The Journal of Nutrition
Symposium: Infant and Young Child Iron Deficiency and Iron Deficiency Anemia in Developing Countries—The Critical Role of Research to Guide Policy and Programs

Why Iron Deficiency Is Important in Infant Development[1–3]

John L. Beard*

Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802

Abstract

Infants who experience iron deficiency during the first 6–12 mo of life are likely to experience persistent effects of the deficiency that alter functioning in adulthood. A lack of sufficient iron intake may significantly delay the development of the central nervous system as a result of alterations in morphology, neurochemistry, and bioenergetics. Depending on the stage of development at the time of iron deficiency, there may be an opportunity to reverse adverse effects, but the success of repletion efforts appear to be time dependent. Publications in the past several years describe the emerging picture of the consequences of iron deficiency in both human and animal studies. The mechanisms for iron accumulation in the brain and perhaps redistribution are being understood. The data in human infants are consistent with altered myelination of white matter, changes in monoamine metabolism in striatum, and functioning of the hippocampus. Rodent studies also show effects of iron deficiency during gestation and lactation that persist into adulthood despite restoration of iron status at weaning. These studies indicate that gestation and early lactation are likely critical periods when iron deficiency will result in long-lasting damage. J. Nutr. 138: 2534–2536, 2008.

Introduction

New insights are emerging from recent and ongoing investigations into the role of iron in neurocognitive and neurobehavioral development. The scope of this brief article is to present an overview of the current state of knowledge concerning the biology of developmental iron deficiency. It also discusses existing animal models and other databases that provide us some biological underpinnings with regard to the human situation.

Biological basis of persistent effects

Iron requirements are most likely to exceed iron intake at 2 time periods in the lifecycle: the first 6 to 18 mo of postnatal life and then, for girls, during adolescence. Iron deficiency in y 1 of life occurs at a time point of rapid neural development, and when morphological, biochemical, and bioenergetic alterations may all influence future functioning (1,2). The structures of the brain can become abnormal because of iron deficiency either in utero or in early postnatal life because iron is essential for proper neurogenesis and differentiation of certain brain cells and brain regions (3–5). The recent studies in rodents clearly identify the hippocampus and striatum as 2 areas in which morphology is altered. There is a decreased arborization of dendrites that decreases the number and complexity of interneuronal connections. A second morphological alteration is the location and functioning of oligodendrocytes, the cells responsible for making myelin. These cells are particularly sensitive to iron deprivation, and their deficiency results in altered composition and amount of myelin in white matter (6,7). These alterations appear to be persistent and do not return to normal levels later in life. Studies in rodents provide the supporting biological evidence pertinent to the human studies from Chile, Costa Rica, and elsewhere in which persistent effects of early iron deficiency are being documented (8–11).

The second biological dimension suspected of being altered by iron deficiency is neurochemistry and specifically the monoaminergic pathways (12–14). In both animal models and cell culture experiments, there are reproducible findings that dopamine and norepinephrine metabolism are altered by iron deficiency. Iron deficiency appears to alter the synthesis and catabolism of the monoamines, and early repletion of iron status after gestational iron deficiency only overcomes the lasting effects (15,16). The evidence for alterations in dopamine or norepinephrine in humans is limited. Oski et al. (17) showed 2 decades ago that urine of iron-deficient infants was particularly high in norepinephrine and returned to normal with the restoration of iron adequacy. Borel et al. (18) showed alterations in plasma norepinephrine levels in iron-deficient women during cold stress. Both dopamine and norepinephrine become important potential biological explanations for human dysfunctions in motor control, sleep cycles and activity, and learning and memory (2). A number of the cognitive and behavioral tasks rely

[1] Published as a supplement to *The Journal of Nutrition.* Presented as part of the symposium "Infant and Young Child Iron Deficiency and Iron Deficiency Anemia in Developing Countries: The Critical Role of Research to Guide Policy and Programs" given at the 2008 Experimental Biology meeting on April 7, 2008, in San Diego, CA. The symposium was sponsored by the American Society for Nutrition. The symposium was chaired by Chessa Lutter and Rebecca Stoltzfus.

[2] Supported in part by NIH HD 39386 and HD 050254.

[3] Author disclosures: J. L. Beard, no conflicts of interest.

* To whom correspondence should be addressed. E-mail: jbeard@psu.edu.

on adequate functioning of the nigrostriatal dopaminergic and mesolimbic pathways as well as the noradrenergic projected fields in the midbrain.

The third biological dimension being actively investigated is the effect of iron deficiency on bioenergetics (4,19). The capacity to utilize specialized nuclear magnetic resonance technology to assess the ability of the brain to produce high-energy phosphate compounds and the metabolism of substrates has been directed to studies of metabolism in the hippocampus and striatum (4) of iron-deficient rodent brain tissue (20). This new approach suggests that fuel utilization in the iron-deficient brain is different from that in control brains. The corollary with human fuel utilization in brain has not been clarified yet, but it is important to recall that the brain is 1 of the most oxidative organs of the body and usually requires glucose as a fuel. It has been known for a long time that iron deficiency alters glucose homeostasis (21), but direct studies of humans with iron deficiency have still not been conducted. It is also relevant to question how widespread these effects of iron deficiency are on brain bioenergetics because only 2 brain regions have been examined. Because iron distribution in the brain is heterogeneous and developmentally dependent, it is likely some regions will be sensitive, whereas others may be unaffected.

These 3 aspects of brain biology impacted by iron deficiency are likely not mutually exclusive events and are interactive in terms of their impact on neural functioning and development. In the next sections of this article, we examine the recent information available in human, monkey, and rodent studies. These studies have attempted to examine the connection among the aforementioned biological alterations and developmental delays and abnormalities when iron deficiency is present in early life.

Human studies of developmental iron deficiency

There are an increasing number of controlled clinical intervention human trials of iron deficiency in y 1 of life and the consequences of such deficiency; these trials have all been reviewed recently (8,22–24). Many earlier human infancy studies used the Bayley Scales of Infant Development as the primary dependent variable, and only half of them were case-controlled intervention trials. Some studies showed significant developmental delays that were irreversible with iron therapy. Three studies showed developmental delays that were mostly reversed with iron therapy, and only a few of the trials evaluated both cognitive and emotional or behavioral measures. Thus, there is a mixed historical perspective (22). An important new step forward, however, was the increased utilization of electrophysiology to begin looking into biological systems (25).

Both visual and auditory evoked potential approaches are being utilized and reveal some very powerful information (26). Auditory brainstem responses (noninvasive) were tested at 6, 12, and 18 mo, and iron therapy was started at 6 mo in infants known to have iron deficiency anemia. Response to the intervention was tested in 85% of infants at 12 mo of age and in 71% of infants at 18 mo of age. The AEP studies showed slowed nerve conduction velocity in iron-deficient infants that did not improve even after several years of iron treatment (27). These are important data in that they strongly suggest hypomyelination and/or alterations in neurotransmitters as a result of iron deficiency in y 1 of life. These children were growing normally, so it is unlikely other nutrient deficiencies may have been present and undetected. The possibility does exist, however, that other nutrient deficiencies may have been present at 6 mo of age and were causally related to this persistent change in central conduction time.

In 2001, a team of researchers began applying more specific questions to the problem of impact of early developmental iron deficiency (2). That group felt that specific questions relative to cognitive and behavioral development needed to be answered, so a broad range of questions, but within highly specific domains, were developed and applied to a study of inner-city African American infants. The project was headed by Betsy Lozoff and investigators from 5 university campuses and included studies in human infants (28–30), monkeys (31–35), and rodents (4,16). The human infant studies are just now being published with results so far oriented toward the motor control and emotionality domains. Gross overall motor control at 9 mo of age was significantly lower in iron-deficient anemic infants than in control (iron-sufficient) infants, and there was a linear effect that included the nonanemic iron-deficient infants (30). This is an important observation because earlier studies failed to find an effect of iron deficiency, with anemia, on functioning. Iron deficiency affected performance on the Peabody Developmental Motor Scales, the Infant Neurological International Battery, the motor quality factor of the Bayley Scales of Infant Development, and a bimanual coordination toy retrieval task. This broad range of motor development tasks indicates that fundamental motor skill development, and the related ability to explore and interact with the environment, were both negatively impacted by iron deficiency in the first 6 mo of life.

The second set of results derived from this study had a focus on social-emotional behavior (36). As with the motor control studies, there was again a strong linear relation between severity of iron deficiency and behaviors of infants at 9 mo of age. The iron-deficient infants had less engagement with the interviewer than iron-sufficient infants, were more shy, had less soothability, and showed less positive affect. These results are highly consistent with other studies that have examined emotionality and behaviors in iron-deficient infants (2,32,36–39). These data are also consistent with a study in South Africa in which maternal iron status was also evaluated (38,40) and in which there was the observation that mother-child interactions were altered by iron deficiency.

This brief update is not exhaustive or inclusive of all the important studies in progress around the world. Nonetheless, it is possible to conclude that new insight into the biology of early developmental iron deficiency strongly indicates irreversible changes in brain structure and function. The most important issues to be defined in the animal models are the time and dose of intervention to optimize success. In humans, this is also an issue because the current animal model data identify a time point in late gestation as being a time after which complete reversibility may not be obtained. But developmental trajectories for brain development are different in rodents and humans, so current work also has a focus on postnatal time points as well. From published data, it appears likely that an intervention needs to occur in the first 6 mo of postnatal life, although that may well depend on whether the infant was iron deficient in utero for a period of time as well as during early postnatal life. As the results of current studies continue to emerge, we will likely be able to identify "critical periods" for different brain regions.

Other articles in this symposium include references (41–44).

Literature Cited

1. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. Semin Fetal Neonatal Med. 2007;12:54–63.

2. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006;64:S34–43.
3. Rao R, Tkac I, Townsend EL, Ennis K, Gruetter R, Georgieff MK. Perinatal iron deficiency predisposes the developing rat hippocampus to greater injury from mild to moderate hypoxia-ischemia. J Cereb Blood Flow Metab. 2007;27:872.
4. Ward KL, Tkac I, Jing Y, Felt B, Beard J, Connor J, Schallert T, Georgieff MK, Rao R. Gestational and lactational iron deficiency alters the developing striatal metabolome and associated behaviors in young rats. J Nutr. 2007;137:1043–9.
5. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. J Nutr. 2003;133:3215–21.
6. Beard JL, Wiesinger JA, Connor JR. Pre- and postweaning iron deficiency alters myelination in Sprague-Dawley rats. Dev Neurosci. 2003;25:308–15.
7. Ortiz E, Pasquini JM, Thompson K, Felt B, Butkus G, Beard J, Connor JR. Effect of manipulation of iron storage, transport, or availability on myelin composition and brain iron content in three different animal models. J Neurosci Res. 2004;77:681–9.
8. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol. 2006;13:158–65.
9. Clark KM, Castillo M, Calatroni A, Walter T, Cayazzo M, Pino P, Lozoff B. Breast-feeding and mental and motor development at 5½ years. Ambul Pediatr. 2006;6:65–71.
10. Corapci F, Radan AE, Lozoff B. Iron deficiency in infancy and mother-child interaction at 5 years. J Dev Behav Pediatr. 2006;27:371–8.
11. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. Arch Pediatr Adolesc Med. 2006;160:1108–13.
12. Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, Beard JL. Iron deficiency: differential effects on monoamine transporters. Nutr Neurosci. 2005;8:31–8.
13. Beard J, Erikson KM, Jones BC. Neonatal iron deficiency results in irreversible changes in dopamine function in rats. J Nutr. 2003;133: 1174–9.
14. Wiesinger JA, Buwen JP, Cifelli CJ, Unger EL, Jones BC, Beard JL. Down-regulation of dopamine transporter by iron chelation in vitro is mediated by altered trafficking, not synthesis. J Neurochem. 2007; 100:167–79.
15. Beard JL, Unger EL, Bianco LE, Paul T, Rundle SE, Jones BC. Early postnatal iron repletion overcomes lasting effects of gestational iron deficiency in rats. J Nutr. 2007;137:1176–82.
16. Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, Georgieff MK, Lozoff B. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. Behav Brain Res. 2006;171: 261–70.
17. Voorhess ML, Stuart MJ, Stockman JA, Oski FA. Iron deficiency anemia and increased urinary norepinephrine excretion. J Pediatr. 1975;86: 542–7.
18. Beard JL, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. Am J Clin Nutr. 1990;52:813–9.
19. Raman L, Tkac I, Ennis K, Georgieff MK, Gruetter R, Rao R. In vivo effect of chronic hypoxia on the neurochemical profile of the developing rat hippocampus. Brain Res Dev Brain Res. 2005;156:202–9.
20. de Deungria M, Rao R, Wobken JD, Luciana M, Nelson CA, Georgieff MK. Perinatal iron deficiency decreases cytochrome c oxidase (CytOx) activity in selected regions of neonatal rat brain. Pediatr Res. 2000; 48:169–76.
21. Borel MJ, Beard JL, Farrell PA. Hepatic glucose production and insulin sensitivity and responsiveness in iron-deficient anemic rats. Am J Physiol. 1993;264:E380–90.
22. Grantham-McGregor S, Ani C. Cognition and undernutrition: evidence for vulnerable period. Forum Nutr. 2003;56:272–5.
23. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA; International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369:824–5.
24. Lozoff B, Kaciroti N, Walter T. Iron deficiency in infancy: applying a physiologic framework for prediction. Am J Clin Nutr. 2006;84: 1412–21.
25. Peirano P, Algarin C, Garrido M, Pizarro F, Roncagliolo M, Lozoff B. Interaction of iron deficiency anemia and neurofunctions in cognitive development. Nestle Nutr Workshop Ser Clin Perform Programme. 2001;5:19–35.
26. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr. 1998;68:683–90.
27. Algarin C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res. 2003;53:217–23.
28. Lozoff B, Lu Angelilli M, Zatakia J, Jacobson SW, Calatroni A, Beard J. Iron status of inner-city African-American infants. Am J Hematol. 2007;112–21.
29. Burden MJ, Westerlund AJ, Armony-Sivan R, Nelson CA, Jacobson SW, Lozoff B, Angelilli ML, Jacobson JL. An event-related potential study of attention and recognition memory in infants with iron-deficiency anemia. Pediatrics. 2007;120:e336–45.
30. Shafir T, Angulo-Barroso R, Jing Y, Angelilli ML, Jacobson SW, Lozoff B. Iron deficiency and infant motor development. Early Hum Dev. 2008;84:479–85.
31. Lubach GR, Coe CL. Preconception maternal iron status is a risk factor for iron deficiency in infant rhesus monkeys (*Macaca mulatta*). J Nutr. 2006;136:2345–9.
32. Golub MS, Hogrefe CE, Germann SL, Capitanio JP, Lozoff B. Behavioral consequences of developmental iron deficiency in infant rhesus monkeys. Neurotoxicol Teratol. 2006;28:3–17.
33. Coe CL, Lubach GR, Shirtcliff EA. Maternal stress during pregnancy predisposes for iron deficiency in infant monkeys impacting innate immunity. Pediatr Res. 2007;61:520–4.
34. Geguchadze RN, Coe CL, Lubach GR, Clardy TW, Beard JL, Connor JR. CSF proteomic analysis reveals persistent iron deficiency-induced alterations in non-human primate infants. J Neurochem. 2008;105: 127–36.
35. Lubach GR, Coe CL. Selective impairment of cognitive performance in the young monkey following recovery from iron deficiency. J Dev Behav Pediatr. 2008;29:11–7.
36. Lozoff B, Clark KM, Jing Y, Armony-Sivan R, Angelilli ML, Jacobson SW. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. J Pediatr. 2008;152:696–702.
37. Wachs TD, Pollitt E, Cueto S, Jacoby E, Creed-Kanashiro H. Relation of neonatal iron status to individual variability in neonatal temperament. Dev Psychobiol. 2005;46:141–53.
38. Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, Irlam J, Isaacs W, Sive A, Tomlinson M. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr. 2005;135:267–72.
39. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Mast D, et al. Young Zanzibari children with iron deficiency, iron deficiency anemia, stunting, or malaria have lower motor activity scores and spend less time in locomotion. J Nutr. 2007; 137:2756–62.
40. Perez EM, Hendricks MK, Beard JL, Murray-Kolb LE, Berg A, Tomlinson M, Irlam J, Isaacs W, Njengele T, et al. Mother-infant interactions and infant development are altered by maternal iron deficiency anemia. J Nutr. 2005;135:850–5.
41. Lutter CK. Iron deficiency in young children in low-income countries and new approaches for its prevention. J Nutr. 2008;138:2523–8.
42. Chaparro CM. Setting the stage for child health and development: prevention of iron deficiency in early infancy. J Nutr. 2008;138: 2529–33.
43. Prentice AM. Iron metabolism, malaria, and other infections: what is all the fuss about? J Nutr. 2008;138:2537–41.
44. Stoltzfus RJ. Developing countries: the critical role of research to guide policy and programs research needed to strengthen science and programs for the control of iron deficiency and its consequences in young children. J Nutr. 2008;138:2542–46.