

A review article:

The Potential Role of Anemia in the Incidence of Schizophrenia

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Abstract:

Schizophrenia (ZP) is a common devastating cognitive disorder; however, the etiology of its incidence remains largely unclear yet. Although some evidence blames both environment and genetic factor as main drivers of ZP, but the clear mechanism of their effect elusive till now. Of interest, severe anemia conditions can lead to hypoxia in CNS which disturbs the normal structures and functions of some area in the brain resulting in abnormalities in the neurons communications and decrease synaptic plasticity. Additionally, modulation of cytoskeleton constituents is thought to participate to ZP development. Recently, it has been revealed that iron deficiency, which is the main cause of anemia, has a significant impact on the cytoskeleton constituent's disassembly. Such conditions are believed to evoke responses to adaptive as increase some neurotransmitter such as dopamine, which in turn exacerbates the disease pathophysiology events. Accordingly, the purpose of this review to provide an insight to the potential impact of anemia on ZP development.

Keywords: Schizophrenia, anemia, hypoxia, BDNF, neurons' cytoskeleton.

دراسة مراجعة : الدور المحتمل لفقر الدم في حدوث فصام الشخصية

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مستخلص

فصام الشخصية (ZP) هو اضطراب إدراكي مدمر شائع. ومع ذلك، فإن أسباب حدوثه لا تزال غير واضحة إلى حد كبير حتى الآن. على الرغم من وجود بعض الأدلة التي تشير إلى دور البيئة والعامل الوراثي كمسببين رئيسيين لمرض ZP، إلا أن الآلية الواضحة لتأثيرهما غير واضحة حتى الآن. ومن المثير للاهتمام أن حالات فقر الدم الشديدة يمكن أن تؤدي إلى نقص الأوكسجين في الجهاز العصبي المركزي مما يؤثر على التركيب والوظائف الطبيعية لبعض المناطق في الدماغ مؤدياً إلى خلل في اتصالات الخلايا العصبية وانخفاض المرونة الاشتباكية. بالإضافة إلى ذلك، يُعتقد أن التغيرات في بنية الهيكل الخلوي يمكن أن تساهم في تطوير ZP وقد تبين مؤخراً أن نقص الحديد، وهو السبب الرئيسي لفقر الدم، له تأثير كبير على تفكيك مكونات الهيكل الخلوي. كما يُعتقد أن مثل هذه الحالات تثير استجابات تكيفية مثل زيادة بعض النواقل العصبية كالـدوبامين، والذي بدوره يؤدي إلى تفاقم أحداث الفيزيولوجيا المرضية. وبناءً على ذلك، فإن الغرض من هذه المراجعة هو تقديم نظرة شاملة لزيادة فهم التأثير المحتمل لفقر الدم في نشو وتطور مرض فصام الشخصية.

الكلمات المفتاحية : فصام الشخصية، فقر الدم، نقص الأوكسجين، BDNF، الهيكل الخلوي للأعصاب.

Introduction:

Schizophrenia is a devastating mental illness results in a dysfunctional lifestyle. It causes social withdrawal, cognitive impairment, and decreased emotional reflection [1-3]. There are no diagnostic tools to detect schizophrenia; diagnosis is depended on behavior observed. This means that the disease cannot be predicted, but rather diagnosed after the symptoms are resulting from damage certain areas in the brain [4]. The global incidence of schizophrenia ranges between 3 to 7.0%, with globally twenty-four million affected cases according to the WHO statistics [5]. Several studies have been shown the higher rate of suicide action in people diagnosed with schizophrenia [6-7]. However, the etiology of schizophrenia is still unclear, but in general it is believed that environment and genetic variations are considered to have involvement in the occurrence of ZP [8].

What is not yet clear is the potential involvement of anemia as a risk factor in schizophrenia. A number of studies have found increased prevalence anemia among patients with schizophrenia [9]. One of the potential effects of

anemia on the CNS is a change in the neuron cytoskeleton, which alters neuronal synapses [10]. Recent evidences suggest the schizophrenia could be related to impaired neuronal connecting caused by abnormality in the shape of the neuron axon [11]. Postmortem studies in schizophrenia have illustrated the most of dysfunctions is consequences of the disturbance in axonal synaptic [12]. Impairment of axonal synapses is the result of poorly performing oligodendrocytes and cells producing myelin. These circumstances increase dopamine secretion as a mechanism to speeding the signaling transmission in the context of axonal connections abnormalities [13].

Severe anemia led to hypoxia in the CNS, and this in turn resulted in elevated levels of hypoxia-inducible factor-1 alpha (HIF-1 α). Under these circumstance miR-210-3p is activated, which suppressing the brain-derived neurotrophic factor (BDNF) [14-15], Furthermore, numerous studies shown the hypoxia can be blocking and alter BDNF intercellular signaling pathway (Fig.1) [16, 17]. The most important relevant roles of BDNF in CNS are enhancing the differentiation of oligodendrocyte precursor cells (OPCs).

Additionally, BDNF controls local translation of neuronal proteins, as well as regulates of cytoskeleton and membrane dynamics [18]. Furthermore,

pathophysiologic link between schizophrenia and perturbed cortical iron biology has been suggested recently[19].

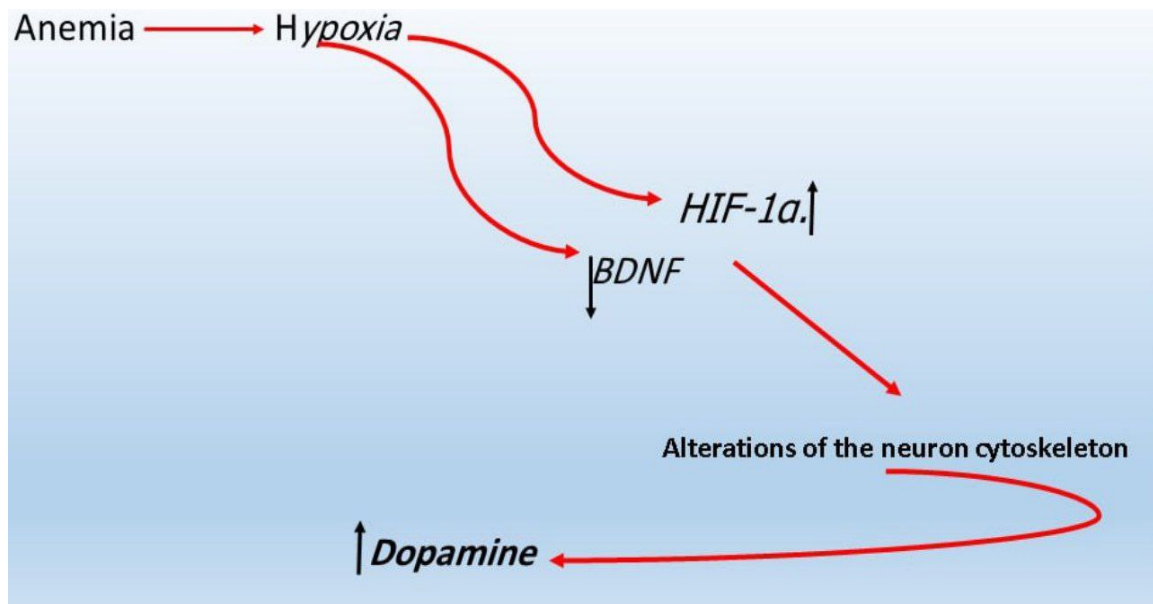


Figure1: The potential underlying effect of anemia in schizophrenia

Effect of anemia on the neuron cytoskeleton via *BDNF* expression modulation

Anemia is state characterized by a lessening the number of erythrocyte, or reduce the quantity of hemoglobin in the blood results to a decrease the capacity of oxygen-carrying [20-22]. The brain responds to the severe chronic anemia via activation the expression of HIF-1 α [4]. HIF-1 α plays crucial role in *BDNF* suppression via direct binding to its promoter region leading to reduced levels of BDNF [23]. Additionally, hy-

poxia can impair the *BDNF* expression through down regulation of its transcription factors such as REST (RE-1 Silencing Transcription factor), which plays important role in upregulation of *BDNF* gene [24]. Furthermore, hypoxia circumstances promote the enzymatic activity of BACE1 (β -site amyloid precursor protein cleaving enzyme 1) that is involved in the degradation of BDNF (Fig.2) [25].

The evidence presented thus far supports the idea that hypoxia can lead to inflammation in CNS [26]. Most

studies in this field have found a significantly negative correlation between hypoxia status and *BDNF* expression in neurons. It is identified that hypoxia can cause epigenetic alternations in

BDNF gene, via increase DNA methylation at specific CpG within promoter of *BDNF* gene, which in turn, reduced or silence the *BDNF* mRNA [27].

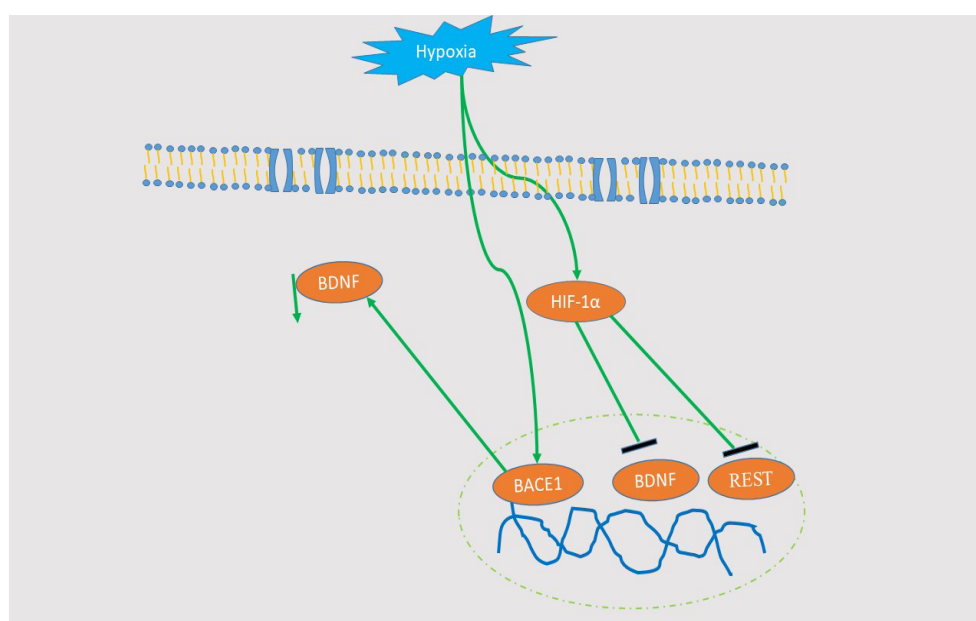


Figure 2: Signaling pathway of under hypoxia circumstance. Hypoxia cause upregulation HIF-a, which in turn downregulation BDNF, as well as downregulation REST which in turn upregulation BDNF. Additionally, hypoxia activation BACE1 which is plays role in degradation of BDNF

As it mentioned earlier, BDNF plays crucial in the neuroplasticity, which means losing the ability of the brain to form new neurons connection if there are any impaired in *BDNF* expression [28]. Additionally, *BDNF* maintain the synaptic modulation and reduced its levels can cause decrease in neuron communication [29]. Furthermore, recent studies have illustrated that any alternation in neuron plasticity can increased dopa-

mine secretion [30]. On the other hand, recent investigations have shown that BDNF induce oligodendrocyte precursor cells (OPC) survival, proliferation and differentiation [31]. There is a large volume of published studies describing the role of oligodendrocyte in maintaining the neuron cytoskeleton, via specific factors expression such as adhesion molecules [32]. As well as growth factors and signaling molecules that enhance

organization the neuron cytoskeleton, while the signaling molecules influences on the cytoskeleton components through assemble and disassemble, such as actin and microtubule [33]. Furthermore, oligodendrocyte considerable main source for myelin sheet, which in turn important to neuron synapse [34]. Recent studies have been investigated the potential mechanism underlying schizophrenia, where it found the alternation in OPCs, such as disturbance of differentiation and myelination of OPC implicated in many cognitive disorder [35].

Effect of anemia on the neuron cytoskeleton via the regulation of actin dynamics

Actin dynamics demonstrate important role in the neuron communication, and development. Previous studies have shown that actin dynamics involved in axonal guidance in a neuron synaptic, as well as, do crucial job in synaptic plasticity *via* regulating the stability and strength of synapses [36]. Moreover, actin dynamics are considered as principal factor in synapse formation by stabilizing the structure of dendritic spines [37]. Furthermore, polymerization and remodeling of actin contribute to long term depression (LTD) and long term potentiation (LTP)[38], where a

number of studies have reported that patients with schizophrenia presented both of the aforementioned abnormalities. The LTP in hippocampus of patients with schizophrenia is reduced compared to their healthy counterparts, and it was correlated with dyscognitive in the schizophrenic patients [39]. Another study investigated the normality of LTP in the hippocampus showed there is more decrease in function of LTP in schizophrenia patients, in comparison to healthy individuals [40].

Increasingly evidence suggest that hypoxia have indirectly impact on adrenergic system in the ventral tegmental area (VTA) via disruption of actin filament, which results in alternation in neuron cytoskeleton [41]. On the other hand, hypoxia status triggers stress in the VTA, which could lead to the disturbance in actin filaments, resulting in alterations in synapse of adrenergic system[42]. Numerous studies confirmed the hypoxia circumstance leading to negative effects on the actin dynamics, via HIF which is activated in response to hypoxia status. Such HIF serves as a transcription factor regulates the expression some protein implicated in actin dynamic, such as, ROCK, cofilin, and RhoA. These proteins involved in actin

organization, polymerization, and actin cytoskeleton[43]. Recent research has shown there is abnormalities in ROCK signaling in patients with schizophrenia, that indicates potential role of ROCK signaling in schizophrenia[44]. Other studies are also shown, there is positive correlation among aberrant Rho GTPase and the disorders in the brain connectivity in individuals with schizophrenia [45]. On the other hand, hypoxia can promote several signaling pathway, which influences on the remodeling the actin dynamics, such as, the MAPK pathway, and PI3K/Akt [46].

Recently, chronic anemias resulted from deficient iron delivery can damage the cytoskeletal framework of hematopoietic progenitor cells suggesting the identifying of targeted strategy for cytoskeletal repair, leading to anemia correction [47]. Additionally several lines of evidence have highlighted the involvement a number of schizophrenia-associated genes (and their encoded proteins) in modulating cytoskeleton constituents of nerve cells that is believed to involve in schizophrenia development. Such findings are summarized in Table 1.

Table1: Genes implicated in both cytoskeleton constituents' modulation and schizophrenia development.

Gene	Potential impact in cytoskeleton modulation that linked to schizophrenia development	Refs
<i>DISC1</i>	Directs microtubule network formation and microtubule organizing centre.	[48]
<i>RTN4R</i>	Regulation of actin cytoskeleton by Rho GTPases and the reorganization of actin cytoskeleton.	[49]
<i>SYN2</i>	Neuronal phosphoprotein covering synaptic vesicles, binds to the cytoskeleton, and regulates the release of neurotransmitter.	[50]
<i>SHANK3</i>	Structural and functional organization of the dendritic spine and synaptic junction plasticity.	[51]
<i>DTNBP1</i>	Plays a role in actin cytoskeleton reorganization and neurite outgrowth.	[52]
<i>ULK4</i>	Regulates neurite branching and elongation via remodeling of cytoskeletal constituents, including alpha-tubulin.	[53]
<i>DLGAP2</i>	An adapter protein linking ion channel to the subsynaptic cytoskeleton regulating and neuronal cell signaling.	[54]
<i>MFAP5</i>	Affect permeability and motility of endothelial cells via cytoskeleton rearrangement.	[55]
<i>HECW2</i>	Involved in the regulation of mitotic metaphase/anaphase transition.	[56]
<i>KATNAL2</i>	Major catalytic subunits of the microtubule-severing enzyme	[57]
<i>BIRC6</i>	Cytoskeleton and microtubules regulator	[58]
<i>GRIN2B</i>	Involves in actin cytoskeleton dynamics	[59]
<i>AKT1</i>	Phosphorylates palladin (PALLD), modulating cytoskeletal organization	[60]

Anemia (iron deficiency) as a risk factor for schizophrenia through neurotransmitter pathway

Iron is the most prevalent transition metal in the brain and is essential for many neurological processes, such as neurogenesis, axon myelination, synaptic development, mitochondrial function, electron transport, neurotransmitter synthesis, and metabolism [61]. Indeed, the disruption of iron homeostasis may influence neurophysiological mechanisms, cognition, and social behavior, ultimately contributing to the development of a wide range of neuropathologies [62]. Iron deficiency (ID) is the most common, avoidable, and treatable cause of anemia in the world [63-65]. Recent research suggests that neurotransmitters such as dopamine, glutamate, γ -aminobutyric acid GABA and serotonin are major contributors to schizophrenia, with dopamine playing the most important role [66]. According to the findings of a recent study [67] iron deficiency results in an alterations of monoamine neurotransmitters. Furthermore, dopamine (DA) is a key monoamine neurotransmitter in the brain that plays critical roles in higher brain activities such as motivation, reward, and cognitive func-

tion. Therefore, it is not surprising that dopaminergic signaling defects have been linked to the pathophysiology of several mental diseases, including attention deficit/hyperactivity disorder (ADHD), Huntington's disease (HD), Parkinson's disease (PD), and schizophrenia [68]. Moreover, iron is a cofactor of tyrosine hydroxylase, the rate-limiting enzyme in dopamine production. Therefore, it seems sense that decreased brain iron levels would decrease the availability of iron in dopamine neurons, which may therefore decrease dopamine activity in the central nervous system. Reduced dopamine activity has been reported to be related to negative symptoms in schizophrenia patients [69].

On the other hand, serotonin is a neurotransmitter involved in the regulation of mood, neuronal activity, and anxiety and iron is necessary for its synthesis [67, 70-71]. Decreased circulating iron leads to disruption of serotonin metabolism and reduced serotonin levels [72]. Finally iron deficiency during pregnancy, as well as in infancy and childhood, is linked to motor, cognitive, and behavioral abnormalities that are like those seen in children who later develop schizophrenia [73 -75].

Conclusions

Considering the scarcity of evidence linked schizophrenia development to anemia and cytoskeleton constituents' disruption, a new insight can be gained by reviewing genes involved in regulating neural cell cytoskeleton in relation to the subsynaptic cytoskeleton regulating and neuronal cell signaling. Although the direct link between anemia and schizophrenia has not established yet, however, the potential link of iron deficiency to cytoskeleton dysregulation opens a new venue for understanding schizophrenia biology and suggesting novel therapeutic targets to tackle such devastating disease.

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Conflicts of Interest

The authors declare have no conflict of interest.

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