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Review article

Glutamine and glutamate: Nonessential or essential amino acids?

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ABSTRACT

Glutamine and glutamate are not considered essential amino acids but they play important roles in maintaining growth and health in both neonates and adults. Although glutamine and glutamate are highly abundant in most feedstuffs there is increasing evidence that they may be limiting during pregnancy, lactation and neonatal growth, particularly when relatively low protein diets are fed. Supplementation of diets with glutamine, glutamate or both at 0.5 to 1.0% to both suckling and recently weaned piglets improves intestinal and immune function and results in better growth. In addition such supplementation to the sow prevents some of the loss of lean body mass during lactation, and increases milk glutamine content. However, a number of important questions related to physiological condition, species under study and the form and amount of the supplements need to be addressed before the full benefits of glutamine and glutamate supplementation in domestic animal production can be realized.

1. Introduction

Glutamate and glutamine are highly abundant amino acids found in most foodstuffs and, in total, comprise somewhere between 5 and 15% of dietary protein (Lenders et al., 2009; Li et al., 2011). Similarly, these two amino acids comprise a large proportion of the body pool of amino acids, both in the free form and incorporated into protein. Traditionally glutamate and glutamine have been considered to be non-essential (dispensable) and, due to the almost complete catabolism of dietary glutamate and glutamine in the intestine, essentially all of the large body pool is synthesized endogenously (Curthoys and Watford, 1995). The definition of what is, and what is not, an essential amino acid however, is not unequivocal. Rose et al. (1948, 1949) defined an essential amino acid as one that the body cannot make in sufficient amounts to maintain growth or nitrogen balance. This definition is noteworthy since it does not say that the body cannot make the amino acid, rather that it cannot make sufficient amounts for a key purpose. Recently there has been a reconsideration of additional functions of amino acids and some, including glutamine, are now considered as conditionally essential at key times (Wernerman, 2008; Wu, 2010). In this paper the nutritional aspects of glutamate and glutamine will be described and the requirements, if any, during gestation and lactation, and for optimal growth in neonates, will be considered particularly with reference to feeding lower protein diets.

2. Glutamate and glutamine

2.1. Metabolism

The healthy adult human contains over 80 g of free glutamine, with >98% of it inside skeletal muscle cells at concentrations of 20 mM and above. In addition, plasma glutamine is turning over at very high rates (60 to 80 g per day in healthy subjects) (Curthoys and Watford, 1995; Watford, 2008; Wernerman, 2008). Glutamine is made via the action of glutamine synthetase from glutamate and ammonia (Fig. 1), primarily in skeletal muscle, lungs, adipose tissue and liver. Glutamine is a precursor for a number of biosynthetic pathways required for growth and cell division (Fig. 2). The bulk of glutamine however, is hydrolyzed by glutaminase Fig. 1 and 2 and ultimately serves as substrate for hepatic gluconeogenesis and urea synthesis, renal ammoniagenesis, and is the major respiratory fuel for enterocytes and cells of the immune system (Curthoys and Watford, 1995). Glutamine is also an important signaling molecule, often acting by activation of the mammalian target of rapamycin (mTOR) (Fig. 2), stimulating anabolic functions such as protein synthesis, cell growth and differentiation, and

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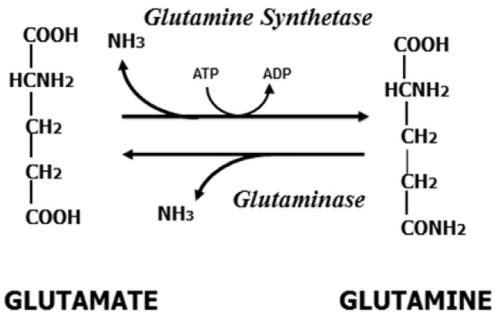

Fig. 1. Glutamine synthetase and glutaminase.

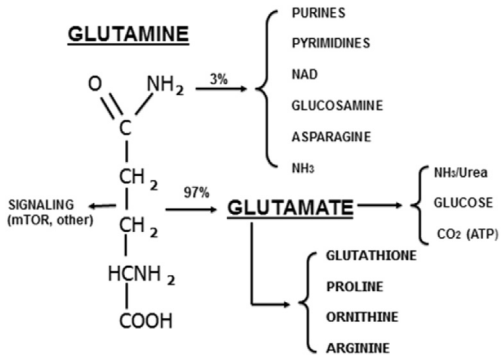

Fig. 2. Pathways of glutamine and glutamate metabolism. The majority of glutamine is degraded to glutamate and then used as a substrate for urea and glucose synthesis or as a fuel (ATP production). Although glutamine is an essential precursor for many important compounds but these represent a small (< 3%) fraction of glutamine metabolism. Glutamine also acts as an anabolic signal, often via activation of mammalian target of rapamycin (mTOR).

inhibiting catabolic functions such as protein degradation and apoptosis (Curi et al., 2007). In addition, during gestation there is a large uptake of glutamine across the placenta, together with placental glutamine synthesis, resulting in large amounts of glutamine available for fetal growth (Fig. 3). Likewise in lactation, free and protein bound glutamate and glutamine, derived from both the circulation and mammary gland synthesis (Fig. 3), are the most abundant amino acids in milk (Wu and Knabe, 1994; Davis et al., 1994; Wang et al., 2008). Thus the maintenance of glutamate and glutamine homeostasis is important for the well-being of a number of tissues in the body, particularly during gestation, lactation and growth.

2.2. Glutamine becomes conditionally essential in hyper-catabolic states

In healthy animals the body is able to synthesize considerable quantities of glutamine and there is no apparent evidence of a shortage. About 30 years ago however, it became apparent that in hyper-catabolic patients glutamine requirements (for the immune system, wound healing, acid–base balance and gluconeogenesis) could increase beyond the endogenous capacity for glutamine synthesis (Wernerman, 2008). An early response to such stress is a rapid release of muscle glutamine and a resultant drop in both muscle and plasma free glutamine concentrations. Subsequently there is an up-regulation of muscle glutamine synthesis from amino acids derived from a net increase in muscle proteolysis. In clinical studies it has been proposed that a plasma glutamine concentration < 0.42 mM (normal 0.6 to 0.8 mM) indicates glutamine insufficiently and exogenous glutamine should be provided (Wernerman, 2008). Although beyond the scope of this text, a

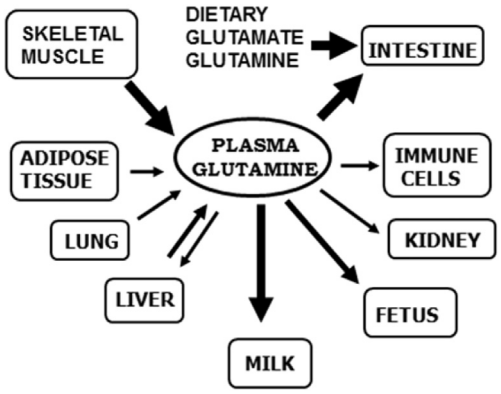

Fig. 3. Glutamine metabolism during pregnancy and lactation. Increased dietary intake provides glutamine and glutamate for the small intestine, but skeletal muscle provides most of the circulating glutamine that is derived from other amino acids, including those from both the diet and muscle proteolysis. The size of the arrows indicates a rough estimate of the magnitude of glutamine flux.

number of studies have shown benefits for supplemental glutamine given to such patients (Wang et al., 2010).

2.3. Glutamine and glutamate are conditionally essential during pregnancy, lactation and growth

In the domestic animal industry the treatment of hyper-catabolic conditions is of little interest and thus the important question is "is glutamine conditionally essential at other times"? We observed that plasma and muscle glutamine concentrations fell steadily throughout lactation in the horse and this was accompanied by a loss of skeletal muscle, representing a mildly catabolic state (Manso Filho et al., 2008) as seen in a number of other species (Manso et al., 2012; Clowes et al., 2005; Pine et al., 1994). Thus the question arises if glutamate or glutamine supplementation would be beneficial during gestation and lactation. As mentioned above these conditions are associated with increased glutamine needs, for fetal growth and milk production, and it was traditionally assumed that such needs were met by catabolism of extra dietary amino acids (Fig. 3). Thus it was surprising to find that such substrates were insufficient and that additional endogenous substrates for glutamine synthesis were drawn from the mother's lean body mass. We proposed that supplementation with glutamine and/or glutamate may provide the extra glutamine required during lactation and thus spare the lean body mass of the mother. Similarly, it is well established that the neonatal gut is particularly sensitive to stress and that weaning, particularly abrupt early weaning, is often associated with negative growth and pathological outcomes that are clearly related to intestinal and immunologicadysfunction. Given that glutamate and glutamine are the preferred fuels of this tissue, and of cells of the immune system, (Curthoys and Watford, 1995; Curi et al., 2007) then supplements may aid to maintain intestinal function throughout weaning.

2.4. Glutamine and glutamate supplements are beneficial during pregnancy, lactation and growth

A number of studies over the past 10 years have shown that glutamine and/or glutamate supplementation can be beneficial to recently weaned piglets (Jiang et al., 2009; López-Pedrosa et al., 2007; Wang et al., 2008; Wu et al., 1996; Yi et al., 2005; Yoo et al., 1997). Such studies have indicated benefits in preventing intestinal atrophy, maintaining anti-oxidant status and lessening the incidence of diarrhea, and result in increased weight gain and improved food efficiency. One study (Haynes et al., 2009) has