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RECENT CYTOARCHITECHTONIC CHANGES IN THE PREFRONTAL CORTEX OF SCHIZOPHRENICS

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1. ABSTRACT

A variety of lines of converging evidence implicate the prefrontal cortex (PFC) in schizophrenia. In the past studies have focused on the various neurotransmitter systems that appear to be involved in schizophrenia such as dopamine, glutamate and serotonin. Recently, the focus of research has shifted away from systems and towards cellular morphology due partly to studies suggesting an increase in neural density in various regions of the PFC (1,2). A plethora of research has come out suggesting possible cytoarchitectural changes in pyramidal cells in the prefrontal cortex as well as alterations of certain GABAergic cells. This review examines the recent data that shows cytoarchitechtonic changes in cells of the prefrontal cortex.

2. INTRODUCTION

Schizophrenia is one of the most disabling of neuropsychiatric disorders whose pathogenic mechanisms are complex and poorly understood. Much evidence suggests that a combination of multigenic factors and early developmental insults could lead to a variety of brain abnormalities involving both cortical and subcortical structures. Mounting evidence appears to implicate the prefrontal cortex in schizophrenia (1, 2, 3 and for review see 4, 5). The prefrontal cortex is an important region involved in higher cognitive function, working memory, mental imagery, willed action and active memory (6). The prefrontal cortex has many outgoing projections primarily feeding-back onto the thalamus and subcortical dopamine neurons (7). The two projection layers in neocortex are V and III. Layer V is important in that these cells are the main projection cells from the cortex to other subcortical and cortical areas. Layer III is important because it projects to homologous regions on the contralateral hemisphere and to different cortical regions on the ipsilateral hemisphere.

Animal studies have shown that changes in functioning of the PFC can alter the firing of dopamine neurons (7, 8). A study of schizophrenics examining the integrity of the PFC and its effects on striatal dopamine release suggest that the greater the pathology in the cortex the less steady state dopamine activity is seen (3). This is similar to data in monkeys with lesions in their meseotemperal cortex (8). The monkeys showed pathology in the PFC and alterations in striatal dopamine activity (8). Other animal studies where the lesions were in the MD nucleus of the thalamus showed behavioral alterations similar to those exhibited by schizophrenics (9, 10, 11, 12). The behavioral changes observed are controlled by the PFC, which is implicated in schizophrenia as seen in the stereotypic behaviors.

Researchers in the past have used a variety of techniques to unlock the mysteries of schizophrenia. However, the etiology of the disease still escapes understanding. Many studies have examined either neurotransmitter systems or synaptic proteins to look for abnormalities in schizophrenic brains (13, 14, 15, 16, 17, 18). This is in part due to the drug treatments for schizophrenics and the systems they affect as well as the above-mentioned animal studies. However, very few studies have examined the morphology of the cells in the prefrontal cortex. Recently there has been a shift from examining neurotransmitter systems to examining cellular architecture in the regions affected in schizophrenics. Several studies have sparked the change in focus from systems to cellular morphology. Two such studies have shown an increase in neural density in the prefrontal cortex and hypothesized that the increase in neuron density was due to a loss of neuropil volume (1, 2). Researchers have begun to test this hypothesis by examining the major components of neuropil such as dendrites, axons and cell bodies. This review will focus on studies showing

cytoarchitectural abnormalities in the prefrontal cortex and what those changes may mean for information processing both locally and at a distance.

3. CYTOARCHITECTURAL ALTERATIONS IN THE PREFRONTAL CORTEX

Two studies have shown an increase in neuron density in the prefrontal cortex. Selemon *et al.* (2) have shown that in area 9 there is an increase in neuron density in layers III-VI and Benes *et al.* (1) have shown a similar increase in area 10 of the prefrontal cortex. As mentioned before both of these studies have hypothesized that the change in neuron density is due to a loss or atrophy of neuropil volume. These two studies sparked researchers into asking the question of whether there are subtle differences in cytoarchitecture of cells in the PFC. To begin to offer evidence to support the above hypothesis researches have begun to examine cellular structures such as basilar dendrite number, cell size and spine density.

Studies examining cell size have shown a decrease in soma size in area 9 of the prefrontal cortex. Rajkowska *et al.* (19) have shown a decrease in soma size in the various layers in area 9 where as Pierri *et al.* (20) being more specific, examined pyramidal neurons in layer III of area 9. Pierri *et al.* (20) found a decrease in soma size of pyramidal cells in deep layer III. The implications of these findings are twofold. First soma size is directly correlative to the number of dendrites put out and maintained by the cell (21, 22). Suggesting therefore, that there may be a concomitant decrease in the number of dendrites on the pyramidal cells in layer III as well as on cells in the other layers of the prefrontal cortex. Secondly, layer III is one of two projection layers from the cortex, layer V being the other projection layer. Layer III projects to homologous regions of the contralateral hemisphere and within the ipsilateral hemisphere (23). In addition, layer III receives a heavy inhibitory input from GABAergic cells. A decrease in soma size would decrease the synaptic surface area for GABAergic cells and suggest a loss therefore of GABAergic input and possible inhibitory control over these pyramidal cells. Recent evidence suggests a decrease in MAP2 immunoreactivity in layers III and V of areas 9 and 32 of the prefrontal cortex (24). MAP2 is a protein found in cell bodies and dendrites and is important for microtubule stabilization (25, 26, 27, 28, 29). Alterations in MAP2 can be an indicator of changes in dendritic integrity (30). These data therefore, suggest a possible alteration in dendritic material in these layers of areas 9 and 32, which would also correlate with a decrease in soma size. Studies from our lab show a decrease in primary and secondary basilar dendrites on pyramidal cells in both layers III and V of area 32 (31). A study by Kalus et al. (32) found no alterations of the apical dendrites of pyramidal cells but also found that the basilar dendritic systems were reduced in schizophrenics. In addition, preliminary evidence from our laboratory shows a decrease in primary and secondary basilar dendrites on pyramidal cells in both layers III and V in area 9 of the prefrontal cortex.

A loss of pyramidal cell dendrites would decrease the surface area for synaptic contact and therefore, may change information processing in layers III and V of the affected cortical regions. Concurrently, a loss of dendrites would also suggest a change in spine density and number in these same regions as well. One study has shown a decrease in spine density in the prefrontal cortex (33). Unfortunately, the study did not examine a specific region or layer for change in spine density. However, a second study saw a decrease in spine density in pyramidal cells in layer III of area 46 of the PFC (34). Spines are the synaptic points for GABA erigc as well as glutametergic and dopaminergic incoming information (35). Therefore, in addition to the loss of synaptic surface for GABAergic cells a loss of spines would also decrease the synaptic contact for glutametergic as well as dopaminergic input into these cortical regions. These data taken together suggest that the change in neuronal density appears to be due in part to a decrease in neuropil through a decrease in number of dendrites, spines and soma size which in turn suggests a possible change in information processing through a decrease of synaptic surface area. Pyramidal cells make up only one part of the picture in the cortex. The decrease in soma size suggests not only a loss of dendrites, but also, a possible loss of GABAergic input because GABAergic cells synapse onto the soma as well as dendrites.

4. EVIDENCE OF LOCAL CIRCUITRY ALTERATIONS IN SCHIZOPHRENIA

A second focus of study in the PFC is aimed at examining GABAergic cells or interneurons. These studies are important for two reasons. First the processes of interneurons contribute to the volume of neuropil in the various layers and may be part of the increase in neuron density. Second, interneurons play a crucial role in local control of input and output of information in the cortex. Changes in number of GABAergic cells or synaptic contact would affect outgoing information by either increasing inhibition of the pyramidal cells or by decreasing inhibition.

There are many different types of GABA cells and they are characterized by the different calcium binding proteins they co-localize as well as upon their location and morphology (36, 37, 38). For example one GABA cell type, chandelier cells, co-localize parvalbumin, one of three calcium binding proteins, and are found predominately in the deeper cortical layers (36, 38) where as other cells co-localize calbindin, a second calcium binding protein, and are found in the more superficial cortical layers (36, 38). Several studies have begun to examine GABAergic cell populations based on their calcium binding proteins to determine if GABAergic cell populations are affected differentially. The results of these studies have shown varying and sometimes conflicting results. Two studies have shown a deficit in parvalbumin positive cells in the prefrontal cortex (39, 40) while two other studies showed no difference in the number of parvalbumin positive cells in the PFC (41, 42). Finally, a third study has shown an increase in parvalbumin positive cells in the anterior cingulate cortex (43). This apparent conflict in data between the PFC and anterior cingulate cortex may be explained in that schizophrenia may affect the various

cortical regions differentially. Interestingly the study by Lewis (42) that found no difference in parvalbumin cell number saw a deficit in GAT-1 immunoreactive axonal cartridges in the prefrontal cortex. GAT-1 is GABA membrane transporter found predominately on chandelier cells (44, 45). A similar study by Woo *et al.* (46) also found a decrease in GAT-1 immunoreactive cartridges in areas 9 and 46 of the prefrontal cortex. Similarly, Pierri *et al.* (47) found a decrease in GAT-1 cartridges in layers II-IV with the most prominent decrease seen in layers IIIb-IV. Interestingly, an increase in the same axonal cartridges was found in the anterior cingulate cortex (48). A loss of axonal cartridges may have direct implications on outgoing information and information processing within the cortical region. Again this difference in data may be reflective of differential effects of the disease on different cortical regions. Axonal cartridges synapse directly on the initial axon segment of pyramidal cells (49). This allows the GABAergic cells to have a powerful inhibitory influence over the pyramidal cells and therefore outgoing information (49, 50). A loss of this inhibition or a decrease in this inhibition could cause aberrant information processing. Researchers have begun to examine two other calcium binding proteins, calbindin and calretinin. A study by Daviss and Lewis (51) found an increase in density of calbindin positive cells in the prefrontal cortex but no study to date has found a change in calretinin positive cells in the prefrontal cortex (39, 51).

5. WHAT DOES THIS ALL MEAN

During central nervous system development the thalamic afferents arrive at the developing cortex and enter the subplate (52, 53, 54, 55). The afferents reach the developing cortex prior to the birth of their target cell layer (subplate (52, 53, 54, 55). For most cortical areas layer IV is the primary target for thalamic afferents, however, in association cortices such as areas 9, 46 and 32 layer IV is very small and the thalamic afferents may synapse also on layer V and II/III (53). In general, the layer IV cells also synapse on layers V and II/III (53, 56, 57). Research suggests that the thalamic afferents aid in the development of the cortex, and more specifically in the process of dendritic pruning. In the cortex, pruning of dendrites is activity-dependent (21, 22, 58, 59). During development neurons adapt their neuritic field to maintain a particular level of bioelectric activity (21, 22, 58, 59). Changes in the perceived activity of a cell will, therefore, be reflected in the number and length of dendritic branches. The size of a cell's neuritic field is dependent upon its own level of electrical activity, which is in-turn is dependent upon Ca^{2+} influx (59, 60). Thus, if a cell's activity is higher than it should be, neurons will retract processes, if it is lower, a cell will decrease or stop its neurite outgrowth (21). A proper balance of excitation and inhibition is needed for proper development of neurite fields of pyramidal cells. Once the level of bioelectric activity is set, changes in activity around the cell are not likely to alter the neurites further (59). In addition to activity–dependent development of morphology there is a function–dependent regulation of cellular development (22, 61). For example, GABAergic phenotypes become fully expressed only if the ongoing level of excitatory activity during development is sufficient (22, 61). A perceivable decrease in excitatory input from the thalamus, therefore, may have adverse affects on the GABAergic cells in the cortex. Because GABAergic cells synapse on the pyramidal cells (53) and are important regulators of pyramidal cell activity (21, 22) changes in GABAergic activity may also affect the pyramidal cells in layers V and II/III. Several studies have shown changes in $GABA_A$ binding (62) and GABA terminals (46) in the anterior cingulate and prefrontal cortices respectively in schizophrenics as compared to controls. One can see that if there is a decrease in the thalamic innervation of the cortex, this could result in a decrease in MAP2, number of dendrites and length of dendrites as well as soma size and number of dendritic spines. In addition, the change in thalamic input could also have adverse affects on the GABAergic cell population. Research shows that the thalamus and the cortex are so intimately linked together that their linked neurons oscillate at the same level, of 40MHz (63). A loss of this binding due to a loss of neurons in the thalamus and connections in the cortex due to a decrease in synapses and dendritic arborization may also lead to the cognitive changes seen in schizophrenia.

The findings discussed in this review suggest a problem in information processing in the PFC. Parvalbumin, a calcium binding protein found in chandelier cells, appears to be a neuroprotectant (64) and is expressed late in cortical development (40). Due to its late expression a neurotoxic event prior to the expression of parvalbumin may leave these cells vulnerable, causing them either to dye or withdraw processes. While the data is mixed as to whether or not there is a loss of parvalbumin cells all of the data does suggest a loss of synapses of chandelier cells onto pyramidal cells. A loss of inhibitory synapses during development may leave the surrounding pyramidal cells at risk to incoming excitatory information causing the cells to perceive the excitatory information as excessive and therefore retract their processes. Alternatively a loss of thalamic input during development via a loss of activity could cause the changes observed in the pyramidal cells, the decrease in soma size, decrease in MAP2, the loss of basilar dendrites both primary and secondary and the loss of spines due to unbalanced excitatory/inhibitory information. Several studies have shown that there is cell loss in the medial dorsal nucleus of the thalamus. The medial dorsal nucleus projects to the prefrontal cortex. The observed changes in GABAergic cells, such as the loss of axonal cartridges and the decrease in GABA cells may therefore, be a secondary response to altered afferent inputs. Many questions remain unanswered such as, does the cell loss in the medial dorsal nucleus of the thalamus correlate to a loss of thalamic input to the prefrontal cortex and could this loss be great enough to cause the observed changes in the pyramidal cells and alternatively the GABAergic cells. The reverse of the above question also needs to be examined, are the GABAergic cells being affected during development and conversely altering the development of the pyramidal cells. To begin to explain the etiology of schizophrenia it is therefore, not only important to continue to examine the morphology of the various cell populations in PFC cortical

areas implicated in schizophrenia, and to begin to understand how these alterations affect cortical processing.

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