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

B Dean

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 longstanding 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 D2longer receptor in the frontal cortex of subjects with schizophrenia. This finding, along with the report of an increase in mRNA for the dopamine D3 receptor in the cortex but not caudate from subjects with schizophrenia, would suggest that there may be abnormalities in the expression of corticol dopamine receptors associated with the illness. Unfortunately, the lack of specific radioligands for the dopamine D1 and D2longer 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 D1-like or dopamine D2-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, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS, central nervous system; GABA, gamma aminobutyric acid; GSK, glycogen synthase kinase; 5HT, serotonin; M, muscarinic; mGlur, metabotropic glutamate receptors; NMDA, N-methylaspartate; SNAP25, synaptosomal associated protein 25

Correspondence to:
Dr Brian Dean, Rebecca L Cooper Research Laboratories, The Mental Health Research Institute of Victoria, Locked Bag 11, Parkville, Victoria 3052, Australia; bdean@mhri.edu.au

Submitted 22 June 2001
Accepted 22 October 2001

www.postgradmedj.com

outcomes. This has meant that increasing attention has been paid to the status of serotoninergic markers in postmortem tissue from subjects with schizophrenia. There are now a number of reports of a decreased density of cortical 5HT<sub>2A</sub> receptors in schizophrenia (for review see Dean), a change that is not part of a generalised change in serotoninergic markers in the frontal cortex of subjects with schizophrenia. Increasingly, evidence suggests that the decrease in cortical 5HT<sub>2A</sub> 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 5HT<sub>2A</sub> receptors in the cortex from humans and rats treated with the same antipsychotic drugs do not marry, that levels of mRNA for the 5HT<sub>2A</sub> receptors are only decreased in the prefrontal cortex from subjects not treated with antipsychotic drugs for six months before death and that cortical 5HT<sub>2A</sub> receptors are not altered in subjects with bipolar disorder receiving antipsychotic drugs up to death. However, concluding that all changes in 5HT<sub>2A</sub> 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 5HT<sub>2A</sub> receptors appear to have arisen because of both pathological and antipsychotic drug effects.

It would be predicted that if the 5HT<sub>2A</sub> receptor was central to the pathology of schizophrenia there would be an association between a specific mutation in the gene for the 5HT<sub>2A</sub> receptor and the illness. Using DNA from peripheral tissue, a number of studies have suggested that mutations in the gene for the 5HT<sub>2A</sub> receptor are associated with schizophrenia. By contrast, studies using tissue obtained postmortem have failed to show an association between specific mutations in the gene for the 5HT<sub>2A</sub> 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 5HT<sub>2A</sub> 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 5HT<sub>2A</sub> 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 suggestions that changes in this system must be involved in 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 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 the hippocampus, cortex, and caudate from subjects 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<sub>1/4</sub> (M<sub>1/4</sub>) receptors have been reported in the caudate putamen and hippocampus from subjects with schizophrenia. The change in M<sub>2</sub> receptors in the caudate was not accompanied by a change in mRNA encoding the M<sub>2</sub> 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 M<sub>2</sub> receptor or that the decrease in receptor protein was not accompanied by a change in levels of mRNA for that receptor.

Using a similar approach, a decrease of M<sub>3</sub> receptors has also been reported in the caudate-putamen in schizophrenia. Significantly, mRNA for the M<sub>3</sub> receptor was either absent, or present at very low levels, in the caudate-putamen from the individuals used in the M<sub>2</sub> radioligand study. One conclusion that can be drawn from these data is that there are no M<sub>3</sub> receptors in the human caudate-putamen and hence the decrease in radioligand binding was solely due to a decrease in M<sub>2</sub> receptors. This proposal would be in line with one possible outcome from the study of M<sub>2</sub> receptor binding in the caudate-putamen. Alternatively, M<sub>2</sub> 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 M<sub>3</sub> receptors act as autoreceptors in the caudate-putamen and that either M<sub>1</sub> or M<sub>3</sub> 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.\textsuperscript{21} As the differential presentation of these binding sites is a function of subunit assembly, these data could suggest that NMDA receptors containing different subunit assemblies are present in the CNS of subjects with schizophrenia.

At present, glutamate receptor subunit specific radioligands are not available and thus non-radioisotopic binding approaches must be used to address the hypothesis of glutamate receptor subunit dysregulation in schizophrenia. In the study that has been reported to show major changes in AMPA or kainate receptors in the hippocampus from subjects with schizophrenia,\textsuperscript{22} 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.\textsuperscript{23} 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, and central medial nuclei. This study also reported lower levels of mRNA for the glrU1 subunit of the AMPA receptor in the dorsomedial nucleus with lower levels of glrU1 and glrU3 subunits 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 or GABA\textsubscript{A} receptor subunit expression is altered in the frontal cortex of subjects with schizophrenia.\textsuperscript{24} This study reported that neither AMPA nor GABA\textsubscript{A} receptor subunit expression is altered in the frontal cortex of subjects with schizophrenia. 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. Further data to support the argument that there are changes in expression of GABA\textsubscript{A} receptor subunit in schizophrenia may reveal that there is a marked decrease in levels of mRNA encoding for the short form of the 32 subunit of the GABA\textsubscript{A} receptor in the prefrontal cortex from schizophrenic patients. 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\textsubscript{A} 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.\textsuperscript{25} 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
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 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>
<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></td>
<td>Acetylcholine</td>
<td>Radioligand binding</td>
<td>↑ and ↓ nicotinic receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA</td>
<td>↑ M1/4 receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ M2/4 receptors</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>Putamen</td>
<td>Glutamate</td>
<td>Radioligand binding</td>
<td>↑ Glycine binding site: NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA</td>
<td>↑ D2 receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ D1 receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ SHT1α receptor: antipsychotic drug free subjects</td>
</tr>
<tr>
<td>BA 11</td>
<td></td>
<td>Acetylcholine</td>
<td>Radioligand binding</td>
<td>↑ Nicotinic receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA</td>
<td>↑ mGluR5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ NR1 subunit : NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ glur1 and glur7 subunit: AMPA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ KA1 subunit: kainate receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ u1 subunit: GABA receptor</td>
</tr>
<tr>
<td>BA 9 and 10</td>
<td></td>
<td>GABA</td>
<td>Radioligand binding</td>
<td>↑ GABA transporter-1</td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
<td>Acetylcholine</td>
<td>Radioligand binding</td>
<td>↑ Cannabis, receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA</td>
<td>↑ Nicotinic receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ M1/4 receptors</td>
</tr>
<tr>
<td>CA3</td>
<td>Dentate</td>
<td>Glutamate</td>
<td>mRNA</td>
<td>↓ Or no change in NMDA receptor</td>
</tr>
<tr>
<td></td>
<td>CA2</td>
<td></td>
<td></td>
<td>↓ NR1 subunit of NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ NR2B subunit of NMDA receptor</td>
</tr>
<tr>
<td>Planum temporale</td>
<td></td>
<td>Serotonin</td>
<td>Radioligand binding</td>
<td>↑ SHT1α receptor binding</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>Glutamate</td>
<td>Radioligand binding</td>
<td>↑ No change in metabotropic glutamate receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mRNA</td>
<td>↓ Glycine binding site on NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ glur1 subunit of the NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ NR1 subunit of the NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ NR2B subunit of the NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ NR2C subunit of the NMDA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ glur1 subunit AMPA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ glur3 subunit AMPA receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ KA2 subunit of kainate receptor</td>
</tr>
</tbody>
</table>
were increased in “younger” subjects with schizophrenia (58–79 years) but were not altered in “older” subjects (80–95 years) with the illness. Another study has shown decreases in SNAP-25 in Brodmann’s area 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. 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 thalamus 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.

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. 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. 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. Notably one of these studies also reported that other components of the Wnt pathway, β-catenin and dishevelled-2, were not altered in schizophrenia. However, as GSK-3β appears to be a rate limiting step in this critical pathway, the change in this protein alone could have significant pathological consequences for subjects with schizophrenia.

Clearly further study is warranted to determine the extent or changes in the Wnt pathway in CNS 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, cell guidance proteins such as reelin, and proteins in the apoptotic pathways such as Bcl-2 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. 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 homogenous 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?

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

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

- (A) Serotonin
- (B) Glutamate
- (C) GABA
- (D) 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

**REFERENCES**

1. Goodman AB, Pardee AB. Meeting report, “Molecular neurobiological
5. Dean B, Hussain T, Hayes W, et al. Changes in serotonin2A and
GABA(A) receptors in schizophrenia studies on the human dorsolateral
7. Dean B. Signal transmission, rather than reception, is the underlying
8. Dean B, Tomaskovic-Crook E, Oesperkn, K, et al. No change in the
density of the serotonin 1A receptor, the serotonin 4 receptor or the
transporter in the dorsolateral prefrontal cortex from subjects with
Brodmann’s area 9 from schizophrenic subjects. A pathological or
10. Hernandez I, Sokolov BP. Abnormalities in SHT2A receptor mRNA
expression in frontal cortex of chronic elderly schizophrenics with varying
[3H]flumazenil, but not [3H]muscimol binding, in Brodmann’s area 9 from
12. Prolong D, Tomaskovic-Crook E, Oesperkn K, et al. Serotonin2A
receptors are reduced in the planum temporale from subjects with
schizophrenia. Schizophr Res 2000;44:35–45.
A1-438G polymorphism in S-HT2A receptor gene promoter and the
polymorphism and steady state receptor expression in schizophrenia.
Lancet 1997;349:1815.
affinity nicotinic receptors in subjects with schizophrenia.
Neuropsychopharmacology 2000;23:351–64.
alpha4beta2 nicotinic acetylcholine receptor density in schizophrenia and
striatum: elevation in schizophrenia and reductions in dementia with
lewy bodies, Parkinson’s disease and Alzheimer’s disease and in relation
22. Dean B, Crook JM, Oesperkn K, et al. The density of muscarinic M1
receptors is decreased in the caudate-putamen of subjects with
muscarinic receptor binding in subjects with schizophrenia: a study of the
24. Dean B, Crook JM, Pavey G, et al. Muscarinic1 and 2 receptor mRNA in
the human caudate-putamen: no change in m1 mRNA in schizophrenia.
25. Crook JM, Dean B, Pavey G, et al. The binding of [3H]AF-DX 384 is
hypothesis” of schizophrenia. Rational for pharmacotherapy with
27. Seeberg PH. The TINS/TIPS lecture. The molecular biology of
excitatory amino acid transporter 2 and metabotropic glutamate
receptors 3 and 5 in the prefrontal cortex from normal individuals and
NMDA receptors in schizophrenia. Synapse 1999;32:67–9.
and expression of N-methyl-d-aspartate receptor subunits in subregions of
binding and subunit mRNA expression in thalamic nuclei in
148 Dean


35 Sokolov BP. Expression of NMDAR1, GluR1, GluR7, and KAI glutamate receptor mRNAs is decreased in frontal cortex of “neuroleptic-free” schizophrenics: evidence on reversible up-regulation by typical neuroleptics. J Neurochem 1998; 71:2454–64.


40 Thompson PM, Sower AC, Perrone-Bizzozero N. Altered levels of the synaptosomal associated protein SNAP-25 in schizophrenia. Biol Psychiatry 1998; 43:239–43.


ANSWERS
1: B and C; 2: C; 3: C; 4: B and D; 5: C and D.
Understanding the pathology of schizophrenia: recent advances from the study of the molecular architecture of postmortem CNS tissue
B Dean

Postgrad Med J 2002 78: 142-148
doi: 10.1136/pmj.78.917.142

Updated information and services can be found at:
http://pmj.bmj.com/content/78/917/142

These include:

References
This article cites 51 articles, 4 of which you can access for free at:
http://pmj.bmj.com/content/78/917/142#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/