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BDNF expression in blood. Study in iron deficient females

Expresión de BDNF en sangre. Estudio en hembras deficientes de hierro

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Abstract

Iron deficiency is a public health problem that greatly impacts women and children, especially at the neurological level, being BDNF a relevant factor involved in such pathogeny. Objectives: To determine in females suffering from chronic iron deficiency, from the perinatal stage to adulthood, the levels of peripheral BDNF in blood. In addition, the effect of iron supplementation after weaning. Methodology: female Wistar rats with chronic iron deficiency and rats supplemented from weaning to adulthood (70 postnatal days) were euthanized to analyze BDNF levels in blood samples. Contribution: we demonstrate that in the presence of chronic iron deficiency, BDNF levels decrease peripherally and supplementation normalizes them. In addition, hemoglobin-bound iron (Fe-Hb) levels correlate positively with BDNF levels in blood. This could indirectly indicate a possible restoration or contribution to the improvement of the patient's cognitive or behavioral processes.

BDNF, iron, sex, deficiency, neurological, perinatal

Resumen

La deficiencia de hierro es un problema de salud pública que impacta sobremanera a mujeres y niños, sobretodo a nivel neurológico, siendo el BDNF un factor relevante implicado en tal patogenia. Objetivos: Determinar en hembras que padecen deficiencia de hierro crónica, desde la etapa perinatal hasta la edad adulta, los niveles de BDNF en sangre. Además, el efecto de la suplementación de hierro a partir del destete. Metodología: ratas Wistar hembras con deficiencia de hierro crónica y ratas suplementadas desde el destete hasta la edad adulta (70 días-posnatales) fueron eutanasiadas para analizar en muestra sanguínea los niveles de BDNF. Contribución: demostramos que ante una deficiencia de hierro crónica, los niveles de BDNF disminuyen periféricamente y la suplementación los normaliza. Además, los niveles de hierro unido a hemoglobina (Fe-Hb) se correlacionan positivamente con los de BDNF en sangre. Lo anterior podría indicar indirectamente un posible restablecimiento o aporte a la mejora de procesos cognitivos o conductuales del paciente.

BDNF, hierro, sexo, deficiencia, neurológico, perinatal

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Introduction

Iron is a trace element that plays a key role in muscle metabolism, DNA synthesis and oxygen transport. Iron deficiency (DFe) is the most common micronutrient deficiency worldwide; it affects 614 million women and 280 million children worldwide (WHO, 2020a). Iron deficiency is the leading cause of anaemia, the most prevalent nutrient deficiency worldwide, affecting 33% of non-pregnant women, 40% of pregnant women and 42% of children (WHO, 2020a). Iron deficiency in foetal life and in children under two years of age can have significant and irreversible effects on brain development, leading to negative repercussions on affective, cognitive, memory, learning and school performance (Burden et al., 2007; Lozoff, 2011; Lozoff & Georgieff, 2006; Riggins et al., 2009). In adults, iron deficiency can also cause negative effects such as fatigue, reduced physical performance and decreased work productivity, as well as affecting socialisation and neurocognitive function. DFe occurs mainly when iron needs increase during periods of rapid growth and development, such as early childhood, adolescence and pregnancy, but can also occur at other stages of life. In pregnant women, iron deficiency can lead to anaemia, low birth weight and shortened gestation (WHO, 2020b).

Brain development during foetal and early postnatal life is an energy-intensive process (Fukumitsu et al., 2016; Kuzawa, 1998; Li et al., 2004) and is impaired in a rat model of foetal-neonatal ID (Brunette et al., 2010; Carlson et al., 2009; Fretham et al., 2012). Various neurocognitive disorders such as those related to iron deficiency, both in humans and in animal models, have been shown to be linked to alterations in neurotrophic factors, such as brain-derived neurotrophic factor (BDNF). BDNF is a polypeptide that acts as a growth factor and plays an important role in neuronal integrity; modulating neurotransmitter synthesis, metabolism and release (Crump et al., 2014), survival, differentiation and synaptic plasticity in the central and peripheral nervous systems (Lu & Figurov, 1997; Morse et al., 2015; Texel et al., 2011).

Long-term low expression and activity of BDNF at the hippocampal level has been demonstrated in subjects with DFe (Tran et al., 2009); in addition to changes in histone methylation at the BDNF locus in hippocampus of adult subjects who suffered fetal-neonatal DFe (Blegen et al., 2013; Tran et al., 2015); in addition to persistent dysregulation of JARIDs (members of the dioxygenase family that require iron as a cofactor to remove methyl groups from histone lysine residues); which was recently shown to be compensated or normalised following iron supplementation (Liu et al., 2021).

An important feature of BDNF is its ability to cross the blood-brain barrier; therefore, serum and cerebrospinal fluid levels are strongly correlated with brain levels (Gururajan et al., 2014; Harris & Barraclough, 1997; St Laurent et al., 2013). It is relevant to consider that an estrogen response element (ERE) is present in the BDNF gene, so estrogens increase the expression of this neurotrophic factor (Singh et al., 1995; Sohrabji et al., 1995), making its expression sex-dependent. As for iron, BDNF is known to increase its accumulation by inhibiting the expression of IRP1 (iron-responsive element-binding protein 1) and DMT1+IRE (divalent metal transporter 1 + iron-responsive element) (Zhang et al., 2014).

Few studies have been conducted in females, and with respect to iron deficiency, it is not known whether chronic iron deficiency in females affects BDNF levels in blood, an indirect determinant of brain levels. It is also unknown whether in females that suffered from perinatal iron deficiency and that after weaning were supplemented with iron, BDNF levels in blood are restored, which would indirectly indicate at the level of the central and peripheral nervous system, the benefits of the incorporation of iron in the diet.

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Methodology

Ethical considerations

The study was conducted according to approved institutional protocols in accordance with the Principles and Procedures described by the National Institute of Health, Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, in accordance with the guidelines of NOM-062-ZOO-1999; technical specifications for the production, care and use of laboratory animals. For sample collection, sacrifice was induced with CO2 to minimise suffering.

Animals and diet

Wistar rats were maintained under standard conditions in the vivarium: 12:12 light/dark cycle (lights were switched on at 05:00 hours), temperature controlled at 22 ± 2°C and free access to food and water.

Twenty 3-month-old or 250-gram female foal rats were used to obtain study subjects. Fourteen days prior to mating conditions, ten rats were subjected to an iron-deficient diet consisting of 10 ppm FeSO4 (Lab diet AIN-76W/10). The other ten rats received a control diet containing 100 ppm FeSO4 (Lab diet AIN-76W/100). Twenty-five days after mating, the offspring were obtained. At weaning, 21 days postnatal (DPN), ten female offspring from iron-deficient dams and ten female offspring from the control group were randomly separated and fed the same diet as their dams until adulthood at 70 days postnatal day 70. Another group of female offspring from iron-deficient dams from 21 to 70 PND were supplemented with 100 ppm FeSO4 iron (Lab diet AIN-76W/100).

Sample collection

At 70 PND, rats were euthanised in a CO2 chamber with a gradual release of O2 at a rate of 0.5 L CO2/min/10 min. Subsequently, two mL of blood was withdrawn by intracardiac puncture using an EDTA syringe. For Fe-Hb measurement, one mL of blood was used. The other mL was used to determine the amount of circulating BDNF; thirty minutes after blood collection, it was centrifuged for 10 minutes at 1000 rpm. The plasma was extracted and kept cold (-80°C) until processing.

Haemoglobin-bound iron (Fe-Hb)

To demonstrate the presence of ID, Fe-Hb levels were indirectly measured in each study group using the following formula (Hernandez et al., 2006; Wienk et al., 1999):

$$Fe - Hb(mg) = \frac{\left(\left(\frac{Hb}{L}\right) * (body\ weight) * 6.7 * 0.335\right)}{10000}$$

Where Hb (g) contains 0.335% iron. The blood volume in growing rats is 6.7% of body weight (g).

To determine Hb, 1 mL of blood was taken from the subjects studied; its concentration was determined in triplicate by the cyanomethaemoglobin method using Drabkin solution (Randox Mexico SA de CV) (Prohaska & Gybina, 2005; Unger et al., 2007).

Determination of BDNF

Blood samples were analysed according to the immunoassay procedure, Milliplex Map Kit, Rat Pituitary Magnetic Bead Panel, Cat. # RPTMAG-86K. Results were expressed in pg/mL.

Statistical analysis

SPSS 22® statistical software was used for statistical analysis; initially a descriptive statistical analysis was performed for each variable considered. The results were presented as means ± standard deviation (mean±SD). To compare differences between two groups (e.g. "Control" and "DFe" or "DFe+S" groups), the Mann-Whitney U-test was used. Results of $p<0.05$ were considered statistically significant, with a 95% confidence interval.

Results

Iron bound to haemoglobin (Fe-Hb)

When studying the ID group with respect to the control group, it was found that the former had 10.9% less Fe-Hb and 3.8% less than the ID+S group, see Table 1.

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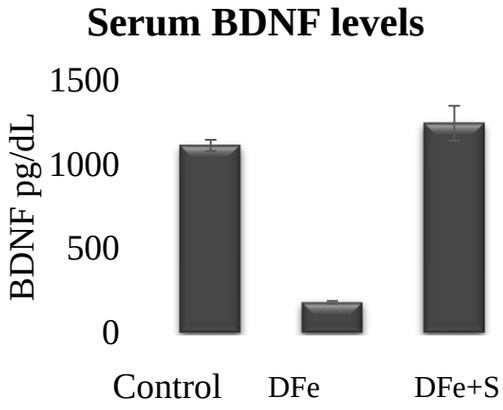
Group	Fe - Hb
Control	3.71±0.11
Iron deficient+supplementation	3.47±0.11
Iron deficient	3.18±0.23*
* Female of control group (p≤0.05).	

Table 1 Levels of iron bound to haemoglobin "Fe-Hb". All values are expressed as mean ± standard deviation

Determination of BDNF

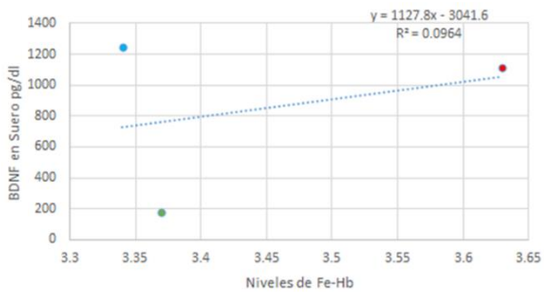
BDNF levels at the peripheral (serum) level were decreased in iron-deficient subjects compared to control subjects; however, iron supplementation resulted in an increase in BDNF levels at the peripheral level, even above the levels of control females (Graphic 1)



* vs. control group female (p≤0.05)
**Female from Iron Deficient+Supplemented group (p≤0.05)

Graphic 1 BDNF levels in blood. Values indicate mean ± standard error

Graphic 2 shows the correlation between serum BDNF levels and haemoglobin-bound iron levels.



Graphic 2 Correlation between BDNF and haemoglobin-bound iron levels. Red dots indicate control females; green DFe and blue DFe+S

Discussion

Iron deficiency during pregnancy has been associated with a high risk of developing schizophrenia (Insel *et al*., 2008) and autism (Schmidt *et al*., 2014) in infants; and in later life with Alzheimer's disease (Faux et al., 2014; Lee *et al*., 2020). A child's cognitive development may also be affected if the mother is iron deficient during the last trimester of pregnancy (WHO, 2020a). Long-term behavioural deficits in hippocampal-dependent learning and memory have been demonstrated in murine models of iron deficiency (Pisansky *et al*., 2013; Schmidt *et al*., 2012), which is associated with altered expression of genes critical for neural development (Brunette *et al*., 2010; Carlson *et al*., 2007; Tran *et al*., 2009) and gene networks implicated in schizophrenia, autism and mood disorders (Tran *et al*., 2016). The neurological alterations mentioned above have also been observed in animal models of foetal-neonatal iron deficiency (Barks *et al*., 2018; Barks *et al*., 2019; Fretham *et al*., 2011). It should be noted that brain development during these stages is an energy intensive process (Fukumitsu et al., 2016; Kuzawa, 1998; Li *et al*., 2004) that has been shown to be altered in a rat model of DFe (Brunette *et al*., 2010; Carlson *et al*., 2007; Fretham *et al*., 2011).

Brain Derived Neurotrophic Factor (BDNF) is the most widely distributed neurotrophin in the central nervous system. In the adult brain, BDNF fulfils certain functions such as regulating neuronal integrity, promoting brain plasticity, modulating synthesis, metabolism and release of neurotransmitters, and intervening in neuroplasticity processes (Crump *et al*., 2014). Importantly, BDNF crosses the blood-brain barrier and serum levels correlate strongly with brain levels (Harris & Barraclough, 1997). Serum BDNF levels have been shown to increase after three months on a reduced-calorie diet (Araya *et al*., 2008) but it is not known what happens in the face of chronic iron deficiency, a situation experienced by a large proportion of the population mainly in developing countries. There is evidence that BDNF levels can undergo short-term changes in response to external stimuli.

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For example, it has been shown that serum levels of the factor increase after three months on a reduced-calorie diet (Araya *et al*., 2008), and decrease in the hippocampus after iron deficiency during the prenatal period and up to 7 days postnatal (Tran *et al*., 2008). However, it has also been found that under dietary restriction there is an increase in BDNF levels (Lee et al., 2002). So far, it was not known what happens in females with chronic iron deficiency. It is worth mentioning that BDNF as well as estrogens share parallel effects in terms of neuroprotection in the processes of neuronal excitotoxicity, enhanced learning (Scharfman & MacLusky, 2006), modulation of synaptic transmission and increased synaptogenesis (McAllister *et al*., 1999). In the present study, iron deficiency over a prolonged period of time was shown to negatively affect BDNF levels. In addition, the impact of iron supplementation on BDNF levels, especially in females, was unknown, although research reports data on BDNF elevation in serum of subjects with Zinc monotherapy, a bivalent element that has similar functions to iron (Solati *et al*., 2015). Our results could demonstrate that iron-supplemented females reestablish homeostatic mechanisms that allow the passage of BDNF back to the peripheral level.

Therefore, the findings of the present research are of great importance for the medical field, since it is known that subjects suffering from iron deficiency have memory and emotion problems that impact on their reasoning and quality of life, which may be associated with alterations in BDNF levels in the central nervous system, data that coincide with previous reports. In addition, it was shown that adequate iron supplementation can balance BDNF levels at the peripheral level, reflecting levels in the central nervous system, which could be applied in the clinic as a prognostic marker to help indicate early improvement or recovery of brain function in patients suffering from iron deficiency from an early age.

Conclusions

A. In chronic iron deficiency, BDNF levels decrease peripherally.

B. Iron supplementation in iron-deficient subjects normalises BDNF levels peripherally.

C. Haemoglobin-bound iron levels correlate positively with BDNF levels in the blood.

Suggestions

Mexico is a nation with risk factors predisposing to iron deficiency. Based on the results obtained, it is recommended to emphasise the determination of haemoglobin values to indirectly identify iron values and thus supplement with this trace element only in the indicated cases. If low iron levels in the infant are determined at an early age, closely monitor the adequate intake of this trace element and continue supplementation during postnatal development until it is deemed necessary, as this prevents cognitive, behavioural and emotional deterioration, entities associated with low BDNF levels.

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