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Iron deficiency on neuronal function

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Abstract Because of the intrinsic ability of iron to catalyze the formation of reactive oxygen species, it has been associated with oxidative stress and neurodegenerative diseases. However, iron deficiency (ID) also negatively impacts various functions of the brain, suggesting that iron plays an important physiological role in neuronal processes such as myelination, synaptogenesis, behavior and synaptic plasticity (SP). ID not only produces changes in the hippocampus, striatum, amygdale or prefrontal cortex, it also affects the interaction among these systems. In both humans and rodents, the perturbations of these structures are associated to cognitive deficits. These cognitive alterations have been well correlated with changes in neural plasticity, the possible cellular substrate of memory and learning. Given that SP is strongly affected by early ID and the lasting-neurological consequences remain even after ID has been corrected, it is important to prevent ID as well as to seek effective therapeutic interventions that reduce or reverse the long-term effects of the ID in the nervous system. This review will give an overview of the literature on the effects of iron deficit in neuronal functions such as behavior, neurotransmission and SP. We also discuss our recent data about the possible oxidative effect of iron on the mechanisms involved in neural plasticity.

Keywords Iron · Synaptic plasticity · Calcium signaling · Hippocampus · Cognitive impartment

Abbreviations

ROS	Reactive oxygen species
ID	Iron deficiency
SP	Synaptic plasticity
CNS	Central nervous system
PFC	Prefrontal cortex
DMT1	Divalent metal transporter 1
DFO	Desferrioxamine
LTP	Long-term potentiation
PPF	Paired-pulse facilitation
ISO	Isoproterenol
NMDAR	*N*-methyl-D-aspartate receptor
Ry	Ryanodine
RyR	Ry receptor
CICR	Calcium-induced calcium release
mEPSCs	Miniature excitatory postsynaptic currents

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ACSF	Artificial cerebrospinal fluid
fEPSP	Field excitatory post-synaptic potential
LIP	Labile iron pool
DCDHF-DA	2′,7′-dichlorodihydrofluorescein-diacetate

Introduction

The ability of iron to catalyze different redox reactions leads to the formation of reactive oxygen species (ROS) (Feng et al. 2010; Kehrer 2000; Valavanidis et al. 2005), which have been associated with oxidative stress and the pathogenesis of several neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Salazar et al. 2008; Smith et al. 2010).

Iron overload is associated with protein oxidation, lipoperoxidation and DNA damage, and all these perturbations have a deleterious impact on the central nervous system (CNS). On the other hand, iron deficiency (ID) also impairs several CNS functions, suggesting that iron plays an important role under physiological conditions.

Consistent with this idea, iron is critical during neuronal differentiation and proliferation (Carlson et al. 2010; Georgieff 2011); its deficiency affects neural processes such as myelination (Todorich et al. 2009; Ward et al. 2007), dendritic arborization (Jorgenson et al. 2003; Ward et al. 2007) and neural plasticity (Jorgenson et al. 2005; Munoz et al. 2011).

At synaptic level, ID-induced alterations in the hippocampus include changes on the electrophysiological properties of neural circuitry and neurotransmitters systems (Agaoglu et al. 2007; Brunette et al. 2010; Carlson et al. 2010; Jorgenson et al. 2005; Jorgenson et al. 2003; Lozoff and Georgieff 2006; McEchron et al. 2008; McEchron et al. 2005; Munoz et al. 2011; Rao and Georgieff 2007; Schmidt et al. 2007).

In humans, the neurological impairments induced by systemic ID persist even after ID recovery by iron supplementation (Beard 2007; Beard 2008; Lozoff et al. 2006; Lozoff et al. 2000; Stoltzfus et al. 2001; Yadav and Chandra 2011).

All these observations emphasize the need to prevent ID as well as to seek effective therapeutic interventions that reduce or reverse the long-term effects of the ID in the CNS, especially during childhood.

This review will give an overview of the literature on hippocampal ID in neuronal functions such as behavioral, monoaminergic neurotransmission and synaptic plasticity.

Iron deficiency and behavior

The effects of ID on children's cognitive development has been studied extensively (Grantham-McGregor and Ani 2001; Herguner et al. 2011; Hernandez-Martinez et al. 2011; Lozoff 2011; Lutter 2008; Madan et al. 2011). However, the neurobiological bases of cognitive deficits observed are not completely understood.

Several studies in both infants and young children have shown that ID decreases mental performance, which can be observed even in adults. The severity of the deleterious effects on myelination, neurotransmission, gene profiles, learning and memory deficit, are dependent on the degree and duration of ID (Lozoff 2007).

Particularly, the hippocampus, involved in spatial learning and memory formation either in humans or rodents (Whitlock et al. 2006), is highly vulnerable to ID during the perinatal period (Schmidt et al. 2007).

Furthermore, it has been well established that hippocampal-dependent memory processes such as recognition memory and fear conditioning are strongly affected by perinatal ID (Lukowski et al. 2010) (Carlson et al. 2009; Gewirtz et al. 2008; Hernandez-Martinez et al. 2011; Lukowski et al. 2010; McEchron et al. 2005; McEchron et al. 2010; Rao et al. 2011; Schmidt et al. 2007; Siddappa et al. 2004).

The functional contributions of the hippocampus, striatum, prefrontal cortex and amygdale in learned behaviors have been well established. Besides, the processing of information inside these structures are cooperative and/or competitive manner (Poldrack and Packard 2003), which implies a direct or indirect interaction between them.

Although there is limited information about the potential impact of ID in the functionality of other learning systems and how they interact, this issue has begun to be explored.

A recent study showed that rats deprived of iron in the perinatal period, acquired a diminished emotional response to the contextual fear conditioning compared with control rats; while the anxiety related to innate emotional responses, showed no differences between

the groups (McEchron et al. 2010). Because both emotional responses, acquired and innate, possess different neurobiological substrates, the data suggest that ID differentially affects hippocampus and others brain areas.

In the same line, a mutant mouse carrying a deletion of the gene DMT1 specifically in the hippocampus using Cre-recombinase system shows a reduced iron content in this region of the brain (Carlson et al. 2009). Although this mutant retains the same iron levels in the striatum, a lower gene expression of iron transporter DMT1 and a decreased metabolic function compared with the wild type mice, is also observed.

As expected, in this mutant it was found that hippocampal-specific ID not only affects behavioral tasks dependent on the hippocampus, but also affects striatum-dependent tasks. Using a behavioral paradigm that alternates both visual and spatial keys, it was shown that the mutant used more visual than spatial cues compared to the WT littermates who used both strategies equally (Carlson et al. 2010).

These data support the idea that ID not only produces changes in the hippocampus, but also exerts a strong effect on the striatum. Moreover, it has been found that both systems differentially responded to iron supplementation therapy (Schmidt et al. 2011).

Interestingly, evidence has also been found that ID, during early stages of development and neuronal differentiation, affects other regions of the brain such as PFC with consequent alterations on cognitive tasks dependent on this region (Schmidt et al. 2010).

Despite the evidence of alterations in the PFC as well as dysfunction in the executive function dependent on the PFC in children exposed to early ID (Beard and Connor 2003), this is the first study to examine the effects of ID in the operation of the PFC. To that end, a PFC-dependent behavioral task of alternating rewards was used with a delay between trials which requires to alternate the answers in order to win a reward (Dalley et al. 2004). Surprisingly, it was found that iron deficient rats have increased this PFC-dependent behavior, compared to control rats without ID. A possible explanation is the interaction between PFC and the limbic system, which is modulated by dopamine release from striatal neurons, resulting in improvements of PFC-dependent behaviors and deterioration in the hippocampus-dependent behaviors (Goto and Grace 2005).

Additional studies are certainly necessary to elucidate and understand the cognitive alterations induced by ID.

Iron deficiency and monoaminergic signaling

ID-induced alterations of cognitive tasks are probably the result of alterations in the synaptic function in brain regions in which cognitive functions have been observed.

In rats fed with a diet deficient in iron, resembling the iron levels found in the human brains of newborns with ID, the hippocampal volume is reduced compared to the control group. Furthermore, hippocampal neurochemical profile was significantly modified, where concentrations of creatine, lactate, glutamate and taurine decreased, and the concentration of glutamine increased (Rao et al. 2011). Other works in rats have shown similar neurochemical profile changes in striatum (Ward et al. 2007), suggesting alteration of the metabolic status of these brain regions.

In particular, alterations in the concentration of creatine can be consequence of a serious anemia triggered for the ID, as it has been shown in the rats subjected to chronic hypoxia (Raman et al. 2005). Low concentrations of lactate and taurine imply a decrease in the oxidative metabolism of the glucose, probably due to an alteration in the mitochondrial enzymes involved in the oxidative phosphorylation, which contain iron and they are strongly affected for ID (Dallman and Schwartz 1965).

On the other hand, the increase in the concentration of glutamine suggests that the glutamate/glutamine cycle, between neurons and glia, is affected in the hippocampus of rats subjected to ID, which is also consistent with a decrease of the taurine levels (Rothman et al. 2003).

A possible consequence of the aberrant neurochemicals profile induced by ID is an impairment of the monoaminergic metabolism, as it has been previously described (Lozoff and Georgieff 2006). This hypothesis is supported by some studies in models of ID in rodents, showing that behavioral changes are due to alterations of the homeostasis of dopamine (Felt et al. 2006).

Since dopamine is involved in several physiological processes of the CNS, changes in the dopaminergic function may affect some cognitive processes such

as mood, attention and reward which in turn, diminished the executive function (Lozoff 2011).

Alterations induced by ID include elevated levels of extracellular DA in the striatum of iron-deficient rats, low density of dopamine transporters (Erikson et al. 2000) and diminished expression of dopamine receptors D1 y D2 (Beard and Connor 2003; Erikson et al. 2001), all these alteration have a negative impact in both striatum and PFC (Erikson et al. 2000; Felt et al. 2006; Goto and Grace 2005).

Some studies suggest that ID-induced alterations in dopaminergic metabolism are the consequence of a depressed glutamatergic neurotransmission (Ward et al. 2007); based on various pieces of evidence that show a complex interaction between both dopaminergic and glutamatergic systems in the striatum, nucleus accumbens, PFC and hippocampus (Sesack et al. 2003). In addition, it has been shown that changes in the glutamatergic input from the hippocampus affect the ability to respond to the striatal dopaminergic neurons (Lisman and Grace 2005).

A body of evidence supports the idea that iron deficit affects not only the dopaminergic system, but it also affects other neurotransmitters systems. A study showed that rats fed a diet deficient in iron, from weaning until adulthood, decreased the density of functional serotonine (5HT) and norepinephrine (NE) transporters in the nucleus accumbens, caudate putamen and substantia nigra, compared to rats fed with iron-sufficient diet (Burhans et al. 2005).

Some of these changes have also been mimicked using neuronal models. A study showed that treatment of PC12 cells with an iron chelator, desferrioxamine (DFO), reduces both the levels of iron and functional levels of the NE transporter (NET). The modest effect found at the level of messengers, suggests that ID disturbs the NET trafficking and degradation than on protein synthesis (Beard et al. 2006).

Finally, it has been shown that iron deficiency in rats decreases the concentration of tryptophan, which might explain why the metabolism of these neurotransmitters is altered (Shukla et al. 1989).

Given the complex interaction between the various systems of neurotransmitters, in the different regions of the brain, it is expectable that iron deficiency has an impact not only on the monoaminergic system. Future research should be pointed in this direction, to have a better understanding about the effects of ID in the different neurotransmitter systems.

Iron and synaptic plasticity

At synaptic levels, ID-induced neurochemical changes may be responsible for the cognitive impairment. These synaptic alterations have a major impact on neuronal plasticity, which is the putative cellular substrate for memory storage in vivo (Pavlopoulos et al. 2011; Shumyatsky et al. 2005).

Long-term potentiation (LTP) of synapses in hippocampal slices is a type of SP that has been studied extensively (Boric et al. 2008; Cao and Harris 2011; Castillo et al. 2011; Munoz et al. 2011). Since this form of SP shares many mechanisms with memory, it provides an excellent model for studying memory-related processes (Savonenko et al. 2009; Whitlock et al. 2006). Despite its importance, there are few studies on the effect of iron deficiency on neural plasticity mechanisms.

In early life, impairment of hippocampal development has negative effects that persist beyond perinatal period, which are associated with cognitive disturbances. Furthermore, it has been found that fetal/neonatal ID decreased apical shaft length in the CA1 region of the hippocampus and these abnormalities persist into adulthood (Jorgenson et al. 2003) even after iron repletion. In this perinatal period, hippocampal neurons modify circuitry involved in cognitive processing. During perinatal period, it has been reported upregulation of protein related with iron transport, suggesting that iron plays an important role in this kind of process.

Interestingly, it has been shown that ID diminished BDNF expression, a neurotrophic factor involved in synaptic remodeling (Tran et al. 2008). On the other hand, it has also been shown that rats fed with iron deficient diet, exhibited lower mRNA levels of several proteins that are critical for dendrite growth and apical dendrite morphology in hippocampus area CA1 (Brunette et al. 2010).

An electrophysiological study evaluated the early ID effects on SP, using rats with iron deficit from embryonic stages until postnatal day 7 (P7), when iron levels in diet are normalized (Jorgenson et al. 2005). Evaluation was performed on P15 up just before peak dendritic development and synaptogenesis (Pokorny and Yamamoto 1981; Steward and Falk 1991), P30 immediately after the end of this period of rapid synaptic development and P65 during adulthood when iron levels in the hippocampus have been normalized.

In order to assess pre-synaptic SP, a paired-pulse facilitation (PPF) ratio was measured in hippocampal slices at four different interstimulus intervals ranging from 25 to 200 ms. Facilitation ratio in hippocampal slices from ID rats was significantly lower during P15 however, no difference was detected at P30, compared with the control group. Interestingly, in P65 the facilitation ratio increased in 25 and 50 ms interstimulus intervals (Jorgenson et al. 2005).

LTP expression was not significantly different at P15, but was higher at P30 with persistence of ID and lower at P65 despite complete iron normalization (Jorgenson et al. 2005).

A recent study explored the effect of the ID in rats on synaptic efficacy mediated by noradrenergic agonists (McEchron et al. 2010). This study examined the effect of isoproterenol (ISO), a β-adrenergic agonist, whose application in the bath produces a long-lasting potentiation of the field recordings and population spikes in hippocampal area CA1 (Gelinas and Nguyen 2005). Hippocampal slices from rats exposed to perinatal ID, did not show enhanced synaptic responses while the control animals did (McEchron et al. 2010).

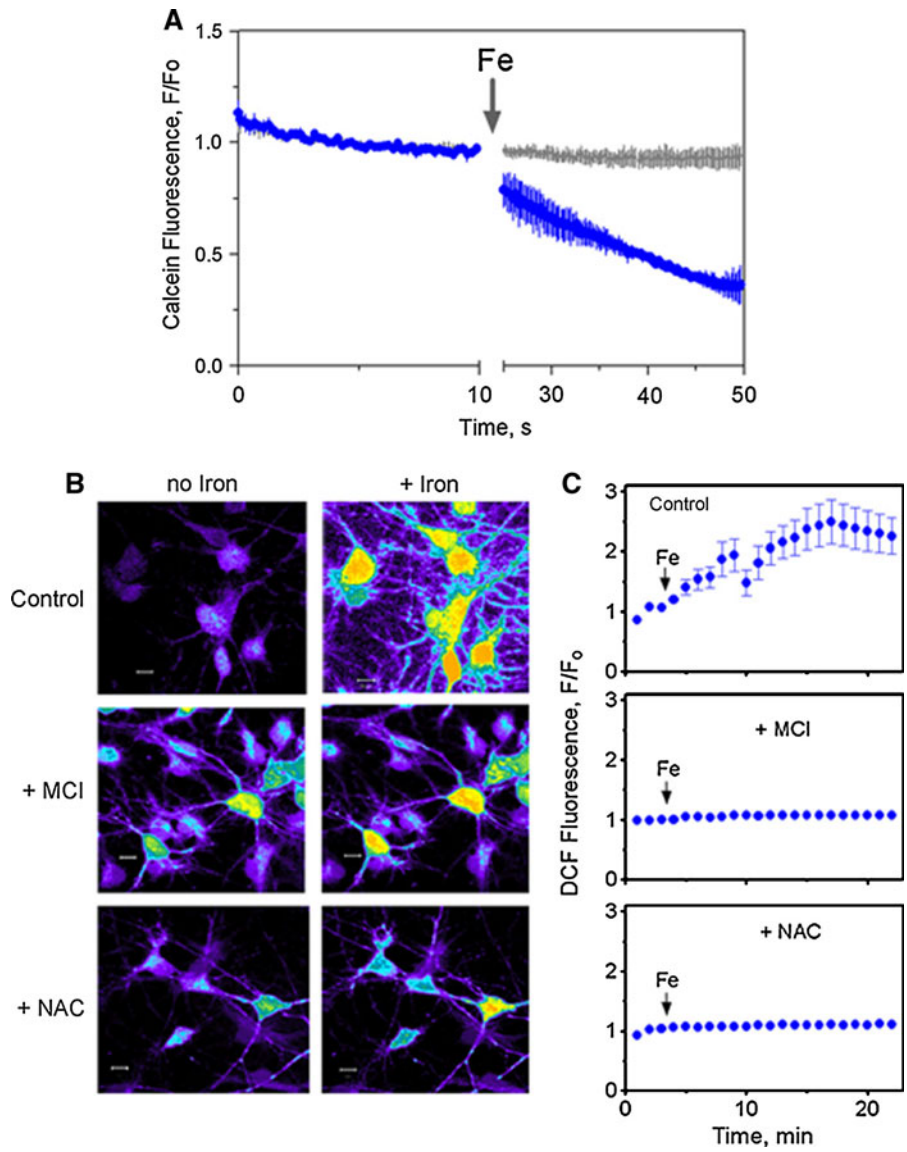

Fig. 1 Extracellular iron enters the cytoplasmic LIP and generates ROS (**a**), Neurons loaded with fluorescent iron sensor calcein, before and after iron addition (*blue* trace). Calcein fluorescence shows that iron addition increased of the LIP, as detected by calcein quenching. **b** Images of neuron loaded with the fluorescent cell permeant redox sensor DCDHF-DA, before or after iron addition, with or without preincubation with MCI or NAC. **c** Graphs correspond to quantifications from **b** (figure from Munoz et al. 2011; with permission from the publisher)

In the previous section we discussed evidence supporting the impact of ID on the noradrenergic system (Beard et al. 2006). In contrast the data reported by McEchron seem contradictory; however, in this latter work only the effect of iron on LTP induced by an agonist of the subtype β is explored while what happens with the subtype alpha is not. The data support the idea that the iron affects differentially the subtypes of these receptors.

To date, studies on the effect of iron deficiency in the brain have focused primarily on abnormalities during critical stages of synaptic development, myelination and neurotransmitter systems. However, we have studied the oxidative effects of iron on synaptic mechanisms involved in neural plasticity (Munoz et al. 2011; Munoz et al. 2006).

Interestingly, iron uptake induced by *N*-methyl-D-aspartate receptor (NMDAR) activation (Cheah et al. 2006) might play an important role in the mechanisms that sustain memory and SP. This idea is supported by a recent work showing that either NMDAR activation or spatial learning task, increased expression of DMT1 (Haeger et al. 2009), suggesting a critical role for iron uptake and the iron-activated signaling pathways that are downstream of the NMDAR.

Iron might play a role, ensuring a basal concentration of ROS necessary for the proper functioning and operation of ROS-sensitive components. We refer to this basal level of ROS maintained by iron as "oxidative tone".

In our recent research we demonstrated that the addition of iron to the cultured hippocampal primary neuron increased the iron labile pool (LIP) and also stimulated ROS generation (Munoz et al. 2011). Furthermore, in similar experiment with MCI-186 (a hydroxyl radical trapping agent) or with *N*-acetyl-cysteine (a precursor of the powerful antioxidant glutathione) these effects were suppressed (Fig. 1). We hypothesized a role for iron uptake providing a neuronal "oxidative tone" necessary for activation of the tone-sensitive neuronal machinery, such as transcription factors, ion channels, protein kinases and, in general, any component that can be modified by oxidation.

In agreement with this proposal, recent studies from several laboratories, have suggested that ROS acts as cellular messengers on different signaling pathways involved in SP (Kemmerling et al. 2007; Massaad and Klann 2010; Munoz et al. 2011) and hippocampus-dependent memory (Hu et al. 2007; Kishida and Klann 2007).

Indeed, ryanodine (Ry) receptor (RyR) involved in both calcium-induced calcium release (CICR) from intracellular stores and synaptic plasticity (Lu and Hawkins 2002), is a redox sensitive-channel (Aracena-Parks et al. 2006).

Previously, using PC12 cells, it has been found that iron induces the release of calcium from Ry-sensitive intracellular compartments (Munoz et al. 2006). Subsequently, these studies were expanded to hippocampal neurons (Munoz et al. 2011), where it was suggested that iron-generated ROS participates in both RyR-mediated Ca^{2+} signals initiated by stimulation of NMDAR (Fig. 2) and calcium signaling pathways that are downstream of the NMDAR (Fig. 3). It has been demonstrated that, both the calcium-induced calcium release from intracellular RY-sensitive compartments and nuclear translocation of ERK, are critical for the induction of the PS. We found that both events are prevented when the neurons were incubated with DFO (Figs. 2, 3).

In addition, using electrophysiological techniques, we found that iron is required for complete expression of LTP induced with four tetanus trains. A brief incubation with DFO, in the absence of electrical

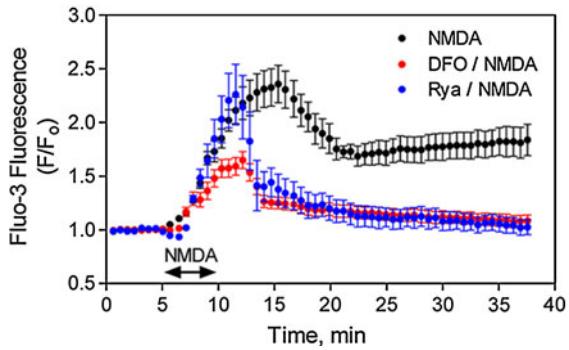

Fig. 2 NMDA-induced Ca^{2+} signals in cultured hippocampal neurons: inhibitory effects of DFO and ryanodine. **a** cultured hippocampal neurons were preincubated for 1 h with culture medium, or with medium containing 50 μM Ry or 500 μM DFO. After washing out these compounds, cells were loaded with calcium sensor Fluo-3-AM and exposed for 5 min to a solution containing 50 μM NMDA. Graph corresponds to quantifications from Fluo-3 fluorescence intensity values normalized against the fluorescence values obtained before NMDA addition (F/Fo) and plotted as a function of time (figures from Munoz et al. 2011; with permission from the publisher)

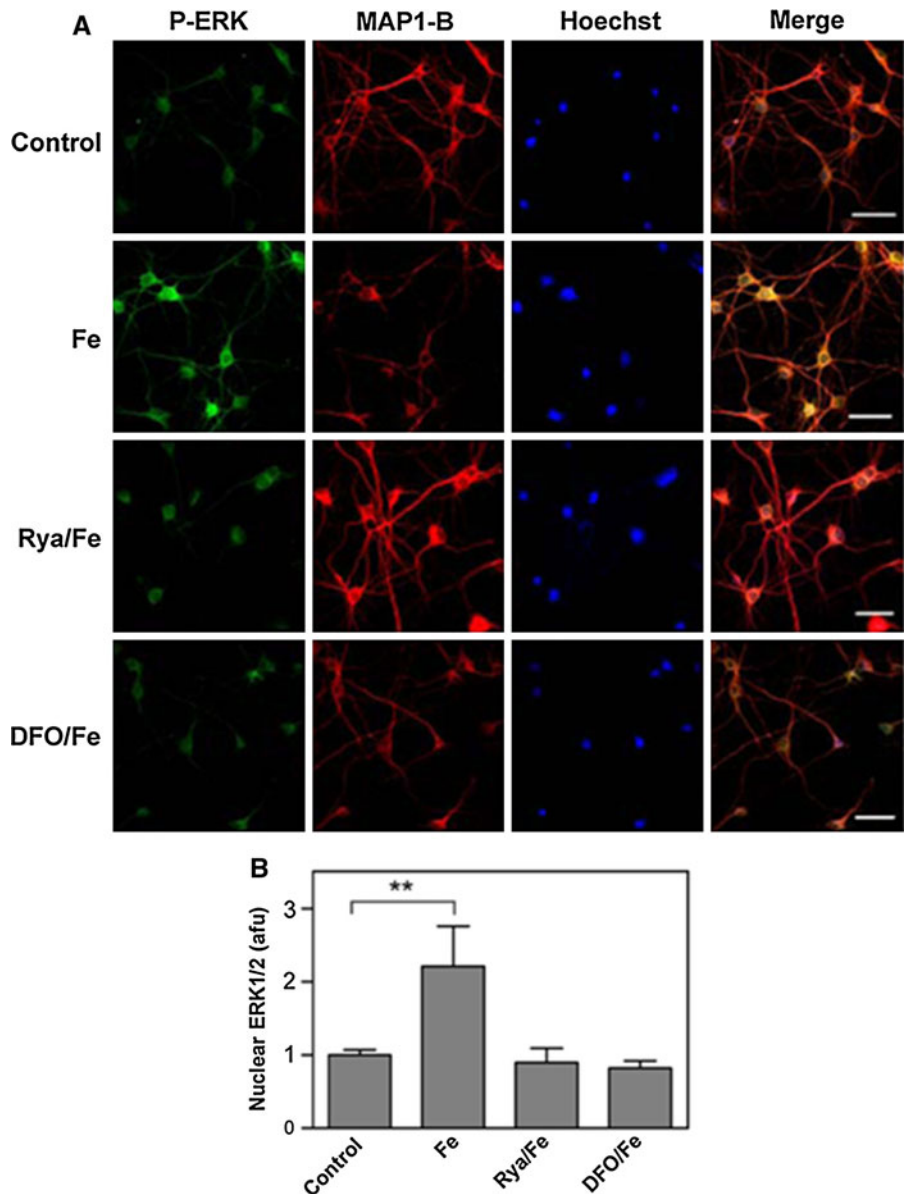

Fig. 3 Iron induced nuclear translocation of phosphorylated ERK1/2. **a** Immunostaining using an antibody against phosphorylated ERK1/2 (*green*, *left panels*) followed by an antibody against the neuronal marker MAP1-B (*red*), nuclei were counterstained with Hoechst (*blue*). The merged images are shown in the *right panels*. Immunostaining was performed before (control) or 1 h after addition of iron with o without preincubation with ryanodine or DFO. **b** Graph represents the nuclear translocation of phosphorylated ERK1/2, expressed in arbitrary fluorescence units (a.f.u.) (figures modified from Munoz et al. 2011; with permission from the publisher)

activity to avoid significant changes in basal transmission, produced a strong impact on the expression of LTP (Fig. 4). Moreover, incubation with low concentrations of iron converts a transient LTP induced with a single tetanus train into a more persistent LTP, suggesting that iron promotes SP (Munoz et al. 2011).

Given the complex interaction between neurotransmitter systems and because the NMDAR activation plays an important role for LTP induced by high frequency stimulation trains, we have studied the glutamatergic transmission in the presence of DFO.

To examine the effect of ID on NMDAR-dependent responses, we isolated NMDAR responses in hippocampal slices using magnesium-free artificial cerebrospinal fluid (ACSF) and in the presence of 10 µm glycine and 10 µm DNQX, an AMPA receptor

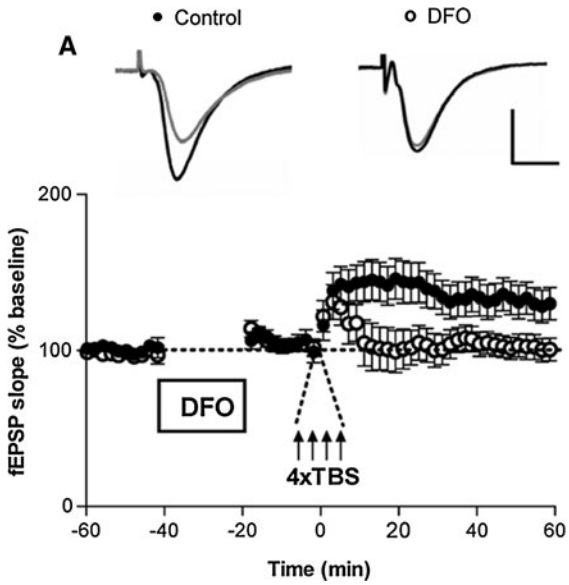

Fig. 4 Iron chelation with DFO inhibits LTP expression. **a** LTP was induced with four trains of tetanic theta burst stimulation (*arrows*) in control slices (*solid circles*; 19 slices, 6 animals) or in slices preincubated 40 min before stimulation with 1 mM DFO for 20 min (open circles, 14 slices, 6 animals). fEPSPs were recorded from the CA1 area The representative traces shown were obtained 10 (*gray* traces) or 60 min (*black* traces) after stimulation. Data are given as mean ± SE statistical differences were analyzed by two-tailed unpaired Student's *t* test. In *all panels*, the calibration bar indicates 0.5 mV and 5 ms (figure from Munoz et al. 2011; with permission from the publisher)

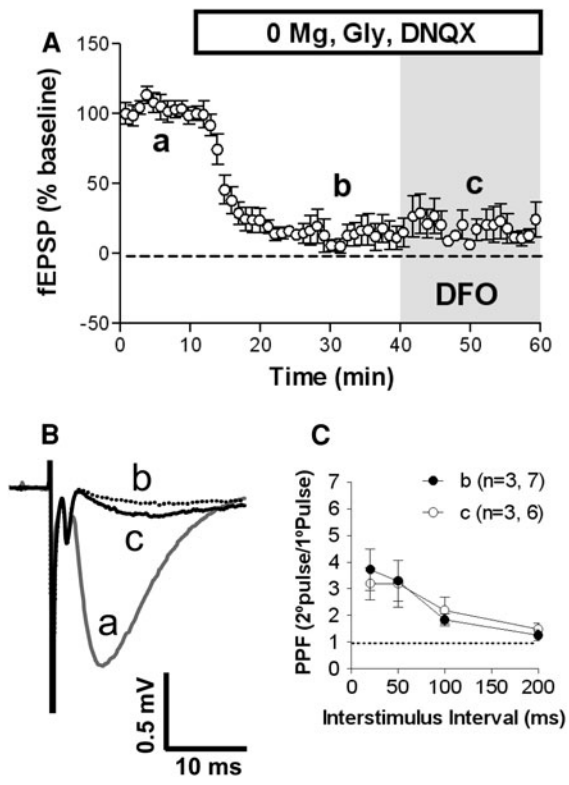

Fig. 5 Iron chelation does not change NMDA receptor function. **a** Hippocampal slices were placed in a perfusion chamber, and fEPSPs were recorded in stratum radiatum in response to stimulation every 60 s. After stable baseline conditions were established, the perfusion medium was changed to magnesium-free artificial cerebrospinal fluid (ACSF) containing glycine and 10 μM DNQX. After stable NMDA receptor fEPSPs were established, 1 mM DFO was added to the medium and EPSPs were recorded. **b** *a–c* are sample traces taken at the times indicated on the top. **c** DFO had no significant effects on NMDA-dependent paired pulse facilitation at different interstimulus intervals (20, 50, 100 and 200 ms), for NMDA receptor EPSP slopes before and after the addition of DFO. Data are given as mean ± SEM. *Open circles* 3 animals, 6 slices. *Closed circles* 3 animals, 7 slices (unpublished data)

antagonist. We found that iron-deficient slices do not show a change of NMDA receptor function (Fig. 5).

Based on the evidence obtained from primary cultures of neurons, we propose that iron deficiency induced by the acute application of an iron chelator, affects the iron-mediated redox homeostasis which in turn affects hippocampal neural plasticity.

Finally, combined data suggest that the oxidative effect of iron is critical to activate processes that are downstream of NMDAR activation which are required for SP, such as calcium release from Ry-sensitive intracellular store, which are required for LTP.

Recent data about the possible role of iron deficit on synaptic processes, together with previous work about ID impact on cognitive processes and synaptic function, could yield valuable information to prevent, reverse and protect against the effects of both ID and iron overload.

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