A role for iron deficiency in dopaminergic neurodegeneration

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Disorders of iron metabolism, manifesting in iron overload or iron deficiency, are implicated in neurodegeneration (1–5). In PNAS, Matak et al. (6) report the specific inactivation of ferroportin (*Fpn*, *Slc40a1*) and transferrin receptor 1 (*TfR1*) in dopaminergic (DA) neurons. The animal models generated in this study demonstrated that *Fpn* did not play a major role in DA neurophysiology, whereas a defect in *Tfr1*-dependent iron uptake caused severe iron deficiency that resulted in neurodegeneration, manifesting in behaviors that are similar to those in Parkinson's disease (6).

Iron transporters play a key role in iron homeostasis and tightly couple intracellular iron levels with cellular requirements (7). This Matak et al. (6) study examines the requirement for FPN, the only known cellular iron exporter (8–10), and TFR1, a key component of the iron uptake machinery, to dissect the effects of iron overload and iron deficiency in the biology of DA neurons. Loss of *Fpn* function in several cell types causes iron overload (11, 12) and has been implicated in myelination defects (13). *TfR1*-mediated iron uptake is the main source of iron for actively proliferating cells, and is essential for iron transport in erythroid cells and neural tissue (14), epithelial enterocytes (15), skeletal muscle (16), and cardiac muscle (17), in addition to DA neurons, as described in Matak et al. (6). *TfR1* deficiency in erythroid cells results in anemia caused by a hemoglobinization defect. In nonerythroid cells, iron defects resulting from TfR1 deficiency result in metabolic defects, defective mitophagy, and increase in gene expression associated with cell death (16, 17). A noncanonical function for TfR1, not related to iron metabolism per se, has been recently reported in some tissues (15, 18).

The Matak et al. (6) study demonstrates that *Fpn*-deficient DA neurons exhibited normal iron homeostasis and had no gross developmental defects, negating a role for *Fpn* in DA pathophysiology (19). In contrast, *TfR1*-deficient neurons were iron-deficient, and as a result exhibited defects in mitochondrial respiration, L-dopa (L-DOPA) production, and changes in gene expression beginning at 7 wk of age (Fig. 1). The metabolic defects in DA neurons, similar to those documented in other

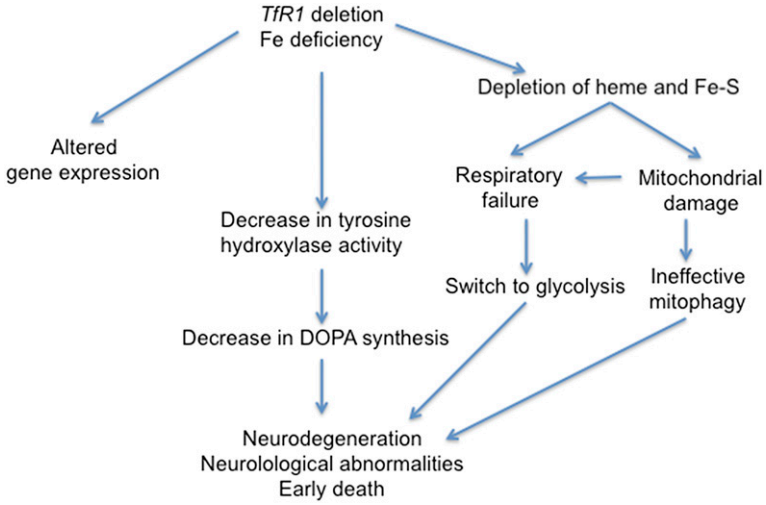

Fig. 1. *Tfr1*-mediated iron uptake is essential for the function of DA neurons. Various perturbations in gene-expression profile and biochemical and metabolic changes in DA neurons occur, leading to their degenerative demise during iron deficiency.

nonerythroid tissues that are iron-deficient, are a result of deficiencies in heme and iron–sulfur cluster formation, which are prosthetic groups required for the stability and function of respiratory complex subunits (17). Although expression of the tyrosine hydroxylase (*Th*) gene, which is required for L-DOPA synthesis, was normal, L-DOPA synthesis was decreased in the *TfR1*-deficient DA neurons, but not in other neurons that were not *TfR1*-deficient. It is likely that the decrease in L-DOPA levels is a direct effect of a decrease in TH activity because of iron deficiency, as TH requires an Fe^{2+}-cofactor in its active catalytic site (20). *TfR1* mutant animals exhibited neurological symptoms, such as decreased locomotion, decreased reflexes, and attenuated responses to visual stimuli. Some of these symptoms were alleviated by treatment with L-DOPA, suggesting that neurological abnormalities in *TfR1* mutant animals were caused by a decrease of TH activity attributable to iron deficiency.

TfR1 mutant animals had gross respiratory defects in their DA neurons, manifesting in dysfunctional gene

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The authors declare no conflict of interest.

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expression that indicated neurodegeneration, oxidative stress, increased apoptosis, and a switch to glycolysis. Neurons in the substantia nigra of mutant mice had enlarged mitochondria at 8 wk of age and contained proteinaceous inclusions, suggesting a defect in mitophagy. *TfR1* mutant mice were dead by 12 wk of age (6).

Until publication of this study (6), the relationship between iron status and pathogenesis of neurodegenerative disorders was a topic of active controversy, in part because of the technical difficulty of isolating specific cell populations within the brain. This study, in the context of other tissue-specific *TfR1* knockout animals generated by the Andrews laboratory, highlights a paradigm by which to investigate a specific cell population in an anatomic region with a high level of cellular heterogeneity. These studies, which demonstrate an important role for iron deficiency in the pathogenesis of Parkinson's disease, pave the way for mechanistic studies on the cell type-specific roles of iron in maintenance of neuronal physiology. In addition, they indicate that *Fpn* is largely dispensable for iron homeostasis in DA neurons, suggesting the existence of other iron exporters that maintain iron levels in the brain.

The absence of a gross phenotype in the DA neurons of *TfR1* mutant mice until 7 wk of age suggests that specific cell types have a developmental-specific requirement for transferrin-mediated iron uptake. Alternatively, the emergence of a neurodegenerative gene-expression profile in DA neurons only at 3 wk of age may indicate that initial iron stores were replete because of maternal iron deposition. The requirement for *TfR1* after 3 wk may indicate the point at which exogenous, dietary iron uptake becomes critical for maintenance of neuronal iron levels.

The reliance of DA neurons on a *TfR1*-dependent pathway for iron uptake is not surprising, and the metabolic phenotype described in the mutant mice is similar to that of other *TfR1*-knockout tissues. However, the data in Matak et al. (6), in combination with other studies, create a biological basis for understanding the relationship between body iron status and neurocognitive function in early childhood. In addition to this study, it has been shown that infants who have abnormally low serum ferritin concentrations, an indicator of severe iron deficiency, have defective auditory recognition memory and neurocognitive development (21, 22). Low serum ferritin is often seen in infants born to severely anemic mothers (23). Hippocampal iron deficiency induced by tissue-specific knockout of *Slc11a2* caused defective hippocampal development and spatial memory (24). Collectively, these studies indicate a critical role for maternal iron status and dietary iron in early neural development. These data may also explain the requirement for a high level of *Sorting Nexin 3* (*Snx3*), *Mitoferrin 1* (*Mfrn1, Slc25a37*), and *-2* (*Mfrn2, Slc25a28*) expression, required for iron import, in vertebrate neural tissues (25–27).

Because whole-embryo knockout of heme and iron metabolism genes causes embryonic death as a result of profound anemia, very little is known about iron metabolism in tissue-specific contexts beyond erythropoiesis. The generation of conditional knockouts via animal models to examine effects of perturbations in iron status within specific cell types—in this case, DA neurons—is an important step in understanding the biology of iron. These studies will have important implications in understanding neurodegenerative disorders and in formulating dietary recommendations, particularly for gravid women and young children.

Acknowledgments

The authors' research is supported by National Institutes of Health Grants K01 DK106156 and F32 DK098866 (to Y.Y.Y.) and R01 DK070838 and P01 HL032262 (to B.H.P.).

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