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Review article

Involvement of vascular endothelial growth factor in schizophrenia

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ABSTRACT

Vascular endothelial growth factor (VEGF), which acts as an angiogenic and neurotrophic factor, is involved the regulation of cerebral blood volume and flow in Schizophrenia (SCZ). Several evidence indicates that modification of brain blood circulation due to alterations in the VEGF system affects cognitive performance and brain function in patients with SCZ. The aim of this study is: 1) To analyze the literature data concerning the role of VEGF in modulating the angiogenic response in SCZ. These data are controversial because some studies found elevated VEGF serum levels of VEGF in patients with SCZ, whereas others demonstrated no significant differences between SCZ patients and controls. 2)To analyze the role of VEGF as a predictive factor on the effects of antipsychotics agents used in the treatment of SCZ. In this context, high VEGF levels, associated to better responses to antipsychotics, might be predictive of the use of first generation antipsycotic drugs, whereas low VEGF levels, expression of resistance to therapy, might be predictive for the use of second generation antipsycotic drugs.

1. Introduction

Schizophrenia (SCZ) is a severe psychiatric condition affecting about 1% of the population worldwide, according to the *Diagnostic and Statistical Manual of Mental Disorders* [1]. Etiopathogenesis of this disorder involves a number of genetic and environmental factors [2]. While Genome Wide Association Studies (GWAS) have indicated that multiple genes and multiple molecular pathways, contribute to the pathophysiology of the illness [3], further studies have related risk for SCZ to environmental stressors including perinatal complications, urbanity, substance abuse, childhood trauma, migration and social isolation [4]. Brain structural and functional studies have contributed to the understanding of biological bases of SCZ and have demonstrated that genetic and environmental factors may interact determining the clinical phenotype. One of the mechanisms impacted is regulation of brain blood flow, which is also a critical function guiding many neuroimaging investigation approaches [5]. Within such a perspective, imaging genetics, genomics, neuroanatomical and preclinical studies have indicated that genetically regulated molecular routes underlying angiogenesis in brain and a molecular network involving Vascular Endothelial Growth Factor (VEGF) may play an important role in brain blood flow regulation supporting SCZ [6].

In this article, we explored existing literature, through a retrospective analysis of articles published in the last twenty years using *Web of Science,* with the aim to clarify the role of VEGF in modulating the angiogenic response in SCZ. These data are controversial because some studies found elevated VEGF serum levels of VEGF in patients with SCZ, whereas others demonstrated no significant differences between SCZ patients and controls. Moreover, we have analyzed the role of VEGF as a predictive factor on the effects of antipsychotics agents used in the treatment of SCZ. In this context, the novelty of this article is to have underlined the non-univocal role played by VEGF as a predictive factor in the progression of SCZ and in the response to therapy with antipsychotics.

2. Vascular endothelial growth factor family

VEGF described as a tumor-secreted vascular permeability factor in 1983 [7], was purified and sequenced in 1989 [8], and induces the formation of new blood vessels. VEGF plays a primary role in the development of the vasculature during embryogenesis and is involved in the pathological angiogenesis in chronic inflammation and tumor growth. The VEGFs family of growth factors includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF) [9]. VEGFs exert their biological activities by binding to the tyrosine kinase receptors, including VEGF receptor-1 (VEGFR-1), -2 (VEGFR-2), and -3

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(VEGFR-3), and to the non-tyrosine kinase receptors, including neuropilin-1 and-2 (NP-1 and NP-2), which function as co-receptors for the VEGFRs [10].

3. VEGF in the nervous system

During embryonic life, in the central nervous system (CNS), angiogenesis is controlled by a temporal and spatial-regulated expression of VEGF by neurons and glial cells [11]. Neurons and glial cells stimulate vascularization of the developing brain, VEGF is released by growing neuronal precursors to recruit blood vessels [12], and neurons proliferate in vascular niches, where the blood vessels provide a substrate for migrating neuronal progenitors during neurodevelopment [13]. Blockade of VEGF impairs angiogenesis, neurogenesis, and cognitive response [11,14–16]. In detail, VEGF favours neuronal and glial cell migration in the developing CNS, displays neuroprotective properties in the adult, and increases the survival of neurons [17–21]. Moreover, VEGF also increases vascular permeability and thereby alters the blood–brain barrier (BBB), promoting inflammatory cell infiltration in the nervous tissue [22].

The putative role of VEGF in depression has been hypothesized in the context of the neurotrophic model of depression, which is is based on the evidence that stress can cause a decreased level of neurotrophins and VEGF [23]. VEGF is also involved in neurodevelopmental disorders including bipolar disorder, mood disorders, and autism, correlated with hypoxia–ischemia insults during early life and are strongly associated with cognitive dysfunction [24]. Severe reductions in VEGF concentrations lead to hypoxia and, subsequently, to degeneration of the cerebral cortex and neonatal death [25].

4. Angiogenesis in schizophrenia

Abnormalities in total cerebral blood volume (CBV) in SCZ have been highlighted using contrast-enhanced MRI methods after intravenous injection of an exogenous contrast agent. Widespread reductions in total CBV in SCZ patients compared to controls have been observed in both brain hemispheres [26], especially in frontal cortex [27–29] and visual cortex [29]. Reduced CBV may lead to chronic tissue hypoactivation and increased levels of free radicals, resulting in neuronal loss and cognitive impairments [26]. An increase in total CBV in SCZ, found less frequently than decreased total CBV, has been reported in the cerebellum and basal ganglia [30,31], and in some regions of the occipital lobe [30], orbitofrontal cortex [28], and hippocampus [28,32–34].

Xenon Xe-133 inhalation during PET scans showed that most SCZ patients display hypofrontality, consistent with frontal hypoperfusion, that, in turn, may result from a reduced number of vessels in the frontal cortex, and related abnormalities in the brain hemodynamic [35,36]. A reduced number of vessels can arise from defects in angiogenesis during early brain development, in turn leading to overall reduced blood flow and lower oxygen supply to brain tissue. This hypoperfusion has been associated with psychotic symptoms [37] showing a possible functional link between angiogenesis alteration and psychosis. Hypoperfusion or decreased blood flow are possible mechanisms underlying smaller brain tissue volumes observed in SCZ [38].

Arterial Spin Labeling (ASL), a novel non-invasive technique that measures regional cerebral blood flow (rCBF) [39], has been used to study CBF changes in patients with SCZ at the resting state condition [40,41]. Within such a framework, using 2D Pseudo-continuous ASL (pCASL), a decreased CBF in frontal, parietal, and occipital lobes, and in functional regions has been observed in SCZ compared to controls [42]. These findings are consistent with studies in SCZ using ASL [39–41], also conducted in non-medicated SCZ patients [43].

Post-mortem analyses have demonstrated morphometric differences in microvessel area and length density in cortical and subcortical regions in SCZ as compared to controls [44–46]. A functional genomics study indicated that SCZ is characterized by the expression of genes associated with PI3K/AKT signalling pathway, which influences vasoconstriction and vasodilatation, through re-uptake of dopamine, serotonin and norepinephrine and modulation of nitric oxide (NO) production, respectively [47]. Post-mortem gene expression studies have reported that genes involved in post-ischemic repair are significantly overexpressed in SCZ compared with healthy individuals [47]. Moreover, SCZ risk genes that are also specific markers of endothelial cells and BBB, showed transcriptional changes in different brain cortical regions and in the hippocampus of individuals with SCZ [37].

5. VEGF in schizophrenia

SCZ patients show impaired vasodilation [48] along with presence of epilepsy. Vascular remodelling and angiogenesis are involved in temporal lobe epilepsy [49,50], and epilepsy is related to an increased expression of VEGF [51]. Moreover, VEGF may be responsible of BBB disruption, and increase in extracellular volume and degeneration in the frontal lobe in SCZ [52].

In the dorsolateral prefrontal cortex of patients with SCZ, VEGF expression was decreased [53]. Otherwise, in the parietal cortex and in the serum of patients with SCZ, VEGF expression was increased [54]. Other studies demonstrated no significant difference in serum and plasma VEGF levels between first-episode SCZ patients and controls [55]. A significant reduction of both hippocampal blood flow and serum VEGF levels was demonstrated in reelin haploinsufficiency-induced SCZ endophenotype and wild type mice exposed to prenatal hypoxia [56]. Serum VEGF levels were related to structural abnormalities and inflammation in the prefrontal cortex of schizophrenic patients, and elevated levels of interleukin-6 (IL-6) were correlated to serum VEGF level and hypofrontality [54].

Since VEGF levels inversely correlate with the severity of cognitive impairment, a critical endo phenotype of SCZ [57], it is plausible VEGF to be involved in cognitive function remission in SCZ by improving neuronal viability and function [58]. Rather consistently, while neonatal hypoxia has been associated with hippocampus damage in SCZ patients [59], SCZ susceptibility genes are controlled by the hypoxia-inducible factor-1 alpha (HIF-1α), which, in turn, can modulate the up-regulation and transcription of VEGF [60].

VEGF gene variation at two Single Nucleotide Polymorphisms, has been associated with smaller hippocampal volumes [61], while genetic variation has been associated with total grey and white matter volume [62] in healthy individuals.

The effect of VEGF-A genetic variation on cognition and psychosis-related phenotypes has been studied in humans [63]. They were associated with reduced odd of psychosis, reduced hallucinations and greater volume in the DLPFC and parahippocampus, highlighting the potential role of VEGF-A gene and related biological function in pathogenesis of psychosis [63]. The expression of a soluble form of VEGFR-1 predicts clinical and brain structural changes in SCZ [64,65].

Further studies have indicated the involvement of VEGF-A signalling in major psychiatric conditions which may manifest with psychotic symptoms, even though not specifically including SCZ. For example, there is evidence for association between *VEGF* polymorphisms and risk for Major Depressive Disorder (MDD) [66,67] and Treatment Resistant Depression [68]. Misiak et al. performed a meta-analysis including 15 eligible studies representing 982 patients and 791 healthy controls [69]. They compared serum plasma levels of VEGF between SCZ patients of first episode psychosis (FEP) and controls and demonstrated elevated levels of VEGF in SCZ patients that are unrelated in FEP ones.

6. VEGF and treatment with antipsychotics

A main topic in literature regarding the role of VEGF in SCZ is whether VEGF molecular pathway is also involved in mechanism of action antipsychotic agents. Several studies have reported serum VEGF levels in patients with SCZ treated with antipsychotics to be higher as

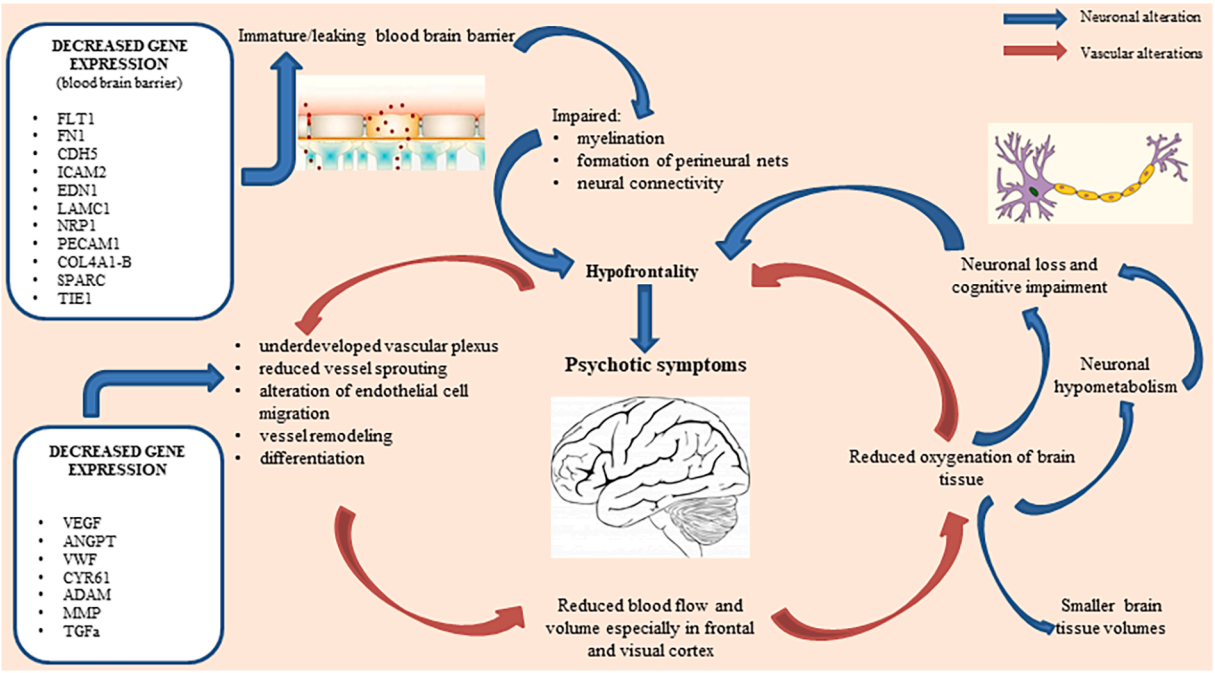

Fig. 1. Mechanistic diagram of neuronal and vascular morpho-functional alterations in schizophrenia.

compared to controls [54,70]. Such an evidence may indicate that antipsychotic therapy exerts their action by directly and/or indirectly increasing VEGF serum level, by inducing *VEGF* gene expression in brain areas of critical relevance to pathophysiology of SCZ.

A proof-of-concept strategy to answer this question may be represented by studies on non-medicated patients. In this context, VEGF levels have been estimated in drug-free patients before and after treatment with antipsychotics. Rather significantly, baseline serum VEGF levels showed a significant positive correlation with antipsychotic efficacy, such that participants with higher baseline serum VEGF levels had better responses to antipsychotic medication, while lower baseline VEGF predicted resistance to drug therapy in acute-stage SCZ [71]. These results indicate that VEGF can serve as a prognostic biomarker in patients with SCZ. In drug-naive first-episode SCZ patients receiving the antipsychotic Quetiapine, basal serum VEGF levels predicted the improvement of two scores [72].

A 14-day administration of haloperidol and olanzapine have shown to increase levels of VEGF and angiogenesis in the hippocampus of rats, and a 45-day treatment with olanzapine can enhance VEGF levels in rats [58]. Chronic administration of haloperidol and risperidone in adult rats with ketamine-induced SCZ produced on neurogenesis and survival associated with the activation of VEGF signalling pathway [73].

Patients with SCZ have lower plasma VEGF levels than controls before treatment, and plasma VEGF levels increased after 6 weeks of treatment with atypical antipsychotics [74]. The changes in serum VEGF might be a component of the disease pathology rather than an effect of the antipsychotic therapy.

Studies have suggested the involvement of VEGF in mechanism of action of other therapeutic approaches to SCZ. For example, VEGF levels were significantly higher in patients with treatment-resistant SCZ treated with Electroconvulsive therapy (ECT) in post-treatment as compared to pre-treatment condition [75].

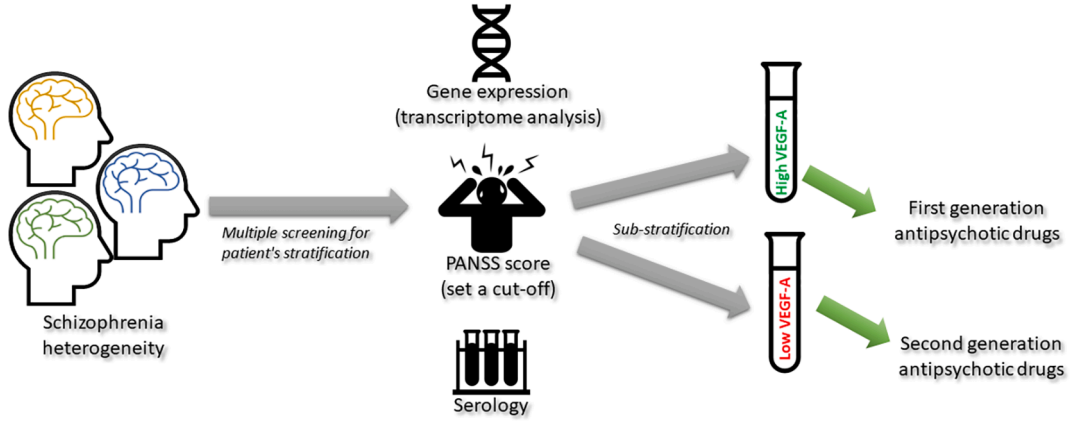

Fig. 2. Schematic representation of possible schizophrenia patient stratification before antipsychotic treatments based on integrated transcriptome analysis, Positive and Negative Syndrome Scale (PANSS) evaluation for rating the symptoms and serology tests to evaluate possible predictive biomarker such as VEGF-A. Based on VEGF-A serum level, patients could be sub-stratified as responders or non-responders to a specific treatment. High VEGF-A levels, associated to better responses to antipsychotics, might be predictive of the use of first generation antipsycotic drugs, whereas low VEGF-A levels, expression of resistance to therapy, might be predictive for the use of second generation antipsychotic drugs.

7. Concluding remarks and therapeutic options

Neuro-vascular alterations occur in SCZ (Fig. 1), and literature highlights a possible role of VEGF molecular pathway in pathophysiology of this disease [6,37].

We have highlighted that the literature data concerning the role of VEGF in modulating the angiogenic response in SCZ are controversial because some studies found elevated VEGF serum levels of VEGF in patients with SCZ, whereas others demonstrated no significant differences between SCZ patients and controls. Due to this controversial issue, the use of VEGF serum level as a biomarker in SCZ should be correlated with a more complete understanding of its role in the regulation of other structural and functional parameters which are altered in the course of the evolution of SCZ. Moreover, it is important underline that beside its role in angiogenesis and blood flow regulation, VEGF is involved also as neurotrophic factor in brain homeostasis. In fact, alteration in VEGF levels have been correlated to changes in brain volumes observed in SCZ [76].

The second issue of our study concerns the analysis of the role of VEGF as a predictive factor on the effects of antipsychotics agents used in the treatment of SCZ. There is evidence that using anti-VEGF therapy to treat unwanted angiogenesis and vascular leakage in cancer might inhibit adult neurogenesis and/or neuroprotection [77]. On the other hand, VEGF-A could be used to treat neurodegenerative and neuropathic conditions by simultaneously enhancing blood vessel growth, neurogenesis, and neuroprotection. Further studies are needed to probe the therapeutic potential of VEGF-mediated pharmacological action in SCZ. Based on VEGF-A serum level, patients could be sub-stratified as responders or non-responders to a specific treatment. High VEGF-A levels, associated to better responses to antipsychotics, might be predictive of the use of classic antipsycotic drugs, whereas low VEGF-A levels, which predict resistance to therapy, might be predictive for the use of new antipsychotic drugs (Fig. 2).

Conflict of interest statement

There are not conflict of interest.

Compliance with ethical standards

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