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Maternal and Perinatal Outcomes of Maternal Creatine Supplementation as a Therapy for Neonatal Encephalopathy

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Keywords

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Abstract

Introduction

Hypoxic ischemic encephalopathy (HIE) occurs in ~4 per 1000 live term births. Infants that receive current treatments may still develop adverse neurologic outcomes. Maternal gestational creatine supplementation has been proposed as a potential prophylactic neuroprotective therapy, with evidence of reduction in perinatal brain injury in rodent and sheep studies. The current study aims to characterize aspects of creatine synthesis, metabolism, and transport in gestational and neonatal tissues following maternal oral creatine supplementation.

Methods

Ten pregnant rhesus macaques were assigned to control (n=5) and creatine supplementation (0.6g/kg, Creatine monohydrate, PO, BID for ~30 days prior to delivery; n=5) groups. Neonates were exposed to 10 min umbilical cord occlusion during C-section delivery (1551 dGA; Term=167d) and maternal fluid and tissue samples were collected. Neonates were resuscitated and received intensive care for four days until post-mortem tissue collection. Creatine concentrations were estimated in biological fluids and tissue samples. RT-qPCR was performed for genes involved in creatine metabolism. Statistical significance (p0.05) was assessed by Student's t-test and F-test to compare variances, or Mann-Whitney U-test after testing for normal distribution (Shapiro-Wilk).

Results

In response to creatine supplementation, a significant increase was observed for genes involved in creatine synthesis (*Gatm*, *Gamt*), creatine transport (*Slc6a8*), and creatine kinases (*Ckmt1*, *Ckmt2*, *Ckb*, *Ckm*) across multiple neonatal tissues. Across gestation, a higher expression of creatine metabolic genes was present during the 2nd and reduced in the 3rd trimester.

Conclusions

Creatine synthetic gene expression across gestation likely signifies the high energy demand for placental and fetal growth and nutrient transfer. Increased creatine kinase and transporter gene expression may indicate increased creatine tissue storage demands with supplementation. Understanding the changes in endogenous creatine synthesis is important for the safe use of creatine as a therapeutic agent during pregnancy.