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COMMENTARY

Perinatal Iron Deficiency and the Developing Brain

Commentary on the article by deUngria *et al.* on page 169

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THE STUDY BY de Ungria and colleagues makes several important contributions. It furthers our understanding of iron's role in the developing brain, bridges basic brain research and developmental cognitive neuroscience, and focuses attention on perinatal iron deficiency. Each of these areas is noteworthy.

In the last decade there has been an exciting burst of research on iron's role during brain development. Recent work in the rodent model shows that brain iron is essential for normal myelination (1–4). In the rat, there is an influx of transferrin and iron into the brain in the immediate postnatal period. As iron and its transport and storage compounds are redistributed in the brain, myelinogenesis and iron uptake are at their peak. In addition, the regulatory genes and proteins controlling these processes are starting to be characterized. Older research also pointed to iron's role in CNS neurotransmitter function, especially implicating the D_2 receptor of the dopaminergic system (see reviews (5, 6)). After almost 20 y of little or no new work, there now are modern studies in this area, confirming dopaminergic alterations in iron deficiency (7, 8) and indicating that the neurotransmitter story is likely to be more complex.

The study by de Ungria *et al.* adds neuronal metabolism to the list of CNS functions impaired by early iron deficiency. The investigators used cytochrome *c* oxidase (CytOx), an iron-dependent enzyme involved in oxidative phosphorylation, as a quantifiable marker of neuronal metabolic activity. They systematically assessed regional differences in brain iron concentration and CytOx activity in young rats born to dams on iron-deficient or iron-sufficient diets throughout gestation and early lactation. The result that neuronal metabolism was most markedly reduced in all regions of the hippocampus is important and novel. This finding extends our appreciation of the vulnerability of the developing hippocampus. Hippocampal changes have now been described in a wide variety of early insults, including hypoxia-ischemia or hypoglycemia (9–12), several developmental neurotoxins (13), and nutrient deficiencies, such as lack of iron. However, the absence of correlation between reductions in iron concentration and CytOx activity in the de Ungria study was an unexpected result that raises further questions. If differing amounts of available iron do not account for differences in reduced CytOx activity, then what is the mechanism? What are the connections, if any, between the functions of iron in the hippocampus and myelination or neurotransmitter function?

Differential effects on the hippocampus appeared specific in this study. However, the hippocampus is not the only area of the brain affected by early iron deficiency. For instance, the nucleus accumbens showed normal CytOx activity in the de Ungria study, but a decrease in dopamine D_2 receptor levels in this structure was reported in earlier research in the postweanling iron-deficient rat (14). Such observations are reminders of the multiple roles that iron plays in the developing CNS, the importance of systematic investigation of different brain regions, and the need for further studies that carefully vary the developmental stage at which iron deficiency occurs and its effects are assessed.

The study makes a contribution beyond showing that neuronal metabolism is affected by iron deficiency. It is an interesting and powerful demonstration of the fruitfulness of interdisciplinary perspectives. Although other studies also demonstrate such cross-fertilization (*eg* linking slower nerve conduction in iron-deficient infants to basic science work on iron's role in myelination (15)), the productive back-and-forth between the bedside and the laboratory is exceptionally well-illustrated by the team involved in the de Ungria study. The study's fundamental hypothesis was that perinatal iron deficiency would differentially reduce neuronal metabolic activity in areas of the brain involved in memory processing. This hypothesis grew out of a close collaboration between Georgieff, a neonatologist, Nelson, a developmental psychologist, and their colleagues in a variety of disciplines. Georgieff and associates had observed that newborn infants of diabetic mothers (IDMs) had lower levels of iron in liver, heart, and brain (16), postulating that abnormal maternal glucose metabolism created chronic fetal hypoxemia, with concomitant increase in red cell mass and depletion of iron stores. Nelson's expertise in the development of memory (17) led them to wonder whether de-

creased brain iron might affect memory functions that depend on certain developing brain regions, especially the hippocampus. The group has been pursuing related studies of these issues, using advanced basic science techniques in the rodent model to answer mechanistic questions and applying sophisticated developmental cognitive neuroscience approaches to assess memory functions in human infants with particular perinatal risks (18, 19). Thus, the result of this multidisciplinary collaboration is sophisticated clinically derived, hypothesis-driven CNS research that breaks new ground in nutrition, brain development, and behavior.

The study's observation of the vulnerability of the developing hippocampus to early iron deficiency, combined with earlier work showing lasting deficits in brain iron in the rodent model (20–24), may also help make sense of some previous research findings. Rodents that were iron deficient in early development appear to have lasting difficulty with spatial navigation (23), a capacity considered to entail normal hippocampal functioning. Young adolescents who were iron deficient as infants show poorer spatial memory (25), which might also relate to the role of the hippocampus in spatial tasks (26). These studies did not include "hippocampal" tasks specifically, but future research should certainly do so, given the findings of the de Ungria study.

A third important contribution of studies such as the one by de Ungria *et al.* is to focus attention on prenatal and perinatal iron deficiency. Recent research in rodents, primates, and humans points to impaired iron transport across the placenta in several prenatal conditions. Examples include diabetes mellitus, prenatal alcohol exposure, intrauterine growth retardation, and maternal stress (16, 27, 28). In some of these conditions, there is direct evidence of decreased brain iron (16, 27) or iron-deficiency anemia in the offspring (28). There are also iron alterations in perinatal hypoxia-ischemia (29, 30), and perinatal iron deficiency increases the vulnerability of the rat hippocampus to hypoxia-ischemia (29). Taken together, these studies raise the possibility that iron deficiency plays an important role in the adverse outcomes observed in these conditions.

These studies also demand that we rethink the traditional dogma that the human fetus suffers few ill effects of maternal iron deficiency, unless severe. Infants born to mothers with nutritional iron deficiency in pregnancy are rarely anemic, but they may have lower iron stores and/or develop iron deficiency sooner postnatally (see reviews (31, 32)). There is now solid evidence that brain iron deficiency can occur even with a normal Hb level. In young animals of every species tested to do date, iron is prioritized to the red cells over all other organs, including brain (16, 33–35). If the developing human hippocampus and other CNS functions are vulnerable to perinatal iron deficiency, as the de Ungria study shows in the rat, there are major public health implications. WHO estimates that more than 30% of pregnant women in developing countries has iron-deficiency anemia (36), and one in four to five babies develops iron-deficiency anemia (37, 38). Anemia is a late manifestation of iron deficiency, and iron deficiency without anemia is even more widespread. If subtle effects of iron deficiency in infancy lay the ground for later problems in cognitive and behavioral functioning, then a large unrecognized population of children could be at risk due to perinatal iron deficiency, a nutritional problem that can be prevented or treated.

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