Understanding the pathology of schizophrenia: recent advances from the study of the molecular architecture of postmortem CNS tissue

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The use of central nervous system (CNS) tissue obtained postmortem has long underpinned efforts to understand the neurobiology of schizophrenia, but the ability to use such tissue in conjunction with a wide variety of methodologies has seen a renaissance of interest in this area of research. Recent findings have shown changes in markers in a number of neurotransmitter systems in the brains of subjects with schizophrenia which include the dopaminergic, serotonergic, cholinergic, glutamatergic, and GABAergic systems of the CNS. Many of these changes also appear to be regionally specific, and abnormalities in non-neurotransmitter specific pathways have been found in schizophrenia. Changes in the neurotransmitter release pathways in schizophrenia may be important in the pathology of the illness, and recent findings suggest that abnormalities in the Wnt pathway, which controls transcription selectivity in cells, may be involved. Studies using CNS material obtained postmortem clearly show that the pathology of schizophrenia is complex while the polygenetic nature of the illness may be adding to this complexity.

Research on tissue obtained postmortem has been an important component of efforts to understand the pathology of schizophrenia. With the realisation that such tissue can be used in conjunction with a wide variety of technologies and probes there has been a renaissance in the use of such tissue to understand the changes in the molecular architecture in the central nervous system (CNS) that underlie schizophrenia. It is therefore timely to review the progress made in identifying proteins and pathways that may be involved in the pathology of schizophrenia.

NEUROTRANSMITTER RECEPTOR AND TRANSPORTERS IN SCHIZOPHRENIA

A major component of the studies using postmortem CNS tissue have been directed towards understanding the role of neurotransmitter receptors and transporters in the pathology of schizophrenia. This is because these sites are amenable to manipulation by therapeutic agents and, in many cases, are the sites of action of drugs with proved antipsychotic activity. Moreover, it is mainly neuropharmacological observations using drugs that target neurotransmitter receptors and transporters that have underpinned the formulation of hypotheses on the pathology of schizophrenia. These hypotheses have implicated the dopaminergic, serotonergic, cholinergic, glutamatergic, or gamma aminobutyric acid (GABA)ergic systems in the pathology of schizophrenia.

Studies on the dopaminergic systems

The findings that antipsychotic drugs are dopamine D2 receptor antagonists and that dopamine receptor agonists can cause or exacerbate psychoses has underpinned the long-standing dopamine hypothesis of schizophrenia. This hypothesis proposes that overactive dopaminergic pathways in the CNS are central to the pathology of the illness. Recent work on dopaminergic systems, using postmortem tissue, has mainly focused on levels of mRNA for the different dopamine receptors in the cortex of subjects with schizophrenia. Thus, one study reported an increase in mRNA for the dopamine D2 longer receptor in the frontal cortex of subjects with schizophrenia. This finding, along with the report of an increase in mRNA for the dopamine D2 receptor in the cortex but not caudate from subjects with schizophrenia, would suggest that there may be abnormalities in the expression of cortical dopamine receptors associated with the illness. Unfortunately, the lack of specific radioligands for the dopamine D2 and D3 receptors means that it is not possible to determine if these changes in levels of expression have resulted in changes in receptor protein in the cortex from subjects with schizophrenia. This is important as there appears to be no change in the density of global dopamine D2-like or dopamine D3-like receptors in the frontal cortex from subjects with schizophrenia.

Studies on the serotonergic systems

There has been an increasing acceptance that antipsychotic drugs that bind to both the dopamine D2-like receptor family and the serotonin (5HT)2A receptor have improved clinical
outcomes. This has meant that increasing attention has been paid to the status of serotonergic markers in postmortem tissue from subjects with schizophrenia. There are now a number of reports of a decreased density of cortical 5HT₄ receptors in schizophrenia (for review see Dean), a change that is not part of a generalised change in serotonergic markers in the frontal cortex of subjects with schizophrenia. Increasingly, evidence suggests that the decrease in cortical 5HT₄ receptors in schizophrenia is related, at least in part, to the pathology of the illness rather than an effect of drug treatment during life. This evidence includes the fact that changes in 5HT₄ receptors in cortex from humans and rats treated with the same antipsychotic drugs do not marry, that levels of mRNA for the 5HT₄ receptors are only decreased in the prefrontal cortex from subjects not treated with antipsychotic drugs for six months before death and that cortical 5HT₄ receptors are not altered in subjects with bipolar disorder receiving antipsychotic drugs up to death. However, concluding that all changes in 5HT₄ receptors in postmortem tissue from subjects with schizophrenia are related to the pathology of the illness needs to be tempered by the observation that, in the planum temporale, complex changes in density of 5HT₄ receptors appear to have arisen because of both pathological and antipsychotic drug effects.

It would be predicted that if the 5HT₄ receptor was central to the pathology of schizophrenia there would be an association between a specific mutation in the gene for the 5HT₄ receptor and the illness. Using DNA from peripheral tissue, a number of studies have suggested that mutations in the gene for the 5HT₄ receptor are associated with schizophrenia. By contrast, studies using tissue obtained post mortem have failed to show an association between specific mutations in the gene for the 5HT₄ receptor with either schizophrenia or the density of the receptor in the cortex. Therefore, data from postmortem tissue do not favour the argument that mutations in the 5HT₄ receptor are either associated with schizophrenia or modulate the levels of the receptor in human cortex. Hence further efforts are required to identify the mechanism that has reduced the density of cortical 5HT₄ receptors in schizophrenia.

Studies on the cholinergic systems

A growing understanding that aberrations in CNS functions that are modulated by the cholinergic system could cause some of the symptoms of schizophrenia has led to the suggestion that changes in this system must be involved the pathology of the illness. In particular, recent studies have focused on the receptors through which acetylcholine can exert its effects in the CNS, which are divided into two broad families, the nicotinic receptors and the muscarinic receptors. The nicotinic receptors can be delineated by their ability to bind nicotine and muscarine respectively and have differing modes of action; the nicotinic receptors are gated ion channels and the muscarinic receptors are G-protein linked.

Confounding issues affecting the study of nicotinic receptors in postmortem tissue are that the inhalation of nicotine increases levels of the nicotinic receptors and there is an increased level of nicotine self administration in schizophrenia. However, decreased levels of nicotinic receptors have been reported in patients with schizophrenia, which would therefore seem to be an effect independent of nicotine self administration. In another study of the caudate a decrease in nicotinic receptors was reported in schizophrenia despite increased levels of the receptors being present in tissue from control subjects who had a history of smoking. One study has reported levels of nicotinic receptors in the striatum from a group of elderly schizophrenic subjects who had received long term treatment with antipsychotic drugs to be above levels in tissue from the control group as whole, and members of that group who had a history of smoking. The data from this study could indicate that either long term antipsychotic drug treatment up-regulates the levels of nicotine receptors, or that there could be an effect of increased smoking in subjects with schizophrenia. The absence of an increase in nicotinic receptors in tissue from rats treated for six weeks with the antipsychotic drug haloperidol would argue against such treatments increasing the same receptors in human tissue. In summary, while the weight of current data support the argument that there is a decrease in nicotinic receptors in the CNS of subjects with schizophrenia, the pathological significance of the finding needs to be elucidated. However, this finding would add credence to the suggestion that subjects with schizophrenia may self medicate with nicotine to alleviate symptoms caused by abnormalities in nicotinic related pathways associated with the illness.

One of the major impediments to studying the muscarinic receptors in the human CNS has been the lack of receptor specific radioligands. However, with the use of selective radioligands and displacing agents it is now possible to study the density of combinations of muscarinic receptors in the postmortem CNS tissue. Using this approach, a decrease in muscarinic M₄ (M₄) receptors have been reported in the caudate putamen and hippocampus from subjects with schizophrenia. The change in M₄ receptors in the caudate was not accompanied by a change in mRNA encoding the M₄ receptor in tissue from the same donors. This could indicate either the decrease in radioligand binding was due to a change in the density of only the M₄ receptor or that the decrease in receptor protein was not accompanied by a change in levels mRNA for that receptor.

Using a similar approach, a decrease of M₃ receptors has also been reported in the caudate-putamen in schizophrenia. Significantly, mRNA for the M₃ receptor was either absent, or present at very low levels, in the caudate-putamen from the individuals used in the M₄ radioligand study. One conclusion that can be drawn from these data is that there are no M₃ receptors in the human caudate-putamen and hence the decrease in radioligand binding was solely due to a decrease in M₃ receptors. This proposal would be in line with one possible outcome from the study of M₃ receptor binding in the caudate-putamen. Alternatively, the M₃ receptors could be present on innervating neurons (hence the absence of mRNA as the cell bodies containing the mRNA would not be present in the caudate-putamen). If this proves to be the case, then this would be evidence to support the argument that M₃ receptors act as autoreceptors in the caudate-putamen and that either M₃ or M₄ receptors could be decreased in the caudate-putamen from subjects with schizophrenia.

Studies on the glutamatergic systems

The ability of phencyclidine, a glutamate receptor ion channel blocker, to induce or exacerbate a schizophrenic-like psychosis, has been central to the hypotheses that changed glutamatergic function is involved in the pathology of schizophrenia. This has led to an extensive investigation of glutamatergic markers in postmortem CNS tissue from subjects with schizophrenia. There are two major families of glutamate receptors. One family is a group of ionotropic glutamate receptors made up of the N-methyl-D-aspartate (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and the kainate receptors. All these receptors are made up of a combination of specific subunits, which assemble in the membrane to form cation conductance channels. The other family of receptors are known as the metabotropic receptors and are G-protein coupled receptors.

Due to the absence of radioligands for the metabotropic glutamate receptors, studies have thus far focused on levels of mRNA encoding for the eight different metabotropic glutamate receptors (mGluR 1–8). One study has reported no...
change in the levels of mRNA encoding any of the eight metabotropic glutamate receptors in the thalamus from subjects with schizophrenia. In the study that reported no major changes in AMPA or kainate receptors in the hippocampus from subjects with schizophrenia, 31 the NMDA receptor contains a number of functional binding domains and it has been suggested that one of these domains, the glycine binding site, is decreased in the thalamus from subjects with schizophrenia without a change in the overall density of the NMDA receptor in that region. 32 Adding to the argument that the glycine binding site on the NMDA receptor may be altered in schizophrenia, another study has reported no change in levels of mRNA encoding the NR2B subunit of the NMDA receptor in Brodmann’s areas 9 and 10 but did show a decrease in mRNA for the mGlur5, but not mGlur3, in Brodmann’s area 11 from subjects with schizophrenia. 33 These early findings suggest that there may be regionally discrete differences in levels of metabotropic receptors in the CNS of subjects with schizophrenia.

As phencyclidine blocks the ion channel of the NMDA receptor it is significant that this receptor has been reported as decreased in the cornu Ammonis (CA) 3 region of the hippocampus in subjects with schizophrenia. 19 However, this finding was not replicated in a study which also failed to show any major changes in AMPA or kainate receptors in the hippocampus from subjects with schizophrenia. 20 The NMDA receptor contains a number of functional binding domains and it has been suggested that one of these domains, the glycine binding site, is decreased in the thalamus from subjects with schizophrenia without a change in the overall density of the NMDA receptor in that region. 21 Adding to the argument that the glycine binding site on the NMDA receptor may be altered in schizophrenia, another study has reported no change in levels of mRNA encoding the NR2B subunit of the NMDA receptor in Brodmann’s areas 9 and 10 but did show a decrease in mRNA for the mGlur5, but not mGlur3, in Brodmann’s area 11 from subjects with schizophrenia. 22 These early findings suggest that there may be regionally discrete differences in levels of metabotropic receptors in the CNS of subjects with schizophrenia.

In addition, mRNA for the NR2B subunit was lower in the central medial nucleus and mRNA for the NR2C subunit was lower in the anterior, dorsomedial, lateral medial, and central medial nuclei. This study also reported lower levels of mRNA for the NR1 subunit in the dorsomedial nucleus with lower levels of glutamate receptors in the hippocampus from subjects with schizophrenia. 28 Levels of mRNA for the NR1 subunit of the NMDA receptor were found to be decreased in the dentate gyrus from subjects with schizophrenia and tended to be lower (−25%) in the CA3 region. By contrast, mRNA for the NR2B subunit of the NMDA receptor was higher in the CA2 region from the schizophrenic subjects. Studies in the thalamus have also reported lower levels of mRNA for the NR1 subunit of the NMDA receptor in the dorsomedial and central medial nuclei. 29 In addition, mRNA for the NR2B subunit was lower in the central medial nucleus and mRNA for the NR2C subunit was lower in the anterior, dorsomedial, lateral medial, and central medial nuclei. This study also reported lower levels of mRNA for the glutamate receptor in the dorsomedial nucleus with lower levels of glutamate receptors being detected in central medial nuclei of subjects with schizophrenia. Finally, mRNA from the KA2 subunit of the kainate receptor was decreased in anterior, dorsomedial, lateral dorsal, central medial, and ventral nuclei of the thalamus from subjects with schizophrenia.

In contrast to studies in the thalamus and hippocampus, it has been reported that neither AMPA nor kainate receptor binding nor levels of mRNA for AMPA receptor subunits are altered in the frontal cortex of subjects with schizophrenia. 30 However, levels of mRNA for the NR1, glutR1, glutR7, and KA1 subunits of glutamate receptors have been reported as being decreased in the cortex of schizophrenic subjects not receiving antipsychotic drugs within six months of death. 31 Significantly, in this study decreased levels of mRNA for subunits of the glutamate receptors were not observed in subjects who were receiving antipsychotic drugs up until death.

In conclusion, current data on ionotropic receptors would suggest that there are regionally specific changes in receptor subunit expression in subjects with schizophrenia. However, one confounding issue is data from one study that suggest that levels of mRNA encoding subunits of the ionotropic glutamate receptors may be affected by antipsychotic drug treatment. 31 Moreover, changes in levels of mRNA encoding subunit of the ionotropic receptor is not necessarily accompanied with changes in radioligand binding to those receptors. This raises the possibility that the changes in rates of expression of receptor subunits do not affect the density of fully assembled, functional receptors and therefore may be of minimal or no physiological consequence. Further studies will need to be completed to attempt to address this hypothesis.

**Studies on the GABAergic systems**

Several lines of evidence implicated the GABAergic system in the pathology of schizophrenia, not the least of which are reports showing changes in the GABA receptor in various regions of the CNS from subjects with schizophrenia. The GABAA receptor belongs to the ligand-gated ion channel receptors that are made up of multiple subunits. The study of mRNA encoding the different subunits has now extended original findings on radioligand binding to show an increase in levels of mRNA encoding the α-1 subunit of the GABAA receptor in Brodmann’s areas 9 and 10 from subjects with schizophrenia. 32 This study also reported a decrease in the concentration of GABA and an increase in the levels of mRNA encoding the GABA transporter-1. These two findings raise the possibility that an increase in the GABA transporter could be resulting in changes in levels of extracellular GABA and a subsequent change in GABA receptor expression. Against this argument is the finding that the absolute levels of mRNA for the GABA transporter-1 was not altered in Brodmann’s areas 9 and 10 from subjects with schizophrenia. 33 However, this study did find a decrease in the number of neurons containing the GABA transporter-1 in layers 1 through 5 in the tissue from the subjects with schizophrenia. The consequence of a loss of GABA transporter-1 containing neurons has yet to be elucidated.

Further data to support the argument that there are changes in expression of GABA receptor subunit in schizophrenic subjects with schizophrenia are the finding that there is a marked decrease in levels of mRNA encoding for the short form of the glutamate receptor in the prefrontal cortex from subjects with schizophrenia. 34 This decrease was not accompanied by a change in mRNA encoding the long form of that receptor subunit. These data seem to add weight to the argument that altered GABA receptor subunit expression and assembly may be important in the pathology of schizophrenia.

**Studies on the cannabinoid systems**

The argument that subjects may self medicate with various compounds may be relevant to findings from a study of cannabis, receptors in postmortem tissue from subjects with schizophrenia. 35 This study reported that cannabis receptors were increased in the frontal cortex of subjects with schizophrenia, whether or not the subjects had used cannabis close to death. By contrast, cannabis receptors were increased in the caudate putamen from subjects who had used cannabis close to death, whether or not they had schizophrenia. These findings could be interpreted as preliminary data to suggest that cannabis use associated with schizophrenia may represent a form of self medication. However, a much more extensive study of the cannabinoid system in the CNS of subjects with schizophrenia is required before significant weight can be given to such an argument.

**EVIDENCE FOR CHANGED NON-NEUROTRANSMITTER SPECIFIC PATHWAYS IN THE PATHOLOGY OF SCHIZOPHRENIA**

A review of the findings relating to neurotransmitter receptors and transporters in postmortem CNS tissue from subjects with schizophrenia clearly shows that multiple pathways in multiple regions of the CNS are affected by the illness (table
Box 1: Findings on neurotransmitter systems in schizophrenia

- Postmortem studies suggest there is severe disruption to a number of neurotransmitter systems in the CNS of subjects with schizophrenia including the dopaminergic, serotonergic, cholinergic, glutamatergic, and GABAergic systems.
- Changes in neurotransmitter systems appear to be regionally specific with the frontal cortex, hippocampus, and thalamus being particularly affected.
- Changes identified in receptors that bind nicotine and the reactive component of cannabis may add weight to the argument that subjects with schizophrenia may attempt to “self medicate” using these compounds.

1). One explanation for such extensive and apparently diverse changes could be that proteins generically involved in all neurotransmitter systems may be altered in schizophrenia. One such group of proteins are those critical to neurotransmitter release and include synaptosomal associated protein-25 (SNAP-25), synaptobrevin, synaptotagmin, syntaxin, synapsin, and synaptophysin. Specific interactions between these and other proteins ensure the fusion of synaptic vesicles with the synaptic membrane and subsequent release of neurotransmitter. Synaptophysin has now been the focus of a number of studies in schizophrenia. A decrease in the levels of mRNA has been reported in CA4 and CA3 of the hippocampus and layers III and V/VI of the entorhinal cortex, however this change was also present in tissue from a group of subjects with mixed psychiatric illnesses other than schizophrenia. By contrast, it has been reported that levels of mRNA for synaptophysin are not altered in the prefrontal cortex from subjects with schizophrenia. These two studies raise the possibilities that changes in synaptophysin may be regionally, but not disease, specific.

The findings regarding the mRNA encoding for synaptophysin appear to contrast with studies of synaptophysin protein which, for example, show an increase in synaptophysin immunoreactivity in the granule cell layer of the dentate gyrus. However, another study has shown a decrease in synaptophysin protein in the gyrus cinguli and hippocampus, but not the thalamus, of subjects with schizophrenia. The same group have also reported that synaptophysin levels are decreased in the thalamus from the left, but not right, hemisphere, raising the possibility of lateralised changes in the protein in schizophrenia. In the frontal cortex, a significant decrease in synaptophysin levels in schizophrenic subjects dying of natural causes has been reported but this difference was not detected in the same CNS region from schizophrenic subjects who died by suicide. The apparent discrepancy between findings on protein and mRNA levels has not been resolved by a study examining levels of synaptophysin mRNA and protein in frontal cortex from subjects with schizophrenia collected in two different locations. This study showed that there was a robust decrease in synaptophysin protein and mRNA in Brodmann’s area 17, but not areas 9/46, 24 or 22, from subjects with schizophrenia collected from only one of the two locations. Overall, evidence would seem to support a change in synaptophysin in the CNS from subjects with schizophrenia but the extent and consequence of these changes are not yet clear.

In a study which examined levels of mRNA for synaptophysin, synaptotagmin I, synaptobrevin I, SNAP-25, and syntaxin 1A it was reported that levels of mRNA for these proteins

<table>
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<tr>
<th>Brain region</th>
<th>Nuclei</th>
<th>Neurotransmitter</th>
<th>Measurement</th>
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<tr>
<td>Caudate-putamen</td>
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<td>Anterior, dorsomedial, lateral dorsal, central medial and ventral</td>
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<td>↓ KA2 subunit of kainate receptor</td>
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Table 1 A summary of changes in different regions of the central nervous system from subjects with schizophrenia
Box 2: Findings on non-neurotransmitter specific proteins in schizophrenia

- Changes in proteins involved in the release of neurotransmitters could be involved in the pathological processes of schizophrenia.
- Such changes could cause the changes in proteins that are thought to be neurotransmitter systems specific that have been observed across systems.
- Changes in the Wnt pathway implicate this pathway in the pathology of schizophrenia.
- Changes in this pathway could have profound effects on brain development and function.

Box 3: The syndrome of schizophrenia

- Schizophrenia is likely to be a syndrome and its symptoms could be generated by different pathologies.
- As is proving the case with Alzheimer’s disease, it is likely that abnormalities in different pathways of the CNS will account for the onset of symptoms in subsets of individuals with schizophrenia.

### Figure 1
A simplified schematic outlining of the Wnt pathway. Activation of the Wnt pathway occurs when Wnt binds to the frizzled receptors. One mechanism by which the frizzled receptor can transmit the Wnt signal is by the recruitment or release of dishevelled proteins. The dishevelled proteins are a family of cytoplasmic proteins that contain putative protein-protein interactive domains. Currently, it is thought that one of the actions of a recruited or released dishevelled protein is to inhibit the activity of GSK-3β. Inhibiting the activity of this enzyme in turn reduces the ability of the enzyme to promote instability of β-catenin in a cell. The resulting increased levels of β-catenin in the cell are then thought to bind to transcription factor-DNA binding factors which results in an activation of gene transcription (for more complete reviews on Wnt pathways see Dale and Kuhl et al.).

Changes in key pathways in schizophrenia would be expected to profoundly disrupt CNS functioning. However, there is now a growing body of data that suggests that changes in non-neurotransmitter specific proteins could be important in the underlying pathology of schizophrenia. It is still not clear whether the extensive changes in neurotransmitter associated proteins are simply a consequence of changes in such proteins.

CONCLUDING REMARKS

In summary, research using postmortem tissue has confirmed that there are multiple changes in the molecular cytoarchitecture of the CNS from subjects with schizophrenia. The challenge is to determine if these changes result from multiple abnormalities in gene expression or are due to a change in a few critical proteins that would produce profound disruption of CNS functioning. Importantly, when considering the outcomes of the study of postmortem CNS tissue associated with schizophrenia, it is important to note that it is most likely this syndrome has a polygenic basis. Thus, it could be that abnormalities in different pathways may be involved in the different forms of the illness. As the genetic basis of schizophrenia unfolds, it would seem that pathways of pathology associated with specific genetically homogeneous populations of subjects with schizophrenia will become apparent. Support for this argument comes from disorders of the CNS, such as Alzheimer’s disease, where it has become...
apparent that changes in different CNS proteins can result in the presentation of apparently homogenous symptoms as end points.

**QUESTIONS (ANSWERS AT END OF PAPER)**

Q1: Abnormalities in which receptors add weight to the argument that subjects with schizophrenia may self-medicate?

- Dopamine receptors
- Nicotinic receptors
- Cannabin receptors
- Serotonin receptors

Q2: In which neurotransmitter systems has there been changes in the presynaptic transporter associated with schizophrenia?

- Serotonin
- Glutamate
- GABA
- Acetylcholine

Q3: Which hypothesis on the pathology of schizophrenia was based in part on the action of antipsychotic drugs?

- Glutamate
- GABA
- Dopamine

Q4: Which proteins, which have been shown to be altered in the CNS from subjects with schizophrenia, are involved in the processes of neurotransmitter release?

- Wnt
- SNAP-25
- Serotonin 1A receptor
- rab3a

Q5: Are the many and varied findings in schizophrenia likely to be due to

- Problems with diagnoses
- An inappropriate use of CNS material
- Genetic variability
- The complexity of the human CNS

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ANSWERS
1: B and C; 2: C; 3: C; 4: B and D; 5: C and D.
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