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 resurgence 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 D3 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 D3 and D4 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 D1-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

Abbreviations: AMPA, N-methyl-D-aspartate; GABA, gamma aminobutyric acid; CNS, central nervous system; GSK, glycogen synthase kinase; 5HT, serotonin; M, muscarinic; mGlur, metabotropic glutamate receptors; NMDA, N-methyl-D-aspartate; SNAP-25, synaptosomal associated protein-25
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 5HT₂A receptors in schizophrenia, for review see Dean.1 A change that is not part of a generalised change in serotonergic markers in the frontal cortex of subjects with schizophrenia.1 Increasingly, evidence suggests that the decrease in cortical 5HT₂A 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 5HT₂A receptors in tissue from humans and rats treated with the same antipsychotic drug haloperidol would argue against such treatments increasing the same receptors in human tissue.8 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 muscarinic₁ (M₁) receptors have been reported in the caudate putamen10 and hippocampus11 from subjects with schizophrenia. The change in M₁ receptors in the caudate was not accompanied by a change in mRNA encoding the M₁ receptor in tissue from the same donors.10 This could indicate either the decrease in radioligand binding was due to a change in the density of only the M₁ 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 M₄ receptors has also been reported in the caudate-putamen in schizophrenia.12 Significantly, mRNA for the M₄ receptor was either absent, or present at very low levels, in the caudate-putamen from the individuals used in the M₄ radioligand study.12 One conclusion that can be drawn from these data is that there are no M₄ receptors in the human caudate-putamen and hence the decrease in radioligand binding was solely due to a decrease in M₄ receptors. This proposal would be in line with one possible outcome from the study of M₄ receptor binding in the caudate-putamen. Alternatively, low density 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 M₄ receptors act as autoreceptors in the caudate-putamen and that either M₁ 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.23 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. These receptors are made up of a combination of specific subunits,24 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.25 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).25 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 most recent study, levels of mRNA encoding the mGluR3 and 5 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. 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. Another study has reported no change in levels of mRNA encoding the mGluR3 and 5 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. These early findings suggest that there may be regionally discrete differences in levels of metabotropic receptors in the CNS of subjects with schizophrenia.

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 GABA 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 α1 subunit of the GABA receptor in Brodmann’s areas 9 and 10 from subjects with schizophrenia. 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.

Further data to support the argument that there are changes in expression of GABA receptor subunit in schizophrenia are the finding that there is a marked decrease in levels of mRNA encoding for the short form of the α2 subunit of the GABA receptor in the prefrontal cortex from subjects with schizophrenia. 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 are 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. 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 systems may be altered in schizophrenia. One example of such a protein is synaptophysin, 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 from 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.

Table 1: A summary of changes in different regions of the central nervous system from subjects with schizophrenia

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Nuclei</th>
<th>Neurotransmitter</th>
<th>Measurement</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate-putamen</td>
<td>Acetylcholine</td>
<td>Radioligand binding</td>
<td>↓ M1/4 receptors</td>
<td>No change in M1 or M4 receptors</td>
</tr>
<tr>
<td>Putamen</td>
<td>Glutamate</td>
<td>mRNA</td>
<td>↑ Glycine binding site: NMDA receptor</td>
<td>No change in M1 or M4 receptors</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>Dopamine</td>
<td>mRNA</td>
<td>↑ D1 receptor</td>
<td>↑ Glycine binding site: NMDA receptor</td>
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<td></td>
<td>Serotonin</td>
<td>Radioligand binding</td>
<td>↑ Glycine binding site: NMDA receptor</td>
<td>↑ Glycine binding site: NMDA receptor</td>
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<td>↑ Nicotinic receptor</td>
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<td>BA 9 and 10</td>
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<td>Hippocampus</td>
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<td>CA3</td>
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<td>↑ NMDA receptor</td>
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<tr>
<td>Planum temporale</td>
<td>Serotonin</td>
<td>Radioligand binding</td>
<td>↑ Glycine binding site: NMDA receptor</td>
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<td>Thalamus</td>
<td>Glutamate</td>
<td>mRNA</td>
<td>↑↓ mGluR5</td>
<td>↑ Glycine binding site: NMDA receptor</td>
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<td>Dorosmedial and central</td>
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were increased in “younger” subjects with schizophrenia (58–79 years) but were not altered in “older” subjects (80–95 years) with the illness.49 Another study has shown decreases in SNAP-25 in Brodmann’s areas 10 and 20, no change in that protein in Brodmann’s area 17, and an increased SNAP-25 in Brodmann’s area 9 from subjects with schizophrenia.46 Hence it would currently seem that there are changes in multiple proteins involved in neurotransmitter release cascades and this could be an important component in the pathology of schizophrenia. This argument is strengthened by the demonstration that rab3a, a synaptic vesicle associated protein, has been shown to be present in decreased levels in the thalamus48 with increased levels of mRNA for the protein present in left superior temporal gyrus from a group of schizophrenic subjects between the ages of 58 and 79 years of age.49

One interesting line of research that has unfolded recently relates to proteins in the Wnt pathway in CNS tissue obtained postmortem. The Wnt pathway is a highly conserved developmental pathway that appears to be involved in determining the fate of cells in the central nervous system of most eukaryotes.50 The Wnt pathway ultimately plays a part in switching on and off of gene transcription (fig 1), which then influences many cellular functions. Significantly, an increase in the number of Wnt-1 immunoreactive neurons has been demonstrated in the pyramidal cell layer of the CA 3 and CA 4 regions of the hippocampus from subjects with schizophrenia.51 Further findings implicating the Wnt pathway in the pathology of schizophrenia come from two reports showing a decrease in glycogen synthase kinase (GSK)-3β, a critical protein in the Wnt pathway (fig 1) in the prefrontal cortex of subjects with schizophrenia.52 53 Notably one of these studies also reported that other components of the Wnt pathway, β-catenin and dishevelled-2, were not altered in schizophrenia.53 However, as GSK-3β appears to be a rate limiting step in this critical pathway,54 the change in this protein alone could have significant pathological consequences for subjects with schizophrenia.

Clearly further study is warranted to determine the extent of changes in the Wnt pathway in postmortem CNS tissue from subjects with schizophrenia and to understand how this pathway may be involved in the pathological processes leading to the onset of the illness.

In addition to the more established lines of experiments on neurotransmitter release and Wnt pathway there are early reports of changes in lipoproteins,55 cell guidance proteins such as reelin,56 and proteins in the apoptotic pathways such as Bcl-257 in the CNS from subjects with schizophrenia. Changes in these 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.58 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,59 it would seem that pathways of pathology associated with specific genetically homogenous populations of subjects with schizophrenia will become apparent. Support for this argument comes from disorders of the CNS, such as Alzheimer’s disease,60 61 where it has become

**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.
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?

- (A) Dopamine receptors
- (B) Nicotinic receptors
- (C) Cannabis receptors
- (D) Serotonin receptors

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

- (A) Serotonin
- (B) GABA
- (C) Acetylcholine

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

- (A) Glutamate
- (B) GABA
- (C) 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?

- (A) Wnt
- (B) SNAP-25
- (C) Serotonin1a receptor
- (D) rab3a

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

- (A) Problems with diagnoses
- (B) An inappropriate use of CNS material
- (C) Genetic variability
- (D) 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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