Proceedings of the Nutrition Society (2018), **77 (OCE2)**, E26 doi:10.1017/S0029665118000204

Spring Conference 2018, 26–27 March 2018, Nutrient-nutrient interaction

The effect of maternal iron deficiency on copper levels and on genes of copper metabolism during pregnancy in the rat

S.C. Cottin[1], G. Roussel[2], L. Gambling[3], H.E. Hayes[3], V.J. Stevens[3] and H.J. McArdle[3]

[1]*Division of Food and Drink, Abertay University, Dundee, DD1 1HG,* [2]*Dept of Physiology and Physiopathology, University Aix Marseille, Marseille, France and* [3]*Rowett Research Institute, University of Aberdeen, AB25 2ZD.*

Iron deficiency is the most prevalent micronutrient deficiency worldwide and is believed to affect nearly 15 percent of pregnant women in the UK. Metabolic crossroads between iron and copper, another trace element that is essential for fetal growth, have been established for decades[(1)] but the effect of iron deficiency on copper metabolism during pregnancy is not fully understood.

54 Rowett Hooded female rats were fed control (50 mg iron/ kg, n = 30) or iron deficient diets (7.5 mg iron / kg, n = 24) for 4 weeks prior to mating and during pregnancy. Maternal liver, placenta and fetal liver were collected at day 21 of pregnancy for the measurement of copper levels and the gene expression of the main proteins involved in copper metabolism (Figure 1).

Copper levels increased in the maternal liver ($p = 0.002$) and placenta ($p = 0.018$) of iron deficient rats while they decreased in the fetal liver ($p = 0.006$). Iron deficiency decreased the expression of the chaperone ATOX1 by −10.5% ($p = 0.042$) and cytochrome c oxidase chaperone (COX17) by −13.8% ($p = 0.020$) in the maternal liver, while COX17 was increased by 15.0% ($p = 0.020$) in the fetal liver. In iron deficient placenta, the copper chaperone for copper/zinc superoxide dismutase complex (CCS) decreased by −9.5% ($p = 0.030$) and ceruloplasmin (CP) by −15.0% ($p = 0.042$) compared to control (Table 1).

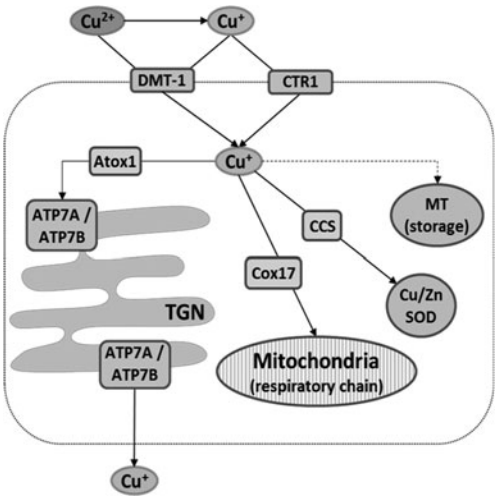

Fig. 1. Outline of cellular copper metabolism and the main proteins involved.

Table 1. Mean % changes ± SD in copper and gene expression in maternal liver, placenta and fetal liver at d21 of pregnancy in iron deficient rats compared to control (* $p < 0.05$, ** $p < 0.01$; Mann-Whitney U test).

Gene	Maternal Liver	Placenta	Fetal Liver
Cu	+10.3 ± 4.0**	+18.8 ± 9.1*	−13.5 ± 8.6**
ATOX1	−10.5 ± 5.0*	+10.8 ± 13.1	−10.3 ± 5.3
COX17	−13.8 ± 5.7*	+5.0 ± 10.8	+15.0 ± 6.2*
CCS	+4.5 ± 8.5	−9.5 ± 4.2*	−2.4 ± 4.5
CP	+18.8 ± 10.2	−15.0 ± 7.1*	−14.0 ± 12.4
ATP7A	−11.0 ± 6.8	−3.3 ± 9.3	−0.2 ± 7.1
ATP7B	+0.8 ± 8.4	−20.0 ± 13	+1.6 ± 5.2
CTR1	+4.1 ± 10.4	−8.4 ± 8.1	−13.1 ± 8.7

The decrease in ATOX1 in the maternal liver could explain – at least partially – the accumulation of copper in the liver, through the reduction of ATP7B trafficking. The alteration in COX17 expression likely reflects the impairment of mitochondrial function well established in iron deficiency[(2)], although whether this is a cause or a consequence is still uncertain. The increase in copper levels in the placenta was accompanied by a reduction in CCS expression, suggesting an alteration of the anti-oxidant defence of the placenta. The role of CP in copper metabolism in the placenta is still unclear, and whether its decreased expression could explain differences in copper levels in placenta and fetal liver needs to be clarified. The results demonstrate that the metabolism of both metals has significant interplay during pregnancy, and that the pathways of interaction may differ between mother and fetus.

1. Gambling L, Kennedy C & McArdle HJ (2011) *Semin Cell Dev Biol* **22**(6), 637–644.
2. Walter PB, Knutson MD, *et al.* (2002) *PNAS* **99**(4), 2264–2269.