Altered Microtubule Associated Proteins in Schizophrenia

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Abstract
In schizophrenia, altered cognitive and affective functions as well as reduced dendritic spine density and diminished synaptic connectivity have been described. The cytoskeleton plays a key role in maintaining axon and dendrite structure as well as the synaptic connections. In this review we will describe evidence supporting that schizophrenia is a cytoskeletal disease. In addition, we will describe current data indicating that microtubule associated proteins are implicated in the abnormal dendrite structure and the lost of synaptic connectivity. Evidence presented here indicates that the cytoskeleton could be a target for drug therapy in schizophrenia.

Key Words: schizophrenia, cytoskeletal disease, microtubule-associated proteins.

In schizophrenia, altered cognitive and affective functions as well as reduced dendritic spine density and diminished synaptic connectivity have been described to occur in the prefrontal cortex and in the limbic system. A brain structure, that plays a key role in affective and cognitive physiology (Garey et al., 1998; Dwork et al., 2005). The cytoskeleton participates in neural morphology and in the highly structural polarization of axons and dendrites. Also, it has been shown that...
dynamic cytoskeletal organization is involved in synaptic connectivity (for review see: Benitez-King et al., 2004). Therefore, pathologic lesions implicating a lost of neuron structural polarization and synaptic connectivity also implicate an abnormal cytoskeletal organization that may have an important role in the aberrant behavior observed in schizophrenia (Garey et al., 1998; Dwork et al., 2005). In particular, microtubules play a key role in the neuronal structural polarization. They are the main cytoskeletal components in the axons, while in dendrites strongly interact with microfilaments. In addition, microtubules are an important part of the structural framework of synaptic connections, which in turn are the functional units where incoming and output signals are transmitted in the brain (For a review see Benitez-King et al, 2004). Scarcie studies indicate that microtubules are absent in dendrites of anterior limbic cortex system of schizophrenic patients (Uranova and Aganova, 1989). However, recent emerging evidence supports the notion that aberrant cytoskeletal organization that underlies the pathologic lesions of schizophrenia may in part due to altered microtubule-associated proteins (MAPs). Among these, DISC-I, STOP and MAP2 are altered in the brain of schizophrenic patients. In general, these proteins bind to microtubules and acts as microtubule stabilizers prompting tubulin polymerization. Disrupted in Schizophrenia 1 (DISC1) has been associated to an aberrant neurodevelopment in schizophrenia. It is a novel gene identified at the breakpoint of chromosomal translocation which was found segregated with schizophrenia in a Scottish family. This protein contributes to a normal microtubule dynamics. It is a component of the microtubule-associated dynein motor complex and essential for maintaining the complex at the centrosome (Miyoshi et al, 2003; Morris et al., 2003; Kamiya et al., 2005). Either, its depletion, or mutated expression in cultured cells impairs neurite outgrowth and a dysfunction in the cerebral cortex development occurs (Kamiya et al., 2005). Another microtubule associated proteins are the stable tubule-only polypeptide proteins (STOP). These proteins are calmodulin-regulated that upon their binding to microtubules confers resistance to these structures maintained in cold conditions. (Bosc et al., 2003) Recently, STOP suppression in mice has been found to induce synaptic defects associated with behavioral disorders similar to those present in schizophrenia. Thus, STOPs are important for synaptic plasticity and apparently are responsible for the aberrant behavior present in STOP null mice, which are alleviated by antipsychotic treatment (Eastwood, et al., 2006). Additionally, a decrease in MAP2 expression in laminae III and V in prefrontal cortex, and decreased expression of MAP2 and MAP1B has been reported to occur in subiculum and entorhineal cortex of hippocampal
formation of schizophrenic patients (Arnold et al, 1991). These MAP proteins contribute to the establishment and maintenance of neuronal polarity, and therefore could underlie some of the cytoarchitectural abnormalities described in schizophrenia and impair signal transduction in the affected dendrites (Arnold et al., 1991).

Additional evidence supporting the notion that schizophrenia is a mental disorder associated with cytoskeletal abnormalities has been obtained by measuring levels of certain cytoskeletal proteins and their phosphorylation degree in specific brain areas. In this regard, increased non-phosphorylated MAP2 in the left-sided subiculum and CA1 hippocampal region has been detected in schizophrenic patients, suggesting that a phosphorylation imbalance of cytoskeletal proteins is involved in the cytoskeletal disorganization observed in schizophrenia (Cotter et al., 1997).

The possibility that schizophrenia could be a cytoskeletal disorder is also supported by the fact that hallucinogens are cytoskeletal disruptors and in humans, drugs such as lysergic acid diethylamide (LSD) and phenylethylamine produce hallucinations and detachment from reality (Van Woerkom, 1990). While antipsychotics, alleviate psychotic symptoms, and at starting therapeutic dosages elicits neurite outgrowth. Video 1 shows dynamic neurite reorganization caused by 1 µM clozapine in N1E-115 neuroblastoma cells. N1E-115 cells were cultured in control conditions followed by the addition of clozapine an atypical antipsychotic, to visualize the morphological changes. In control conditions, neuroblastoma cells are bipolar and show a basal neurite formation (Pink video frames). After clozapine addition (Cyan video frames), cells shown dynamic neurite extension and the neurites are thinner and longer than in control conditions suggesting that the antipsychotic induces the cytoskeleton reorganization. Moreover, antipsychotics cause neurocytoskeletal protection to the damage induced by oxidative stress (Benítez-King et al., 2004) and microtubule enlargement in vitro and in cultured cells (Huerto-Delgadillo et al., 1994; Benítez-King et al., 2004). Together, these studies strongly suggest that antipsychotic symptoms are associated with microtubule disruption, while alleviation can be associated with microtubule reorganization a necessary step for synaptic connectivity reestablishment.

In conclusion, cytoskeletal disorganization found in brain regions of schizophrenic patients, together with the fact that hallucinogens disorganize the cytoskeletal structure, while antipsychotic restore it, support the idea that schizophrenia is a cytoskeletal disease, and the concept that the cytoskeleton is a therapeutic target in the treatment of schizophrenic patients.

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References


Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J Neurol Neurosurg Psychiatry 1998;65:446-453.


