflammation and oxidative stress [4] was reported. Studies on titration of supplemental oxygen are suggestive of a primary role of hyperoxia in these lesions [5]. In fact, the optimal concentration of oxygen for resuscitation of preterm infants to limit both hyper- and hypo-oxygenation is still a matter of debate [6]. Limited premature ventilation was found to be less associated to systemic oxidative stress [7]. On the other hand, chronic hypoxemia was observed in extremely preterm infants, which 100% supplemental oxygen saturation could not amend [8]. Standard therapy is positive pressure ventilation to prevent alveolar atelectasis and methyl xanthine (essentially caffeine) administration [9].

Recently, to assess that initial resuscitation in air is preferable to 100% oxygen, markers of oxidative stress status *in vivo* were utilized, such as advanced oxidative protein products and isoprostanes (prostaglandin F_2-like compounds non-enzymatically formed *in vivo* from peroxidation of arachidonate) [10]. Among markers of oxidative stress, adenosine (Ado) is emerging. Interestingly, Ado concentration was found significantly higher in the foetal circulation in patients with preeclampsia than in normal pregnancies [11]. Ado induces respiratory depression [12], likely via its A(2A) receptors expressed by GABAergic neurons. It is also a potent immunosupressor molecule [13] and a suppressor of synaptic function [14,15]. Ado produced inside the axons and released in case of axonal hypometabolism is a signal to premyelinating Schwann Cells and oligodendrocytes [16], promoting oligodendrocyte development [17]. It was shown that most extracellular Ado derives from extracellular adenosine 5′-triphosphate (eATP), [18], due to the action of the widely distributed ectonucleotidases NTPDase I (CD39), and NT5E (CD73) on eATP. Signals delivered by eATP and Ado are transduced by functional P1, P2Y and P2X receptor subtypes, respectively [19]. ATP can be generated by oxidative phosphorylation occurring inside the mitochondrion, occasionally released outside the cells due to death or lysis. Other mechanisms have been proposed, i.e. ATP-permeable release channels; non-conductive transporters of ATP [18] [20], release through pannexin hemichannels [21]. Also an ectopic ATP synthesis may be invoked, reported in many cell types, and some reports have shown that an ATP synthesis can occur at the surface of some cells.

The hypothesis

It is proposed that the trigger of Ado production is the premature exposure to atmospheric oxygen, i.e. the most prominent challenge VLBW infants face upon birth. The source of blood Ado concentration rise can be both ecto- and endo-cellular. We hypothesize that a substantial part of Ado in the blood of very preterm infants derives from inside the hypometabolic brain axons. This fact is known [16,17], but in our opinion it needs careful reconsidering. The VLBW newborns are prematurely subject to multilevel sensory stimuli they were not supposed to experience. As yet unmyelinated axons involved in sensory neurotransmission display high firing in response to the environmental stimuli, extruding Ado. Brain accounts for a substantial percentage of the newborn body, and the blood–brain barrier is inefficient in the preterm infant. Further studies may tell whether the Ado concentration is high in the CSF. Considering its short blood half-life (about 15 s) [22], Ado production must be massive to reach the observed blood concentrations. Another Ado source in the systemic circulation should be postulated: this may be the metabolism of eATP produced by an extra-mitochondrial ectopic ATP synthesis in endothelial cells, due to the sequential activity of CD39 and CD73 [20]. Some of us have pioneered the hypothesis of a functional extra-mitochondrial aerobic ATP production, through the ectopic functional expression of respiratory chain complexes I–IV and of F_1F_o-ATP synthase (ecto-ATP synthase) [23]. Oxygen availability in the lung endothelium would prematurely switch on the extra-mitochondrial oxidative phosphorylation (OXPHOS) machinery in endothelial cells. Notably, in both cases the abrupt increase in oxygen availability for the premature newborn (considering the hypoxic state of the fetus, living with an oxygen concentration ranging between 3% and 11%) would be the cause of the high production of Ado.

Evaluation of the hypothesis

Posing that the premature axons reach inadequate energy charge for their metabolic needs, these will produce excess Ado. This can be bidirectionally transported across the membranes by the equilibrative nucleoside transporters (ENTs) or by concentrative nucleoside transporters (CNTs) [18]. In turn, Ado would promote myelination to sustain firing, acting as a potent neuron–glial transmitter to inhibit proliferation and stimulate differentiation of the OPCs [17]. Ado plays the same action potential-dependent signaling between axons and premyelinating Schwann Cells (SCs), which express functional adenosine and ATP receptors [16]. Moreover, Ado would play a double role, as it was shown to be able to efficiently suppress synaptic function [14,15], thereby relieving the hypometabolic neurons. OPCs express all four subtypes of adenosine receptors that are activated in response to action potential firing in Central NS [17,24,25]. Conversely, when energy charge is adequate, an excess ATP is released. Myelination is regulated by an electrical activity-dependent mechanism promoting or depressing it, which involves opposite roles for ATP and Ado signaling [26]. ATP is a signal inhibiting Schwann Cells (SCs) myelination: nonsynaptic ATP release from dorsal root ganglion axons inhibits SCs proliferation [16].

Another source of Ado would be the eATP produced by the extra-mitochondrial OXPHOS in the endothelial cell plasma membrane. An extra-mitochondrial aerobic ATP synthesis was reported on the membranes of the HUVEC endothelial cells [27,28], and in other membranes [29–31]. In the immature lung of the VLWB newborn, atmospheric oxygen levels are bound to stimulate an ecto-ATP synthesis. ATP would then be metabolized to Ado by the sequential action of two ectocellular enzymes, namely CD39 and CD73 [20]. If this were the case, the generation of reactive oxygen species in the preterm infant would be concurrent rather than subsequent to the generation of Ado. Indeed, hypoxia/reoxygenation episodes in VLBW infants are the consequence of immature respiratory system [5], which can sustain a proinflammatory cascade and oxidative stress. A primary cause of mortality and long-term sequelae of VLBW infants is oxidative stress consequent to exposure to excessive oxygen concentrations. The premature operativity of the ectopic OXPHOS, due to the availability of oxygen, could produce both ATP and oxidative stress. In fact, an over functioning OXPHOS is a primary source of ROS [32]. Premyelinating axons are particularly sensitive to oxidative stress, recently implicated in OPC death [4]. The oligodendrocyte lineage in the human premature brain is a vulnerable cell population (reviewed in [33]). It has been shown that perinatal oxidative stress in the mouse causes a long-term decrease in oligodendrocyte number and impairs myelination. Intermittent hypoxemia episodes reproduced in neonatal mice were shown to replicate the phenotype of non-cystic WM injury [34]. Purines, especially eATP and its metabolite Ado are potent mediators of inflammation [35]. Ado and reactive oxygen species are among the principal chemical mediators involved in white matter injury. Endothelial cell oxidative damage is a primary cause of the fearsome intra-ventricular brain hemorrhage and neonatal respiratory distress syndrome (NRDS).

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