Changes in Arginine Metabolism during Sepsis and Critical Illness in Children

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Sepsis is a significant health problem in children and the most common cause of death worldwide, but it is different from adult sepsis in epidemiology and pathophysiology. In adults, the amino acid arginine has received much attention in the context of critical illness and sepsis, but is less known in children.

Arginine Metabolism

Besides being needed for protein synthesis, arginine has other important functions [1]. It is catabolized by arginase to ornithine and urea, and by nitric oxide synthase (NOS) isoenzymes to nitric oxide (NO) and citrulline. Furthermore, arginine is metabolized into agmatine and creatine. Hence, it has a role in ureagenesis, immune function, wound healing, cell growth and differentiation and vasodilatation. Arginine is derived from dietary intake, body protein breakdown and de novo arginine synthesis from citrulline. During inflammation, NOS isoenzyme 2 is induced to a great extent, enhancing cytotoxic effects in macrophages on the one hand, but leading to (excessive) vasodilatation on the other hand. Meanwhile, microcirculation is compromised due to reduced NOS3 activity [2].

Arginine Deficiency during Critical Illness and Sepsis

In critically ill adults and children, plasma arginine and citrulline concentrations are severely decreased, especially during sepsis. This points to an arginine-deficient state. From stable isotope studies, it became apparent that arginine availability is reduced because of increased arginine disposal (in part by increased arginase activity and increased protein synthesis) on the one hand, which is not met by endogenous arginine production on the other hand. Important in this respect is the reduced de
novo arginine synthesis [3]. The latter most likely results from reduced citrulline availability, which is either caused by reduced precursor availability (glutamine) or impaired intestinal function. As a result of arginine deficiency, NO synthesis may be reduced. These metabolic changes seem to be dependent on the severity of inflammation [4]. See figure 1 for a proposed hypothesis.

Factors Affecting NO Synthesis

Reduced arginine availability, as a substrate for NOS, may limit NO synthesis. Other factors are competition between NOS and arginase for arginine, competition between arginine and lysine and ornithine for transport into the cell and inhibition of NO synthesis by asymmetrical dimethylarginine (ADMA) [2]. The latter is increased in critically ill adults and related to increased mortality. Especially the ratio between arginine and ADMA seems of importance, which is reduced in septic adults, primarily by reduced arginine concentrations, and associated with increased hospital mortality. Restoration of the arginine-ADMA balance by increasing arginine availability could therefore be a therapeutic target [5].

Arginine Supplementation

Hence, arginine or citrulline supplementation in severe inflammation seems to be a logical next step. Reviews on immunonutrition containing arginine in adults have been not been uniform. In critically ill children, one group has studied immunonutrition, but no effects on clinical outcome were found. Arginine and citrulline supplementation in critically ill children has not been studied. Arginine supplementation in critically ill adults improved arginine concentrations, without adverse effects on hemodynamics. Oral and intravenous citrulline supplementation improved arginine and citrulline concentrations in children undergoing cardiac surgery, which may be valuable in critically ill children as well. Another approach to improve arginine availability and NO synthesis could be to use a protein-energy-enriched formula, as we have recently shown.

Conclusion

Critical illness and sepsis in children are arginine-deficient states, the extent of which depends on the severity of inflammation. There may be a role for arginine or citrulline supplementation, although the use of protein-energy-enriched formulas may be an initial step to improve arginine
Fig. 1. Hypothesis of changes in arginine (Arg) metabolism in moderate inflammation and severe inflammation (or sepsis). Plasma arginine is slightly reduced during moderate inflammation. This is due to a slight reduction in arginine synthesis, because of moderately reduced citrulline availability, and a moderate increase in arginine catabolism. These changes are augmented during severe inflammation, leading to a severe reduction in de novo arginine synthesis and extensively enhanced arginine utilization for protein synthesis and by arginase. As a result, plasma arginine concentrations are further decreased, leading to reduced availability for NO synthesis, possibly compromising microcirculation via NOS isoform NOS3. Reproduced with permission from American Society for Nutrition [6].
availability. Because pediatric sepsis is a significant health problem differing from adult sepsis, pathophysiological mechanisms and possible interventions in arginine metabolism in critically ill and septic children should be investigated.

References