Betaine is as effective as folate at re-synthesizing methionine for protein synthesis during moderate methionine deficiency in piglets

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Abstract

Methionine is an essential amino acid that is in high demand in neonates for protein synthesis as well as for transmethylation (TM) reactions, such as creatine synthesis and DNA methylation. TM reactions produce homocysteine, which can be either converted to cysteine or re-methylated to methionine via folate or betaine (synthesized from choline). It is unclear whether both remethylation pathways are equally important in neonates for remethylation. The objective of this study was to determine whether supplementation with folate, betaine or a combination of both is effective at re-methylating methionine.

Methods

Protocol

- 8-day old Yucatan miniature piglets were fed an intra-gastric elemental diet moderately deficient in methionine (0.2 g kg⁻¹ day⁻¹) and void of folate, betaine and choline for 6 days.
- On day 6, piglets were transferred to a sealed Plexiglas box fitted with a tether and swivel system. Piglets received a primed (7 mg/kg) constant (2.4 mg/kg administered every 30 minutes) infusion of L-[¹³C]phenylalanine for 6 hours. Blood was collected every 30 minutes for determination of plasma L-[¹³C]-phenylalanine enrichment and 20 min breath samples were collected in 1M NaOH every ~45 minutes during the final 3 hours to determine ¹³CO₂ enrichment. A CO₂ analyzer was used to determine the concentration of ¹³CO₂ in the chamber.
- On the evening of day 7 piglets were supplemented with folate, betaine or a combination of both (n=6).
- On day 9 piglets underwent a second L-[¹³C]phenylalanine infusion as described above.
- Blood was collected at baseline, day 7 and day 10 for analysis of plasma metabolites.

Results

Plasma enrichment of [¹³C]-Phenylalanine

- Derivatization with fluoroisobutyryl bromide and hexane followed by analysis via GC/MS. Area under the curve for each ion was used to calculate the ratio of [M+1] phenylalanine as compared to [M+0] phenylalanine.

Discussion

• The amino acid methionine is important in the neonate for both growth and synthesis of S-adenosylmethionine (SAM), the universal methyl donor in over 50 transmethylation (TM) reactions.
• The pools of TM products, including creatine and phosphatidylcholine, are expanding in the neonate, placing a high demand on methionine.
• These reactions produce homocysteine which can either be irreversibly converted to cysteine or remethylated to methionine by receiving a methyl group from folate or betaine (oxidation product of choline).
• In the neonatal piglet, ~50% of methionine is converted to SAM and ~45% of homocysteine is remethylated by folate and betaine, highlighting the importance of these nutrients.
• Although the methionine requirement has been determined in both the infant and piglet, it is not known whether folate and/or betaine can remethylate methionine for protein synthesis when methionine is limiting.

• This is important to consider as the neonatal diet is variable in levels of both sulfur amino acids (methionine/cysteine) and remethylation nutrients

 objectives

- To determine whether provision of methyl donors can re-synthesize methionine for protein synthesis
- To determine whether folate, betaine or a combination of both is effective at re-methylating methionine