CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
scnp

Iron Depletion Affects Dopamine Neurotransmissions

Takahiko Nagamine, M.D., Ph.D.,* Nobuyuki Yamaoka, M.D.,**
and Masaru Nakamura, M.D., Ph.D.***

* *Department of Psychiatric Internal Medicine, Ishii Memorial Hospital*
** *Department of Psychiatry, Tokuyama-Seiyouin Hospital*
*** *Department of Psychiatric Internal Medicine, Kouseikai-Kusatsu Hospital*

Received March 31, 2016 / Accepted April 5, 2016 / Published April 28, 2016

Patients with schizophrenia suffer not only from psychotic symptoms such as delusions and hallucinations but also from cognitive and social functioning deficits that are partially related to decreased dopaminergic neurotransmission in the prefrontal cortex [1]. Iron deficiency causes detrimental cognitive sequelae, many of which are associated with alterations in dopamine synthesis and the modulation of dopaminergic neurotransmission [2]. We experienced a schizophrenia patient with iron deficiency whose negative symptoms and antipsychotic-induced hyperprolactinemia were improved by iron supplementation, suggesting that iron depletion affects dopamine signaling.

The patient is a 47 year-old woman who had been afflicted with schizophrenia. Cognitive deficits and negative symptoms such as avolition and anhedonia put her in our hospital, and she was treated with risperidone 3 mg daily. Two weeks after admission, laboratory examination revealed mild microcytic hypochromic anemia and hyperprolactinemia of 102 ng/mL. We examined her serum ferritin level and she was diagnosed as having iron deficiency because of her ferritin level of 5 ng/mL. We therefore started giving her iron with 50 mg of ferrous citrate sodium daily. Although the dose of risperidone remained unchanged, her negative symptoms and hyperprolactinemia gradually improved as her serum ferritin level increased. The changes in the ferritin and prolactin levels during iron supplementation are shown in Figure 1. The prolactin level was significantly inversely correlated with the ferritin level based on the Spearman rank correlation ($r_s = -0.986$; $p = 0.0275$). Six months later she was vigorous and was discharged; her ferritin level had increased to 43.1 ng/mL and her prolactin level had dropped to 45 ng/mL.

In terms of the basic science, L-DOPA, the direct precursor of dopamine, can be synthesized from L-tyrosine, which is transformed into L-DOPA by the enzyme tyrosine hydroxylase with tetrahydrobiopterin and iron as cofactors [3]. Moreover, in an animal model using rats, nutritional iron deficiency induced the reduction of dopamine receptor binding sites, resulting in down-regulation of dopaminergic activity similar to that observed in antipsychotic-treated animals [4]. Thus, iron deficiency can impair the synthesis of dopamine and is an important factor in the development of reduced dopamine signaling.

Negative symptoms like avolition and anhedonia are thought to involve hypofunction in dopaminergic system related reward processing and motivation. Alterations in the mesocortical pathway, where dopamine plays a major role in behavioral activation, may help explain altered social-emotional behavior in schizophrenia patients. Decreased dopamine signaling associated with iron deficiency can be related not only to the mesocortical pathway but also to the tuberoinfundibular pathway. Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Most antipsychotic drugs except aripiprazole are dopamine antagonists, which reduce dopamine activity, resulting in hyperprolactinemia. Iron deficiency accentuates the antipsychotic-induced elevation in prolactin [5].

Corresponding Author: Takahiko Nagamine, M.D., Ph.D., Department of Psychiatric Internal Medicine, Ishii Memorial Hospital, 3-102-1Tada, Iwakuni City, Yamaguchi, 741-8585, Japan.
e-mail: anagamine@yahoo.co.jp

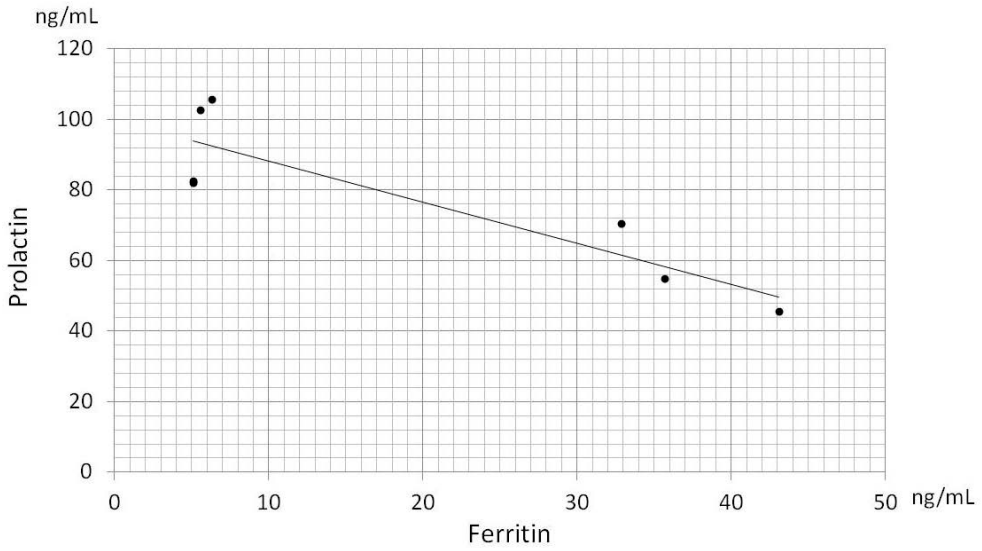

Figure 1. Relationship between serum ferritin and prolactin levels

Importantly, we found that serum ferritin levels reflecting a storage of iron were associated with a reduction in prolactin and with amelioration of negative symptoms in a schizophrenia patient with iron deficiency. Iron supplementation may normalize dopamine neurotransmissions not only in the meso-cortical pathway but also in the tuberoinfundibular pathway in patients with iron deficiency. Negative symptoms are more prominent in chronic schizophrenia patients, and are key predictors of worse functional and clinical outcomes. Future research is needed to understand physical factors which may be related to cognitive and social impairments in schizophrenia, because dopamine signaling is regulated by various physical factors.

CONFLICTS OF INTEREST

No funding was received for the preparation of this article. The authors have no conflicts of interest relevant to the content of this letter.

REFERENCES

[1] Sarkar S, Hillner K, Velligan DI. Conceptualization and treatment of negative symptoms in schizophrenia. World J Psychiatry. 2015 ;5(4): 352-61.

[2] Lozoff B. Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. J Nutr. 2011;141(4):740S-746S.

[3] Bianco LE, Wiesinger J, Earley CJ, Jones BC, Beard JL. Iron deficiency alters dopamine uptake and response to L-DOPA injection in Sprague-Dawley rats. J Neurochem. 2008; 106(1):205-15.

[4] Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. Pharmacol Biochem Behav. 2001;69(3-4):409-18.

[5] Calarge CA, Ziegler EE. Iron deficiency in pediatric patients in long-term risperidone treatment. J Child Adolesc Psychopharmacol. 2013 ;23(2):101-9.