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The Potential of Cerebrolysin in the Treatment of Schizophrenia

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Abstract

Schizophrenia and psychosis are psychiatric condition whose neural mechanisms are yet incompletely known, and for which pharmacological treatment is too often ineffective in a growing clinical cohort. Recently, dendritic morphological changes in arborization and dendritic spine density in limbic regions has been reported in postmortem tissue from schizophrenic patients and in animal models of schizophrenia, suggesting that the use of medication improving synaptogenesis may be beneficial as additional treatment of psychotic patients. Cerebrolysin (Cbl) is a drug available for clinical with active neuropeptides fragments that mimics the action of endogenous neurotrophic factors such as BDNF, GDNF, CNTF and NGF, which improves the integrity of the neuronal circuits as well as cognitive and behavioral performance by exerting a neuroprotective effect and promoting the generation of new functional synapses. Recent work from our laboratory has shown that Cbl ameliorates synaptic and dendritic pathology in animal models of schizophrenia by increasing synaptic density and restoring neuronal cytoarchitecture. This neuroprotective effect improves the integrity of the neuronal circuits and improves cognitive and behavioral performance. Importantly, Cbl treatment seems to be safe when used in combination with neuroleptics such as risperidone. The present article analyzes the potential of Cbl in the treatment of neurodevelopmental disease, and reviews the current literature on the effects of Cbl in *in vivo* animal models of neurodevelopmental disorders like schizophrenia.

Keywords

Cerebrolysin, Neurotrophic Factors, Schizophrenia, Prefrontal Cortex, Hippocampus, Amygdala

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1. Introduction

Schizophrenia is a complex disorder of thought, perception and social interactions affecting 1% of the world population. This severe mental disorder starts at early adulthood during the synaptic pruning and myelination process [1] with an individual combination of positive, negative, and affective symptoms as well as cognitive deficits, while the severity of these symptoms can change over time depending on the disease stage [1]. Various theories have been advanced to explain schizophrenia; amongst them, the altered communication between temporal-prefrontal circuits theory postulates an altered synaptic communications between temporal regions as hippocampus and basolateral amygdala (BLA) with the prefrontal cortex (PFC) in mediating some of the behavioral manifestations of this disorder. In recent years, clinical imaging and pathological studies have provided strong evidence for structural and molecular changes in the PFC, BLA and hippocampal formation (HF) of schizophrenic brains that are suggestive of abnormalities in brain development and plasticity. It has been suggested that neuropathologies associated with schizophrenia may result from developmental abnormalities in BLA, hippocampus and/or PFC efferents that alter normal maturation and functionality of limbic system. In addition, postmortem studies of schizophrenic patients have demonstrated a significant reduction in the dendritic arbor and dendritic spine density [2] [3], whereas, molecular studies have demonstrated that neurotrophins such as brain-derived neurotrophic factor (BDNF) are altered in cortical regions of schizophrenic patients [4]. Moreover, a recent report [5] has shown that serum levels of another neurotrophic factor, neural grow factor (NGF), are altered in the schizophrenic patients [5]. Interestingly, animal studies clearly indicate a role of hippocampal, BLA and PFC inputs in modulating nucleus accumbens (NAcc) and mesolimbic dopaminergic activity. For example, recent studies with neonatal lesions of the ventral hippocampus in rats have revealed a postpubertal emergence of heightened sensitivity of the mesolimbic dopaminergic system. In addition, these animals have also shown changes in dendritic arborization and dendritic spine density at the level of the prefrontal cortex and nucleus [6]-[11]. Furthermore, bilateral neonatal ventral hippocampal lesion (NVHL) also caused a reduction in BDNF levels in the PFC at postpubertal age [12]. These findings suggest that schizophrenia is a disorder of brain connectivity with reduced synaptic communication at level of the PFC, BLA and hippocampus.

Cerebrolysin (Cbl) improves the integrity of the neuronal circuits as well as cognitive and behavioral performance [10] [11] [13]-[15] by exerting a neuroprotective effect and promoting the generation of new functional synapses. These findings induced us to decide to analyze the potential of Cbl in the treatment of neurodevelopmental disease, such as schizophrenia, and review the current literature on its possible mechanisms of action in studies using in vivo animal models of neurodevelopmental disorders such as schizophrenia.

2. Prefrontal Cortex Neuropathology in Schizophrenia

The PFC participates in the regulation of attention, inhibition, cognitive control, motivation, and emotion through connections with posterior cortical and subcortical structures such as the hippocampus, the amygdala, and the nucleus accumbens (for review sees Arnsten *et al*. [16]). Interestingly, patients with schizophrenia exhibit profound deficits in PFC functions that are a fundamental component of this illness (for review see Arnsten *et al*. [16]. Multiple lines of evidence suggest that the PFC is a primary site of dysfunction in schizophrenia [16]. For example, Glantz and Lewis [17] demonstrated reduced levels of synaptophysin (SYP) inmunoreactivity in the PFC of schizophrenic patients. SYP protein has been shown to be critical for regulating neurotransmitter release and synaptic plasticity, a process thought to be disrupted in schizophrenia. However, recent reports of postmortem brain studies from schizophrenic patients have shown that not only the PFC, but also other brain regions such as the medial temporal cortex, the visual association cortex, the hippocampus, and the thalamus also exhibit a decreased expression in the levels of [17]-[32], suggestive of gross synaptic alterations in the brain of schizophrenic patients.

Consistent with these findings, schizophrenia has been postulated to derive from a neurodevelopmental aberration that interferes with cortical neuronal maturation and abnormal network architecture at adolescence [33]. Interestingly, in animal models, chronic stress such as social isolation or movement restriction may alter the synaptic connectivity at the level of PFC and hippocampus [7] [34]-[37]. For all these reasons, exposure to stress may be a key factor in the precipitation of schizophrenic psychosis in adolescence and in the subsequent exacerbation of its symptoms [38]-[41], suggesting that the environment can and does interact with an already vulnerable circuitry to aggravate cortical deterioration.

The findings of abnormal placement of pre-alpha cell clusters, heterotopic displacement of neurons, and ab-

normal orientation of pyramidal cells in the entorhinal cortex and hippocampus of post-mortem schizophrenic brain are indicative of developmental aberrations in neuronal migration [42]-[45].

It is interesting to note that decreases in PFC and hippocampal immunoreactivity to markers for GABaergic interneurons-particularly the calcium binding protein parvalbumin but also the modulatory peptide, somatostatin [46]-[50] are one of the most consistent findings in post-mortem schizophrenic brains. A growing number of reports suggest that PFC GABAergic interneurons are critical in the development of the normal puberty [51]-[53].

It is known that brain axonal tracts are myelinated progressively across the lifespan in a region- and function-specific manner. Interestingly, post-mortem brain studies from patients with schizophrenia have implicated a myelin dysfunction in this disorder. In this framework, it is tempting to speculate that PFC myelination deficits [54] [55] and structural abnormalities in white matter detected in post-mortem brains from schizophrenic patients [56] may be caused by a developmental alteration of the myelination process that occurs within the brain in a region- and function-specific fashion during a lifespan. These observations together with a reduction in mRNA [55] and protein levels [45] [57] of myelin basic protein (MBP) in schizophrenia, supports the brain communication disorder hypothesis with emphasis in PFC functions.

The laminar distribution of NADPH-diaphorase-positive neurons, in the temporal and frontal cortices, suggests unusual neuronal migration [58]. Interestingly, since the finding by Weinberger *et al*. [59] that lateral ventricular size in schizophrenic patients is bigger than control, more than 300 peer-reviewed articles have delineated the subtle neuroanatomic abnormalities in this mental illness (for review sees Glahn *et al*. [60]. Considerable evidence from neuroimaging and epidemiological studies has now accumulated in support of a neurodevelopmental hypothesis of schizophrenia. Magnetic Resonance Image (MRI) studies have detected cortical volume reduction over time in patients with schizophrenia [61]. Furthermore, neural densities in the schizophrenic frontal cortex and hippocampus are reported to be decreased without concomitant gliosis [62] [63], although evidence to the contrary has also been reported [64].

Despite an impressive array of evidence implicating abnormal neurodevelopment in schizophrenia, few studies have provided conclusive evidence with respect to the biochemical substrates of such abnormalities. However, reports of a reduced expression of synapsin, microtubule associated proteins MAP2, DARPP-32, the dendritic protein neurogranin, and synaptophysin in the PFC of post-mortem schizophrenic brains provide molecular indication of disturbed synapse development and plasticity [65] [66].

3. Hippocampus and Amygdala in Schizophrenia

Similar to PFC, hippocampal and amygdala abnormalities have been reported in schizophrenia [67]-[72]. Structural and functional neuroimaging studies now provide strong evidence that hippocampal and amygdala volume are reduced in schizophrenia [73]-[79]. In addition, the extent of the volume loss has been correlated with positive, negative, and cognitive symptoms [80] [81]. Consistent with this idea such synaptic alterations in schizophrenia may—at least in part—be a cause for brain impaired (long-range) connectivity in this disorder. Specifically, post-mortem studies of schizophrenic patients show a reduced dendritic spine density in the subiculum andin the CA3 area [82] [83], as well as reduced spine size on CA3 pyramidal neurons [83]. Moreover, a lower number of synaptic contacts formed by individual mossy fibers tracts on CA3 pyramidal neurons have been reported in schizophrenia [84]. Interestingly, several reports show that cerebral blood flow of the schizophrenic patients is higher at hippocampus level [85] [86]. Furthermore, Schobel *et al*. [87] have shown that hippocampal basal blood flow volume correlates with both positive and negative symptoms in the schizophrenia.

In addition, in the post-mortem schizophrenic hippocampus and PFC the polysialylated form of the neural cell adhesion molecule (PSA-NCAM)—which is expressed specifically in PFC and hippocampal interneurons [88] is altered [89]-[91]. Interestingly, several reports show a dysfunction of GABAergic inhibition and a consequent imbalance between excitation and inhibition in the cerebral cortex in schizophrenia animal models [92]-[96]. In addition, various isoforms of NCAM, expressed in a developmentally regulated manner, play a crucial role in the migration of neural cells as well as in the guidance of growing axons, and, in the adult brain, are implicated in maintaining synaptic plasticity in structures such as the hippocampus, where a persistent expression of the embryonic form of the molecule is observed [90].

Consistent with these findings the cell pattern and orientation of cells in the hippocampus [97], and the dendritic arborization and density of dendritic spines in subicular pyramidal neurons from post-mortem schizoph-

renic patients are disrupted [98]. All these data are indicative of a dysfunctional hippocampal and amygdala circuitry in schizophrenia.

4. Neurotrophic-Like Factor Such as Cerebrolysin in Neuropsychiatric Disorders

Cerebrolysin (Cbl) is the only drug available for clinical use containing active fragments of important neurotrophic factors [99]. The active fragments are small neuropeptides which cross the blood-brain barrier (BBB) and mimic the action of endogenous neurotrophic factors such as BDNF, GDNF, CNTF and NGF and others [100] [101]. The neurotrophic action of the Cbl helps in the survival of neurons and prevents the cell death [102]. In addition, several reports suggest that Cbl induces neuroprotection when there is a damage of the brain and also induce neurogenesis. These two actions (neuroprotection and neurogenesis) maintain [99] [102]. These may be some of the reasons why Cbl is effective in the treatment of neurodegenerative diseases like multiple sclerosis, Parkinson's disease, Alzheimer's disease, dementia, and acute or chronic stroke [99]. In addition, recent reports suggest that Cbl increases synaptic communication by increasing dendritic arborization as well as the number of dendritic spines in cortical regions such as PFC and hippocampus [10] [11] [13] [14]. Moreover, Cbl is also effective in the treatment of neurodevelopmental disorder such as autism and schizophrenia [103]-[106].

5. Neonatal Ventral Hippocampus Lesion and Cerebrolysin

Rats with bilateral excitotoxic neonatal ventral hippocampal lesion (nVHL) have been widely accepted as a neurodevelopmental model of schizophrenia-related behaviors [107]-[110]. These rats exhibit behavioral and neurochemical changes that manifest mainly after puberty [109]-[111]. Behavioral and neurochemical changes include locomotor hyperresponsiveness to stress [7] [107] [108] [112], deficits in social interaction [113] [114], sensorimotor gating [115] [116], spatial learning and working memory problems [112] [117], decreased attention [116], low levels of brain-derived neurotrophic factor (BDNF) [118] [119] and nerve growth factor-inducible B (NGFB) [120]. Together with the behavioral and neurochemical alterations, neural morphological changes have been reported in this model [6] [7] [9]-[11]. Post-pubertally, nVHLs induce atrophy of pyramidal neurons of the prefrontal cortex (PFC), basolateral amygdala (BLA), and medium spiny neurons of the nucleus accumbens (Nacc) [6] [7] [9] [10]. Our recent report suggests that Cbl promotes recovery of dendritic and neuronal damage of the pyramidal neurons of the PFC and medium spiny neurons of the Nacc in post-pubertal nVHL rats [10]. In addition, behavioral changes such as locomotor hyperresponsiveness to stress and deficits in social interaction and sensorimotor gating were in part also recovered by Cbl treatment in nVH-lesion animals [10]. As we mention before, several reports have suggested that the BLA is dysfunctional in schizophrenic patients [121] and our group recently reported that nVHL animals show dendritic atrophy and reduced spinogenesis in the BLA at adult age [9] [10]. However, Cbl does not produce any amelioration after dendritic alterations of the BLA pyramidal neurons following nVHL in rats [11]. Another finding in the nVHL schizophrenia model is the reduction in the number of neurons in the PFC and BLA, measured by stereological analysis [10] [11]. Interestingly, Cbl treatment ameliorates the cells loss observed in the PFC and BLA of the post-puberal nVHL animals [10] [11]. All these data suggest that Cbl has a potential use in the treatment of schizophrenia.

6. Neurotropic-Like Factor in Schizophrenia

Neurotrophins are a large family of dimeric polypeptides that promote the growth and the differentiation of developing neurons in the central and peripheral nervous systems as well as the survival of neuronal cells in response to stress. The fact that schizophrenia is a neurodevelopmental disorder with reduced connectivity amount limbic regions induced by synaptic alterations [68] explains the growing interest in the role of neurotrophins in the pathophysiology of schizophrenia. Several recent reports have shown a reduced plasma and serum level of neural grow factor (NGF) and brain-derived neurotrophic factor (BDNF) levels in drug-naïve as well as medicated schizophrenic patients compared to healthy controls. In addition low serum BDNF levels were associated with reduction in hippocampal volume at the onset of schizophrenia [122]. Furthermore, a recent report has shown significantly higher levels of methylation of BDNF promoter in patients with schizophrenia compared to controls [123]. Consistently with these findings, risperidone-atypical antipsychotic drugs—elevates BDNF—but not NGF-levels in schizophrenic patients [124]. All these data support the hypothesis that schizophrenia is a neurodevelopmental disorder with impaired synaptic communication between the hippocampus and the amyg-

dala on one hand, and the PFC on the other hand. Accordingly, drugs with neurotrophic-like effects that increase BDNF and NGF levels result in better synaptic communication with beneficial effects in schizophrenia.

Cbl has recently been used in the therapy of the schizophrenic symptoms [106], where it was found to improve cognitive and memory functions in patients dominated by negative symptoms. Interestingly, a recent report suggests that low BDNF is associated with cognitive impairment in chronic patients with schizophrenia [125]. In addition, a growing body of evidence shows that oxidative stress damage may relate to the range of cognitive deficits associated with schizophrenia [126]. Interestingly, oxidative stress is the condition arising from imbalance between toxic oxygen species and antioxidant system. Brain tissue is highly vulnerable to oxidative stress damage due to relatively low levels of endogenous antioxidants, high metal content and levels of polyunsaturated fatty acids, with elevated oxygen [127]-[129]. In addition, protective mechanism includes various antioxidant enzymes such as superoxide dismutase (SOD) and gluthatione peroxidase (GPX) [126] [130]. In the schizophrenic brains, a dysfunction in the protective mechanisms of oxidative stress has been suggested [126] [130]. An increase in oxidative stress together with a decline in membrane essential polyunsaturated fatty acids leads to enhanced lipid peroxidation [131]. In addition, antioxidant enzymes such as superoxide dismutase (SOD), glutathion peroxidase (GpX) and catalase (CAT) are often measured for quantifying antioxidant defense in schizophrenia [132] with conflicting results. Some studies report increased antioxidant defense in schizophrenia, whereas others report opposite conclusion [126] [130]. We measured the two biomarkers of oxidative stress, serum superoxide dismutase (SOD) activity and concentration of nitrites as indicator of the nitric oxide (NO) levels in the psychotic schizophrenic patients before and after 4 weeks with Cbl (10 mL/day) on top of the standard haloperidol treatment. Interestingly, the NO levels and SOD activity were reduced in the schizophrenic patients with Cbl treatment (data unpublished). In agreement with our results, another report suggests that Cbl induces a decrease on the CAT and SOD levels [133].

7. Activity of Cerebrolysin on Neuroimmune Antigens

A new hypothesis associates neurodevelopmental conditions including schizophrenia but also autism spectrum disorder (ASD) with alterations of the immune system response, either during fetal development [134] or as sensitization of the response to stressors during adulthood [135]-[137]. These considerations suggest the possibility that among the actions of the peptidic mixture making up Cbl is the decrease of a neuroinflammation associated with neuropsychiatric disease. While—at the current state—this possibility is only theoretical, it is worth to consider the potential of this avenue of research. Among the few exploratory studies on the effects of Cbl on the innate or adaptive immune system are an early report that in vitro treatment of mouse bone marrow with Cbl stimulated the response to Thy-1 (or CD90) [138], which is a marker for neuronal axons, and a second clinical study on children, which showed that 1-month intramuscular treatment with Cbl results in increased activation of CD19+ cells, with “simultaneous normalization of IgA and IgG” immunoglobulins and normalization of the otherwise altered levels of CD25+ and HLA DR in lymphocytes, achieving the parameters of the control group, together with activation of T-cells [139]. The same results were repeated and widened in a later study on a cohort of ADHD children affected by recurrent acute viral respiratory infections with parallel alterations in systemic blood immune parameters [139]. A more recent study identified cytoprotective properties of Cbl towards both B and T lymphocytes, favoring the survival of immunocompetent cells, and possibly stimulating the formation of immune memory B cells [140]. While it is premature to even formulate a hypothesis on whether any avenue of action of Cbl occurs through an interaction with the immune system, the efficacy of this peptide mixture in the treatment of conditions with an obvious immune component is worth being further investigated.

8. Conclusion

A growing body of evidence shows that schizophrenia is a disorder of brain connectivity with reduced synaptic communication at level of the PFC, BLA and hippocampus. This disconnection is expressed at puberty when exposure to stress, which may be a key factor in the precipitation of schizophrenic psychosis in adolescence together with the subsequent exacerbation of its symptoms [38]-[41]. Therefore, the interaction between stresses with a vulnerable limbic circuitry exacerbates cortical dysfunction. Consistent with these data, neurotrophins, a family of polypeptides or small proteins that exert robust effects on neuronal survival, synapse stabilization, and synaptic function [141], may play a critical role in this interaction. These considerations suggest the possibility that Cbl a drug available for clinical with active neuropeptides fragments that mimics the action of endogenous

neurotrophic factors such as BDNF, GDNF, CNTF and NGF and others [100] [101], may help in the treatment of the schizophrenia.

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Conflict of Interest

All authors have no conflicts of interest.

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Abbreviations

BDNF: Brain-Derived Neurotrophic Factor
BLA: Basolateral Amígdala
Cbl: Cerebrolysin
DA: Dopamine
EEG: Electroencephalography
Hc: Hippocampus
MRI: Magnetic Resonance Imaging
MBP: Myelin Basic Protein
NVHL: Neonatal Ventral Hippocampus Lesion
NAcc: Nucleus Accumbens
NGF: Neural Grow Factor
PD: Postnatal Day
PFC: Prefrontal Cortex
PSA-NCAM: Polisyalic Acid Neural Cell Adhesion Molecule
VTA: Ventral Tegmental Area