

Research Interests: The link between prenatal infections/alcohol abuse and cognitive deficits in offspring

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1) Binge (acute) alcohol exposure in early pregnancy predisposes offspring to neurological deficits by a metallothionein-mediated mechanism

Damage to the developing brain is the major social and economic consequence of prenatal alcohol exposure and in some communities affects as many as 9/1000 births and causes life-long learning and behavioural problems. We hypothesize that the zinc-binding protein, metallothionein (MT), plays a major causative role in alcohol-related cognitive deficits by causing a transient zinc deficiency in the fetus (see Figure). Zinc nutrition is essential for pre- and post-natal development. Intake of zinc is often less than recommended and zinc deficiency can have severe adverse consequences to the fetus. We have shown in mice that dietary zinc supplementation throughout pregnancy can prevent deficits in spatial memory resulting from a single “binge” of alcohol early in pregnancy (equivalent to weeks 3-6 in humans). We will now determine the role of zinc and the zinc-binding protein metallothionein in prenatal alcohol-mediated cognitive deficits by performing behavioural studies on offspring of MT-knockout mice treated with alcohol in utero.

2) Infections in early pregnancy cause impairments in object recognition memory in adult offspring through a metallothionein-mediated mechanism.

Epidemiological studies have associated infections during pregnancy with the pathogenesis of, schizophrenia, non-genetic forms of autism, cerebral palsy and mental retardation. While it remains unclear how a broad range of infectious agents cause neurodevelopment anomalies, accumulating evidence suggest that the damage may be due to the maternal immune response rather than the infectious agent itself. We hypothesize that the zinc-binding protein, metallothionein (MT), induced in the mother’s liver as a result of the inflammatory response, causes a fetal zinc deficiency which is a major inhibitor of neurodevelopment (see Figure). We have previously shown that an inflammatory response in the mother early in pregnancy causes impairments in object recognition memory in adult offspring and have further shown that this can be prevented by dietary zinc supplementation throughout pregnancy. In this study we will use an MT-knockout mouse (that cannot produce MT) to determine 1) whether infection-mediated induction of MT in early pregnancy underpins the anxiety-like behaviour of adult offspring and, 2) whether dietary zinc-supplementation throughout pregnancy protects through a MT-dependent or independent mechanism.

3) The influence of metallothionein on the expression of neurodevelopmental genes after acute alcohol exposure in early pregnancy

Studies in animals demonstrate that a single in utero exposure associated with high blood alcohol concentration causes gene expression changes in the fetal brain that persist into adulthood and are associated with poor cognition. We hypothesize that the zinc-binding protein, metallothionein (MT), which is induced in the maternal liver by

exposure to alcohol, plays a key role in this process by causing a fetal zinc deficiency (see Figure). Zinc is essential for normal neurodevelopment. We have shown that dietary zinc supplementation throughout pregnancy can prevent deficits in spatial memory resulting from a single “binge” of alcohol early in pregnancy (equivalent to weeks 3-6 in humans). In this study we will 1) determine the role of MT in alcohol-mediated changes in the expression of key neurodevelopmental genes (BDNF, NMDA receptor subunits and GABA receptor subunits) and, 2) determine whether dietary zinc supplementation throughout pregnancy can prevent these alcohol-related changes

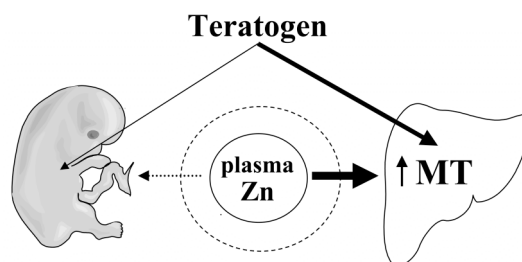


Figure The effect of teratogens (ethanol or inflammatory cytokines; *IL-1 α* , *IL-6* or *TNF α*) on maternal-fetal zinc homeostasis. The teratogens induce maternal liver metallothionein (MT) causing a flux of zinc out of the plasma compartment into the liver where it is bound by MT. There is a resultant decrease in plasma zinc concentration. As the plasma zinc falls the delivery of zinc to the fetus is impaired. Thus transient zinc deficiency is either detrimental in itself or exacerbates the direct effects of alcohol/inflammatory response on the fetus.

Key references (list up to five):

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3. Summers B, Rofe AM, & Coyle P. (2006) Prenatal zinc treatment at the time of acute ethanol exposure limits cognitive impairments in mouse offspring. *Pediatric Res.* 59 (1) 66-71.
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