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Review Article

Iron status: an update on learning, memory, and implications for addiction

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Abstract

In a follow-up to the 2016 paper "Preweaning iron deficiency increases non-contingent responding during cocaine self-administration in rats", we briefly discuss relevant new data regarding iron deficiency published through August, 2021. The original work investigated if early iron deficiency would increase later vulnerability for substance use disorder. The results of that study suggest that iron deficiency caused deficits in learning and memory. Considerable research since that publication indicates that early-life iron deficiency (ID) indeed significantly impacts the nervous system in ways that can affect learning and memory. Recent studies indicate cognitive, behavioral, and developmental effects on the nervous systems which serve learning and memory processes. While no research has directly tested individual vulnerability to substance use disorder since our initial findings, substantial research has since been published which suggests iron deficiency leads to learning and memory difficulties that in turn could increase risk for substance use disorder later in life.

Keywords: Iron deficiency, Learning impairment, Addiction, Substance use disorder

Abbreviations: ID: Iron Deficiency; IDA: Iron Deficiency Anemia; PFC: Prefrontal Cortex; SUD: Substance Use Disorder; TBV: Total Brain Volume

Introduction

The paper "Preweaning iron deficiency increases non-contingent responding during cocaine self-administration in rats" published in 2016 showed that, while there was little to no difference in drug seeking behavior between iron deficient (ID) and control rats, iron deficiency in rats during the perinatal period "negatively affected learning and memory". The study originally sought to determine any correlation between ID and vulnerability to substance use disorder (SUD), comparing the drug seeking behavior of control rats and iron deficient rats using i.v. self-administration of cocaine. The ID rats, while appearing to be equally motivated to obtain the drug, failed to distinguish between active and inactive operant levers, suggestive of learning impairments. We hypothesized that these deficits "may be due to the irreversible molecular changes in the dopaminergic reward system caused by acute ID during a critical period of development" that is comparable in humans to the third trimester of pregnancy [1].

The experimental design contained two levers, an "active" lever and an "inactive" lever. The active lever, when pressed a predetermined number of times, resulted in the i.v. administration of drug. The other, inactive lever never resulted in drug administration regardless of the number of times pressed. The ability to differentiate between the lever that resulted in drug administration and the lever that did not suggests learning the task; by selecting the active lever more frequently as time progresses, the rats displayed reward-based learning. Given that the iron deficient rats never displayed a significant difference in active vs. inactive lever pressing across the study, this suggests the early life ID resulted in impaired learning and memory capabilities evidenced by the failure in reward-based learning.

The study originally investigated the effects of early ID on later susceptibility to SUD. Though there was little data supporting this, substantial research published since supports our speculation of learning impairment as a result of ID during critical periods of development. No studies, of which we are aware, have since looked directly at any relationship between ID and susceptibility

to SUD. However, as discussed below, substantial evidence exists suggesting that ID and/or iron deficiency anemia (IDA) during pregnancy and infancy does indeed increase the risk of impaired learning and memory abilities. Additionally, we discuss literature showing increased neurobehavioral impairments, psychopathologies including schizophrenia or depression which potentially exacerbate risk of addiction. Other studies have shown substantial evidence to suggest that significant ID during embryonic development and early infancy can impair brain structures in a myriad of ways, varying from a decrease in total brain volume to altered methylation of hippocampal DNA. In addition to these cognitive and neurological impairments, further studies have shown that neonatal or infant ID can lead to moderate to severe cardiovascular, metabolic impairments, and microbiome deficiencies.

Since the initial publication of our study, significant research has expanded the knowledge of the impact of neonatal and infantile ID on learning and memory. This work is neither a comprehensive nor a systematic review of all research regarding early-life ID. This commentary is an update of the recent research relevant to the work published in "Preweaning iron deficiency increases non-contingent responding during cocaine self-administration in rats." We focus only on the more applicable research as it relates to having the potential to negatively affect learning or memory, and other cognitive or psychological disorders which also may have the potential for influencing later vulnerability for substance abuse.

ID and Learning and Memory Impairment

Cognitive impairments

Several studies indicate that maternal IDA can severely disrupt embryonic development, leading to premature birth and deficits in learning and memory. Zhang et al. found that, compared to iron sufficient dams, IDA rats produced smaller offspring with fewer pups per litter. Not only did the iron insufficient dams produce smaller and fewer offspring, but the offspring produced presented moderate to severe neurological developmental problems, displaying decreased levels of spatial learning ability and memory recognition. In that study, the impaired learning and memory were only moderately reversible with sufficient post-birth iron repletion [2]. However, human studies and observations indicate that the neurological impairments associated with ID during pregnancy persist regardless of later iron supplementation [3]. The decrease in learning and memory of the offspring of IDA dams was found to be in part due to a decrease in synaptic growth and development proteins such as Synapsin I (SYN1). Caused by insufficient iron during fetal development, these impairments also lead to a delayed development of proper reflexes including the surface righting reflex, cliff avoidance, and air righting reflex [2].

Behavioral and psychological impairments

Disrupted cognition thought to be due to fetal or infantile ID is accompanied by a host of behavioral and psychological impairments. Observational studies found that 5-year-old children who had neonatal ID exhibited worse behaviors than children who were iron sufficient. Compared via the Child Behavior Checklist (CBCL) test, children were tested for internal and external problematic behaviors such as excess emotional reactivity and attention seeking behaviors [4]. Offspring of iron insufficient pregnant women have an increased risk of psychopathologies, including but not limited to depression, bipolar disorder, ADHD, and schizophrenia [3,5]. Adolescents born iron sufficient but were iron deficient during infancy appear to be more likely to engage in problematic alcohol use, high-risk sexual behaviors, and rule-breaking activities compared with those who did not suffer from IDA during infancy. Children, at age 10, who were IDA during infancy were found to display lower attention spans with more sluggish cognitive tempo symptoms than children who were iron sufficient [6]. Associations between fetal and infant ID and autism spectrum disorder have been proposed, but preliminary investigation does not suggest any correlation or causation [7].

Brain structure and metabolism

The cognitive and behavioral problems consistent with fetal and infant ID appear to stem from structural and functional changes or delays in the developing brain. Vlasova et al. found that infantile iron deficiency in monkeys appeared to lead to a decrease in total brain volume (TBV) at one year of age. Monkeys later treated with iron maintained smaller TBV than fully iron sufficient monkeys [8]. The decrease in TBV primarily consisted of less total gray matter, most notably in the parietal and prefrontal cortices [8]. The prefrontal cortex (PFC) is critical in executive functions, including personality, decision making, and behavior modulation. The PFC enables acceptable social behavior, differentiating between good and bad decisions, and considering the consequences of actions [9]. Even though behaviors and interactions are significantly more complicated than any single section of the brain, many of the aforementioned behavioral impairments associated with iron deficiency are regulated, in large part, by the PFC. Thus, even though the study analyzed the brains of monkeys rather than humans, it is possible that the behavioral impairments are impacted by or related to the decrease in TBV and gray matter associated with neonatal and infantile ID.

Further, evidence suggests that neonatal ID may disrupt hippocampal development. Barks et al. studied the effects of neonatal iron deficiency, specifically hippocampal ID, in mice by disrupting hippocampal neuronal iron uptake in utero. They found that iron insufficiency appeared to cause 148 genes in the hippocampus to be dysregulated, altering the expression of the adult hippocampal transcriptome. Neurocognitive functions and diseases, including but not limited to cognition, learning, and schizophrenia, are associated with 58 of these dysregulated genes [10]. Other studies have also found evidence to suggest that neonatal ID leads to the altered regulation and methylation of hippocampal DNA and hippocampal formation, resulting in smaller hippocampal volume and dysregulation of genes associated with hypoxia and angiogenesis [11,12].

Neonatal and infantile brain energy metabolism appears to be critical in creating cellular pathways, specifically pathways associated with hippocampal-mediated learning and memory function. However, evidence suggests that ID compromises mitochondrial capacity, inhibiting brain energy metabolism, both significantly decreasing the energetic capacity of the brain and disrupting hippocampal formation. Continuous lack of hippocampal energy can lead to long term hippocampal dysfunction due to a perpetual lack of mitochondrial energy and an irreversibly simplified neuronal structure. Even with iron supplementation, the simplified neuronal structure remains into adulthood with up to a 12% decrease in hippocampal volume [3,5]. Given the simplification of the neuronal structure and lowering of metabolic energy, the pathways associated

with hippocampal-mediated learning and memory function appear to be persistently impaired by fetal and infantile ID. These impairments are likely additional influences to the aforementioned psychopathologies, further perpetuating the deleterious effects of early life ID on the brain.

Additional evidence of stunted brain development due to ID was found by analyzing the blood of umbilical cords of IDA women; umbilical cords of women who were pregnant with IDA displayed lower BDNF levels. BDNF is a key regulator for learning and memory, important in synaptic development and plasticity to aid in pre and postnatal brain development [11].

Other recent studies

There have been studies showing deleterious cardiovascular [13,14] and gut microbiome [15] effects from ID, but little to no evidence linking them with negatively affecting learning, memory, or later substance use. It is plausible that these cardiovascular effects could negatively affect the central nervous system due to hypoxia, and there are much emerging data showing bidirectional effects between the gut microbiome and the brain (for a review see [16]).

Discussion and Conclusion

Our original supposition was that iron deficiency caused irreversible changes in the dopamine reward pathways and this disrupted the learning necessary for the development of drug seeking behavior. Considerable evidence since then has shown deficits in many other learning and memory systems in the brain are caused by iron deficiency. This makes our original conclusion of a learning problem now more likely to be the case. From an increased risk of mental health disorders to a decrease in overall brain development, neonatal and infantile ID can severely impact an organism's functioning. Here we have shown recent data which further supports the deleterious effects of ID, particularly on effects which alter the process of learning and memory. Early life ID affects embryonic development which directly affects learning and memory. Iron deficiency has led to reduced brain volume and disrupted hippocampal growth.

Recent evidence shows ID increases risk of emotional reactivity and mental disorders such as depression. Given the high comorbidity between mental illnesses and SUD, early-life ID may have an indirect effect on susceptibility to SUD. A 2014 cohort study focusing on the contextual factors in SUD found that 70% of the patients suffered from at least one personality disorder, and that 50-60% of the patients suffered from severe anxiety or depression at least once in their lives [17]. Early life-ID appears to increase the risk of mental illness, which in turn appears to increase the risk for SUD, thus, early-life ID might increase the risk for SUD later in life.

A considerable amount of new research is now available which supports the original hypothesis regarding the potential association between learning and memory disabilities from ID which have the potential for increasing later vulnerability to SUD. However, no studies since the publication of our 2016 paper, of which we are aware, have looked directly at any relationship between ID and susceptibility to SUD. Still, one study discussed herein did find a small increase in risky alcohol use by adults who were iron deficient during infancy [6]. More research is necessary to further elucidate the extent to which early-life ID might increase the risk for SUD later in life.

Conflicts of Interest

The authors have no conflict of interest.

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