Iron Deficiency Alters Brain Development and Functioning 1,2
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ABSTRACT

Iron deficiency anemia in early life is related to altered behavioral and neural development. Studies in human infants suggest that this is an irreversible effect that may be related to changes in chemistry of neurotransmitters, organization and morphology of neuronal networks, and neurobiology of myelination. The acquisition of iron by the brain is an age-related and brain-region-dependent process with tightly controlled rates of movement of iron across the blood–brain barrier. Dopamine receptors and transporters are altered as are behaviors related to this neurotransmitter. The growing body of evidence suggests that brain iron deficiency in early life has multiple consequences in neurochemistry and neurobiology.

KEY WORDS: iron deficiency · brain development · behavior · rats · humans · neurotransmitters

Iron deficiency is reported to be the most prevalent nutritional problem in the world today with an estimated 2.5–5 billion people so afflicted (1, 2). Among the numerous biological effects of iron, there is considerable evidence that iron is also important for neurological functioning and development (3–7). This biological basis of the behavioral and cognitive developmental delays observed in iron-deficient infants is not completely understood but possibilities include: i) abnormalities in neurotransmitter metabolism (3, 6, 8, 9); ii) decreased myelin formation (10); and iii) alterations in brain energy metabolism (11). Although the most recent evidence from human studies using auditory-evoked potential changes in iron-deficient infants does not distinguish between these three biological possibilities, it does point toward slowed central neural processing as a key component in neural dysfunction in iron deficiency (5, 12).

This article will focus on distinct bodies of evidence regarding the role of iron in neural functioning and its relationship to cognition and behavior.

How does the brain get iron and where does it go?

Within the brain, there is a system for the acquisition of iron from the plasma pool (transferrin (Tf) receptor), a mechanism for the dispersal or mobilization of iron (Tf)2, a mechanism for cell–specific iron storage (H and L isoforms of ferritin) and a functional pool of iron within each cell (3, 13, 14). The blood–brain barrier provides an effective regulatory point for iron movement from the plasma pool to the cerebral spinal fluid whereas the choroids plexus is also a likely source of iron movement into and out of the brain. Not all brain regions contain the same amount of iron with the basal ganglia, substantia nigra and deep cerebellar nuclei particularly rich in iron (14, 15). Magnetic resonance imaging (MRI) has recently been used to map iron distribution in the brains of children and adolescents (15,
response to dietary iron deprivation, or iron loading. Areas of the brain that are iron rich in adult rat brains are not iron rich for the first 60 d of life (17). Interestingly, the same is true in humans, where the substantia nigra does not become rich in iron until the age of 12–15 y (16). The concentration of iron is highest in the brain at birth, decreases through weaning, and then begins to increase coincident with the onset of myelination and an increased expression of Tf mRNA (5, 17, 18).

(35CNSU), and rats given an iron supplemented diet (>350 μg Fe/g diet) from postnatal days 10–35 (35SSUS).

The brain obtains iron primarily via Tf and Tf receptors expressed in endothelial cells on the brain microvasculature (2, 19). There appears to be a regulatory role for adjacent astrocytes in the regulation of this uptake across the blood–brain barrier (Fig. 2). We, and others, have studied this process as a function of both iron status of the brain and the potential role of plasma Tf saturation on rates of iron uptake (20–22). The rate of uptake of iron is affected by iron status; there is an increased rate when the iron status is low and a decreased rate when it is high (23). In addition, this uptake process is highly selective and not reflective of overall blood–brain barrier permeability (24, 25). Our collaborative efforts with the laboratory of Dr. James Connor demonstrated a heterogeneous loss of iron from the brain with dietary iron deficiency and a heterogeneous “restoration” of iron with iron therapy (20–22). The heterogeneous distribution of iron in brain may very well be the result of regional regulation of uptake and redistribution processes that are dependent on the distributions of Tf receptor and newly described endosomal metal transport protein DMT1 (divalent metal transporter) and a proposed cellular iron exporter, ferroportin (MTP1 or FPN1) (26). The regional distributions of Tf protein and mRNA levels lend support to the notion that the bulk of brain Tf protein is translocated to those regions because the locations of Tf and Tf mRNA are distinct (27) (Fig. 3).

FIGURE 1 Changes in brain iron (Fe), transferrin (Tf), ferritin (ferr) and transferrin receptor (TfR) in rats that were iron deficient from postnatal day 10–21 (21ID), from postnatal days 10–35 (35IDID), iron deficient from days 10–21 and then iron repleted with a large amount of iron until day 35 (35IDSU), control diet until postnatal day 35 (35CN), iron deficient from postnatal days 21–35 (35CNID), control diet until day 21 and then an iron supplemented diet to day 35 (35CNSU), and rats given an iron supplemented diet (>350 μg Fe/g diet) from postnatal days 10–35 (35SUS).

FIGURE 2 Diagrammatic portrayal of the blood–brain barrier and the iron transport proteins believed to play a role in iron movement into the brain. Abbreviations are: DMT1 (divalent metal transporter 1), Tf (transferrin), TfR (transferrin receptor), MTP (metal transport protein or ferroportin).

FIGURE 3 Effects of feeding a low iron or adequate iron diet on Tf and TfR mRNA distributions in young adult rat brain and age-matched control. (Han et al. (26))
Does timing of iron deficiency matter?

The previously mentioned studies in human infants of nerve conduction provide some evidence that the effects of iron deficiency on biological neural functioning are irreversible (5, 12). The issue of timing of iron deficiency, therefore, is of great importance. These biological measurements are the first data that directly support the contention that human toddlers with iron deficiency anemia suffer developmental delays due to biological abnormalities. Given the fact that nearly all of the published clinical intervention trials in human infants also fail to show a complete normalization in functioning despite a normalization of iron status, investigators are forced to consider the question of “critical periods” of development that absolutely require adequate iron nutrure for “normal” development. A number of animal studies have been conducted in an attempt to mimic and model the human condition and the timing of nutrient deficiency to coincide with the timing of peak risk of human infant iron deficiency (28). As autopsy data of human infants suffering solely from iron deficiency is nonexistent, we have relied on animal models and imaging methods to argue for the existence of “a critical period”. Although the course of development in the rat is more compressed than in humans, in both species there is the same sequence of cell migration, significant myelination, cellular differentiation, and increased expression of neuropeptides. What appears to occur from 3–16 mo postnatal in humans occurs from 7–25 d postnatal in rats (28). Iron deficiency during lactation in the rat results in significant loss of regional brain iron that is distinct from those regions that lose iron with dietary restrictions later in life (22) (Fig. 4). Importantly, the restoration of brain iron with later aggressive dietary iron repletion also resulted in incomplete restoration of abnormalities in dopamine (DA) metabolism and in behaviors related to DA (22, 29, 30); i.e., the sensitivity of a brain region to loss of iron during development is likely to be related to the regional development requirements for iron during that period. In contrast to the perception that brain iron is “resistant” to iron depletion, these experiments demonstrate quite clearly that in the rodent, dietary treatments can decrease brain iron within 10 d and replete iron within 14 d. Comparative data in human infants or primate models are lacking, thus there remains uncertainty regarding the completeness of brain iron recovery in humans despite full restoration of hematological indices of iron status (5, 12).

FIGURE 4 Microdialysis dopamine (DA) content from caudate putamen of iron deficient anemic (IDA), control (CN), iron repleted (IR) and hemolytic anemic rats (P2). All animals were injected with saline at 45 min and then with 50 mg/kg of cocaine intraperitoneal at 1.5 h. Dialysate was collected every 20 min and measured by HPLC. (Nelson et al. (29))

The great ado concerning irreversibility of effects of iron deficiency in infancy is thus based on several features: i) the vast majority of studies in humans have had a focus on iron-deficient infants 12–24 mo of age without similar careful examinations of children who are older. ii) Animal models show very clear irreversible abnormalities resulting from gestational and early lactational iron deficiency. iii) Reports of adolescent and adult iron deficiency and brain functioning generally show a normalization in behaviors with correction of the iron deficiency (31). A recently described clinical condition called Restless Legs Syndrome (RLS) appears to be related to deficits in brain iron content and metabolism (32). MRI images demonstrate a decrease in substantia nigra and red nucleus iron content. The severity of this decrease in brain iron content is correlated with the severity of symptoms. A number of patients are quite resistant to dietary iron repletion but do resolve symptoms in a majority of cases with high
metabolism and iron metabolism.

Iron and neurotransmitters

The dopaminergic system develops rapidly during early postnatal life with a rapid increase in the number and density of DA transporters, and receptors in terminal field up to early puberty. Other monoamine transporters and receptors are also being actively expressed in developing neuronal tracts during this time period with continued modification in density up through puberty and into adulthood. These monoamine projections play an important role in the organization of axonal growth and synapse formation during early stages of brain growth but convert to their more traditional role of neurotransmission with aging. The role of iron, or other micronutrients, in this “pruning” of neuronal connections with development is not generally known, nor is there an awareness of the impact of this potential role of iron in brain biology on subsequent developmental achievement.

The potential, or demonstrated, role of iron in neurotransmitter metabolism has been investigated by a number of research groups over the past four decades. As a result, we know that iron is essential for a number of enzymes involved in neurotransmitter synthesis (3, 14) including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine (NE) and DA). In addition, iron is a cofactor for ribonucleotide reductase, and is essential for the functioning of a number of electron transfer reactions related to both lipid metabolism and brain-energy metabolism (14). Iron is related to the activity of monoamine oxidase, an enzyme critical for proper rates of degradation of these neurotransmitters. Apart from these biochemical roles of iron there are several other fundamental observations: i) iron is colocalized with dopaminergic neurons throughout the brain (6, 14); ii) extracellular DA and NE are elevated in brains of iron-deficient rats, but other neurotransmitters are not (8, 30, 33); iii) as brain iron concentration drops due to dietary iron restriction, there are decreases in density of D2 and D1 receptors and DA transporters in striatum (8, 29, 35); iv) the loss of brain iron with dietary iron deficiency is region specific and leads to a heterogeneous effect on DA neurobiology, i.e., in the regions where iron does not fall, there are no changes in DA biology (8, 9); and v) the effects of iron deficiency on brain DA are not due to anemia, per se, because hemolytic anemia in the absence of iron deficiency does not produce these abnormalities in DA neurobiology (Fig. 4) (6, 8, 35).

Although most of the research activity on brain iron and neurotransmitters has focused on DA, there is evidence that both serotonin and NE metabolism are also altered in brain iron insufficiency. The serotonin transporter density was significantly lower in brains of iron-deficient mice (34) whereas in vivo microdialysis in rats provided evidence for decreased rates of uptake of NE (33). Our own studies of cold tolerance and thermoregulation showed that iron-deficient anemic women and rats had elevated plasma NE levels (36). This is consistent with a more rapid loss of NE from peripheral sympathetic nervous system pools and are suggestive of an effect of iron deficiency on monoamine uptake mechanisms. It is important to recall that serotonin, NE and DA transporters are all members of the same family of Na+ cotransporters and show similar characteristics with respect to regulation and translocation (37). The only other neurotransmitter studied relative to brain iron status has been γ-aminobutyric acid (38).

A direct mechanism of effect of cellular iron status on monoamine metabolism has yet to be demonstrated although recent cell culture experiments from our laboratory support such a concept (39). Experiments with pheochromocytoma (PC12) cells and neuroblastoma cells demonstrated a dose response relationship between iron chelation and expression of the DA and the NE transporter (Fig. 5a, b). These experiments demonstrate for the first time direct evidence for a cellular relationship of iron and monoamine metabolism.

FIGURE 5  (a and b) Dopamine transporter and norepinephrine transporter
How is behavior related to brain iron and neurotransmitter biology?

Iron-deficient animals and human infants have changes in behavior that are resistant to iron therapy (2–5, 40). We demonstrated, in animal models, that behavioral changes are robustly associated with changes to central DA and iron concentrations (8, 22, 29). Our most recent analysis of behavior, DA and regional brain iron, however, reveals some relevant relationships:

- Multivariate regression analysis of spontaneous activity demonstrates that as much as 65% of the variability in exploration of the novel environment is associated with ventral midbrain iron, and DA D1 receptor density in midbrain and caudate putamen (41).
- Multivariate analysis of anxiety-like behaviors demonstrates that nearly 45% of the variance in latency to move to a "safer" environment can be attributed to variation in nucleus accumbens DA transporter and D2 receptor density (40).
- Preweaning iron deficiency and postweaning iron deficiency in rats results in decreased exploration and decreased movement (41, 42). Iron repletion results in the normalization of several of these behaviors as well as normalization of most of the alterations in DA biology.

Adult iron deficiency and cognitive functioning

A limited number of studies have been conducted to determine if iron deficiency during nondevelopmental periods of life are associated with changes in behavior, cognition and brain function (31, 43). Studies in adolescents who were iron deficient, but not anemic, revealed alterations in cognitive functioning that could be attributed to iron depletion but not anemia (31). When specific tests of attention are performed, iron-deficient anemic adolescents perform less well than iron-sufficient teens and also respond to iron therapy.

This brief article has highlighted several of the known biologic roles of brain iron on neural metabolism and functioning. Although much of the work has focused on early development as the "critical period", there is not yet certainty that that period has been exactly defined or limited to infants less than 2 y of age. The more recent evidence with adults with RLS, iron deficiency in renal disease and simple postpartum iron deficiency all suggest that neural functioning and behavioral consequences to brain iron deficits are not limited to infants.

ACKNOWLEDGMENTS

The author is thankful for long and fruitful collaborations with Dr. James Connor, Dr. Byron Jones, members of the Brain and Behavior in Early Iron Deficiency Program Project, the postdoctoral fellows, the graduate students and the undergraduate researchers who have spent many hours in discussions, and work, to help formulate these findings.

FOOTNOTES
Animals (TEMA)” in Berkeley, California, June 2–6, 2002. This meeting was supported by grants from the National Institutes of Health and the U.S. Department of Agriculture, and by donations from Akzo Nobel Chemicals, Singapore; California Dried Plum Board, California; Cattlemen’s Beef Board and National Cattlemen’s Beef Association, Colorado; Clinical Nutrition Research Unit, University of California, Davis; Dairy Council of California, California; GlaxoSmithKline, New Jersey; International Atomic Energy Agency, Austria; International Copper Association, New York; International Life Sciences Institute Research Foundation, Washington, D.C.; International Zinc Association, Belgium; Mead Johnson Nutritional, Indiana; Minute Maid Company, Texas; Perrier Vittel Water Institute, France; U.S. Borax Inc., California; USDA/ARS Western Human Nutrition Research Center, California; Wyeth–Ayerst Global Pharmaceuticals, Pennsylvania. Guest editors for the supplement publication were Janet C. King, USDA/ARS WHNRC and the University of California at Davis; Lindsay H. Allen, University of California at Davis; James R. Coughlin, Coughlin & Associates, Newport Coast, California; K. Michael Hambidge, University of Colorado, Denver; Carl L. Keen, University of California at Davis; Bo L. Lönnerdal, University of California at Davis and Robert B. Rucker, University of California at Davis.

We acknowledge support for our research from National Institutes of Health (grants: RO1–NS35088, RO1–NS34280, PO1–HD39386) and U.S. Department of Agriculture (grant 99–35200–7610).

Abbreviations used: DA, dopamine; Tf, transferrin; NE, norepinephrine; RLS, restless legs syndrome.

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623–628. [Medline]


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