

LETTER TO THE EDITOR

Hypophosphatemia and sudden infant death syndrome (SIDS)—is ATP the link?

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In their recent letter Van Kempen and co-workers presented an intriguing hypothesis linking hypophosphatemia and sudden infant death syndrome (SIDS) (1), founded on the work by Siren and Siren on the critical diaphragm failure being the cause of SIDS incidences (2,3). Van Kempen and co-workers argued that both etiology and symptoms of SIDS can be explained by low concentrations in erythrocytes of phosphate metabolites, mainly 2,3-biphosphoglycerate (2,3-BPG, also known as 2,3-diphosphoglycerate, 2,3-DPG), which in effect would impair muscle function (especially diaphragm) and lead to respiratory failure as Siren and Siren originally stated. We find the hypothesis interesting and definitely worth further investigation; however, we would assign the main role to ATP, not to 2,3-BPG.

First of all, 2,3-BPG binds weakly to fetal hemoglobin in comparison to adult hemoglobin (4). Analyses of oxygen equilibrium curves in infants indeed showed a correlation between P_{50} and 2,3-BPG concentration (5), but it was the so-called ‘functioning DPG fraction’, that is, a multiplication of total red cell 2,3-BPG content and the percentage of adult hemoglobin. Fetal hemoglobin is being replaced by adult hemoglobin within the first few months of the infant’s life. However, its concentration does not seem to correlate with the log-normal distribution of age in SIDS incidents. Furthermore, the concentration of 2,3-BPG is tightly regulated as synthesis and degradation are separated and catalyzed by different enzymes (6). This process is one of the

slowest in the whole metabolic system of the red blood cell (7). As a result, changes in the concentration of 2,3-BPG in erythrocytes in response to external stimuli (for example, high altitude or acidosis (8,9)) usually take several hours. Even more, in case of exchange transfusion with acid-citrate-dextrose (ACD) preserved blood in infants, adjustment of 2,3-BPG concentrations occurs over days not hours (10). It is hard to envision a sudden drop in the concentration of 2,3-BPG, but if it indeed occurs it will influence blood oxygen affinity only in older infants whose blood is already composed mainly of adult hemoglobin. That said, the hypothesis on the affected oxygen transport in SIDS is supported by the correlations between the levels of fetal hemoglobin and incidences of SIDS (11,12). However, we would like to extend the work of Van Kempen and co-workers by pointing in the direction of the major player in the regulation of oxygen delivery—ATP.

In recent years a substantial body of evidence has accumulated for the hypothesis that erythrocytes themselves are the vascular controller adjusting blood flow on the basis of the local oxygen needs (reviewed in (13)). That regulation is executed mainly by an O_2 saturation-dependent ATP release. However, the ATP signaling is not limited to vessel walls—it affects all rheological properties of blood. As shown recently, viscosity of blood is affected by cell-deformation-dependent ATP release (14). In contrast to 2,3-BPG, the metabolism of ATP is fast (7), and similarly rapid is also its release (15). Therefore, effects of ATP on blood flow are also relatively quick.

In other words, in blood, ATP signaling has an immediate mode of action.

ATP deficiency impairs the contractile properties of the diaphragm in patients with acute respiratory failure (16). Also, phosphate depletion is frequently associated with chronic obstructive pulmonary disease (17). Both observations inspired Van Kempen and co-workers to establish a link between hypophosphatemia and SIDS. However, given the role of ATP in regulation of blood flow, it is ATP not 2,3-BPG that seems to play the major role in the observed effects. Furthermore, the common bacterial toxin hypothesis of SIDS (18), supported by both pathological findings and epidemiological risk factors (19), can be easily merged with the hypophosphatemia hypothesis. Inflammatory mediators trigger strong ATP release outside of the cells and down-modulate levels of ecto-ATP/ADPases (CD39) (20), interfering with the delicate balance of phosphate concentrations in the organism. Similar conclusions on the critical role of ATP have been reached by Deixler (21), who founded her hypothesis on the analysis of SIDS risk factors. Siren and Siren (2) implicated impaired ATP metabolism in critical diaphragm failure pointing out reduction in the mitochondrial function (including ATP-generating capacity) in systemic infections via increase in mitochondrial free radical generation (22).

To conclude, 2,3-BPG plays an important role as a major allosteric effector of adult hemoglobin, but its concentration neither affects oxygen affinity of fetal hemoglobin nor changes rapidly to be a mediator in sudden infant death syndrome incidences. The substantial body of evidence for impaired ATP metabolism being a causative factor in infection-induced muscle dysfunction indicates that ATP is the most plausible link between hypophosphatemia and SIDS.

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