Gestational marginal zinc deficiency impaired fetal neural progenitor cell proliferation by disrupting the ERK1/2 signaling pathway.

Nuttall JR, Supasai S, Kha J, Vaeth BM, Mackenzie GG, Adamo AM, Oteiza PI.

OBJECTIVE: This study investigated if a marginal zinc deficiency during gestation in rats could affect fetal neural progenitor cell (NPC) proliferation through a down-regulation of the extracellular signal-regulated kinase (ERK1/2) signaling pathway.

METHODS: Rats were fed a marginally zinc-deficient or adequate diet from the beginning of gestation until embryonic day (E)19.

RESULTS: The proportion of proliferating cells in the E19 fetal ventricular zone was decreased by marginal zinc deficiency. Immunostaining for phosphorylated ERK1/2 in the cerebral cortex was decreased in the marginal zinc fetuses, and this effect was strongest in the ventricular zone. Furthermore, phosphorylation of the upstream mitogen-activated ERK kinases (MEK1/2) was not affected, suggesting that marginal zinc deficiency could have increased ERK-directed phosphatase activity. Similar findings were observed in cultured rat embryonic cortical neurons and in IMR-32 neuroblastoma cells, in which zinc-deficiency decreased ERK1/2 phosphorylation without affecting MEK1/2 phosphorylation. Indeed, zinc deficiency increased the activity of the ERK-directed phosphatase protein phosphatase 2A (PP2A) in the fetal cortex and IMR-32 cells. Inhibition of PP2A with okadaic acid prevented the decrease in ERK phosphorylation and proliferation of zinc-deficient IMR-32 cells.

CONCLUSION: Together these results demonstrated that decreased zinc availability reduces ERK1/2 signaling and decreased NPC proliferation as a consequence of PP2A activation. Disruption of fetal neurogenesis could underlie irreversible neurobehavioral impairments observed after even marginal zinc nutrition during a critical period of early brain development.

PMID: 26153680