The Neuropathology of Schizophrenia

by Joel E. Kleinman, Manuel F. Casanova, and George E. Jaskiw

Abstract

Insofar as schizophrenia is a neuropsychiatric syndrome involving the brain, neuropathology is a promising, if not essential investigative approach. Although traditional neuropathology has yet to yield a pathognomonic lesion in schizophrenia, there have been no shortages of findings. Unfortunately, many of these findings have not only failed to be pathognomonic, but they have not been consistently replicated. Fortunately, newer neuropathological techniques, such as post-mortem neurochemistry, have resulted in findings among the most reproducible in schizophrenia research. Although one of these, increased dopamine receptors in the basal ganglia of schizophrenic patients, has been replicated many times, it suffers from doubts as to its clinical relevance. Are these increases in dopamine receptors primary to the illness or a side effect of the treatment? This article discusses the relevance of this finding, reviews other highlights of post-mortem neurochemistry and traditional neuropathology, and discusses new horizons such as autoradiography, immunocytochemistry, and neuronal morphometrics.

Post-mortem Neurochemistry

Basal Ganglia (Caudate, Putamen, and Globus Pallidus). Probably the most reproducible neuropathological finding in the schizophrenic syndrome to date is that of increased numbers of dopamine type II (D$_2$) receptors (which are neither linked to nor responsible for a decrease in adenylate cyclase activity) in the caudate and putamen (see table 1). Insofar as neuroleptics are thought to exert their therapeutic effect by D$_2$ blockade (Creese et al. 1976), this finding may explain some of the psychopathology of the schizophrenic syndrome. Unfortunately, the vast majority of subjects studied to date have received neuroleptic treatment, which can increase D$_2$ receptors by virtue of a denervation supersensitivity effect (Clow et al. 1980; Murugaiah et al. 1984). For a more detailed discussion of post-mortem studies of dopamine receptors in schizophrenia, a recent review is available (Jaskiw and Kleinman, in press). Attempts to resolve this conundrum with “in vivo” positron emission tomography of D$_2$ receptors in drug-naive schizophrenic patients have yielded conflicting results (Wong et al. 1986; Farde et al. 1987).

The second form of dopamine receptor, type I (D$_1$) receptors (those linked to an increase in adenylate cyclase activity), has been studied far less. Although several studies have failed to find any differences between patients and controls (Carenzi et al. 1975; Cross et al. 1981; Pimoule et al. 1985), one report has found increased responsiveness of D$_1$ receptors in caudate nuclei of schizophrenic patients (Memo et al. 1983). Unfortunately, this finding has not been replicated, and a neuroleptic effect has not been excluded. The finding received some support from one binding study of D$_1$ receptors in which reduced dissociation constants (indicating increased affinity) were reported (Hess et al. 1987). Interestingly enough, this is the

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one study in which D_1 receptor numbers were reduced (Hess et al. 1987), a finding not supported by others (Cross et al. 1981, Pimoule et al. 1985).

Although a number of other receptors, neurotransmitters, metabolites, neuromodulators, and enzymes have been studied in schizophrenic brains, the only replicable finding has been increased serotonin in the putamen (Crow et al. 1979; Korpi et al. 1986) and globus pallidus (Farley et al. 1978, Kleinman et al. 1982). A more detailed review of this topic is available elsewhere (Jaskiw and Kleinman, in press).

**Table 1. D_2 receptor number in the basal ganglia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Caudate</th>
<th>Putamen</th>
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<tbody>
<tr>
<td>Lee et al. (1978); and Lee and Seeman (1980)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Powen et al. (1978)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Reisine et al. (1980)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Mackay et al. (1980)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Reynolds et al. (1980)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cross et al. (1981)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Kleinman et al. (1982)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Seeman et al. (1984)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pimoule et al. (1985)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Toru et al. (1986)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Mita et al. (1986)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hess et al. (1987)</td>
<td>↑</td>
<td></td>
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</tbody>
</table>

**Note**: ↑ = increased, NC = no change.

A second finding, increased norepinephrine concentration in the nucleus accumbens of chronic paranoid schizophrenic patients (Farley et al. 1978, Kleinman et al. 1982), has not been seen in studies which fail to examine schizophrenic subtypes (Birn et al. 1979, Crow et al. 1979). Moreover, a concomitant increase in a major norepinephrine metabolite, 3 methoxy-4-hydroxy-phenylglycol was reported in one of the positive studies (Kleinman et al. 1982). Lastly, increases in norepinephrine concentrations have been observed in several other limbic structures (Farley et al. 1978). Insofar as these findings (especially in the nucleus accumbens) have not been seen in treated undifferentiated schizophrenic patients (Kleinman et al. 1982), the increased norepinephrine concentrations found in paranoid patients may not be a neuroleptic effect.

A third intriguing finding involves increased dopamine (Reynolds 1983, Reynolds and Czudek 1986) and homovanillic acid (a major dopamine metabolite) concentrations (Reynolds and Czudek 1986) in the left amygdala. Failures to replicate this finding have involved comparisons where both

**Table 2. Positive findings in cerebral cortex**

<table>
<thead>
<tr>
<th>Study</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Bennett et al. (1979)</td>
<td>↑ 3H-LSD (5HT) binding in FCx</td>
</tr>
<tr>
<td>Whitaker et al. (1981)</td>
<td>↑ 3H-LSD (5HT) binding in FCx</td>
</tr>
<tr>
<td>Quirion et al. (1982)</td>
<td>↑ Neurotensin binding in FCx</td>
</tr>
<tr>
<td>Nishikawa et al. (1983)</td>
<td>↑ KA binding in FCx</td>
</tr>
<tr>
<td>Nemeroff et al. (1982)</td>
<td>↑ Neurotensin in FCx</td>
</tr>
<tr>
<td>Ferrier et al. (1983)</td>
<td>↑ CCK &amp; somatostatin in temporal Cx</td>
</tr>
<tr>
<td>Farmery et al. (1985)</td>
<td>↑ CCK binding in FCx</td>
</tr>
<tr>
<td>Manberg et al. (1985)</td>
<td>TRH &amp; SRIF in FCx (BA 12), ↑ TRH in FC x (BA 32)</td>
</tr>
<tr>
<td>Mita et al. (1986)</td>
<td>↑ Ketanserin (5HT type II) binding in PFCx</td>
</tr>
<tr>
<td>Toru et al. (1986)</td>
<td>↑ 3H-KA (GLU receptor) binding in medial FCx &amp; eye movement area</td>
</tr>
<tr>
<td>Hanada et al. (1986)</td>
<td>↑ 3H-QNB (muscarnic binding) in medial FCx</td>
</tr>
<tr>
<td></td>
<td>↑ 3H-muscimol (GABA) binding in PFCx</td>
</tr>
</tbody>
</table>

**Note**: ↑ = increased, ↓ = decreased. FCx = frontal cortex. PFCx = prefrontal cortex. GLU = glutamate. BA = Brodmann area. TRH = thyrotropin-releasing hormone. SRIF = somatostatin. CCK = cholecystokinin. 5HT = serotonin. KA = kainic acid. GABA = γ-aminobutyric acid.
Table 3. Neuropathological findings in the basal ganglia

<table>
<thead>
<tr>
<th>Study</th>
<th>Finding</th>
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</thead>
<tbody>
<tr>
<td>Buscaino (1920)</td>
<td>Cellular alteration in globus pallidus of catatonia</td>
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<tr>
<td>Vogt and Vogt (1952)</td>
<td>Cellular alteration in globus pallidus of catatonia</td>
</tr>
<tr>
<td>Josephy (1930)</td>
<td>Increased mineralization of globus pallidus</td>
</tr>
<tr>
<td>Stevens (1982)</td>
<td>Increased mineralization of globus pallidus</td>
</tr>
<tr>
<td>Neuman (personal communication)</td>
<td>Increased iron deposits in globus pallidus</td>
</tr>
<tr>
<td>Hopf (1952)</td>
<td>Reduced Nissl substance, increased lipofuscin in globus pallidus &amp; striatum with cell loss in globus pallidus in catatonia</td>
</tr>
<tr>
<td>Bogerts et al. (1985)</td>
<td>Decreased volume of internal globus pallidus</td>
</tr>
<tr>
<td>Dom et al. (1981)</td>
<td>Smaller striatal microneurons &amp; Golgi type II neuron loss in pulvinar</td>
</tr>
</tbody>
</table>

the left and right amygdala were not from the same subject. Since dopamine and homovanillic acid are both unstable post-mortem, comparisons of left and right nuclei from the same subject reduce the variability and enhance the opportunity to see neurochemical differences. This finding deserves an attempt at replication with the same methodology in other laboratories.

Cerebral Cortex. Despite the size and importance of the cerebral cortex in the human brain, there have been relatively few studies (for a review, see Jaskiw and Kleinman, in press) and still fewer positive findings (see table 2). This is regrettable as the cerebral cortex is worthy of study in schizophrenia for a number of reasons some of which are described in detail elsewhere (Weinberger and Berman, this issue). Moreover, the cortex is a major innervator and regulator of the basal ganglia (Carpenter and Sutin 1983) with the potential to regulate and increase $D_2$ receptors (Pycock et al. 1980). Perhaps, the difficulties in dissecting cerebral cortex may account for the paucity of studies in this particularly “human” part of the brain.

Brainstem and Other Areas.
Although the source of many of the catecholamines and indoleamines in the basal ganglia, limbic system, and cerebral cortex is the brainstem and related structures, these latter areas have been infrequently investigated in post-mortem neurochemistry. Of special interest are reports of increased $D_2$ receptors in substantia nigra (Owen et al. 1984) and increased norepinephrine concentrations in the pons (Carlsson et al. 1980). Obviously, more work needs to be done in this area. A more extensive review is available elsewhere (Jaskiw and Kleinman, in press).

Traditional Neuropathology

Basal Ganglia. Unlike the neurochemistry of the basal ganglia, there are no consistent neuropathological changes in these nuclei. Some of the more promising findings over the last several decades have focused on the globus pallidus of catatonic patients as summarized in table 3. As a major route of exit from the caudate and putamen, the globus pallidus deserves further study in relation to post-mortem neurochemical findings in schizophrenia.

Limbic System. Two groups of neuropathological changes have been reported in the limbic system in schizophrenic patients: gliosis in the hypothalamus (Nieto and Escobar 1972; Stevens 1982) and hippocampal structural abnormalities (Bogerts et al. 1985). Diffuse gliosis has been reported in peri-

Table 4. Neuropathological findings in the cerebral cortex

<table>
<thead>
<tr>
<th>Study</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Hecker (1871)</td>
<td>Darkening</td>
</tr>
<tr>
<td>Alzheimer (1897)</td>
<td>Cell loss, tangles, gliosis in layers II &amp; III</td>
</tr>
<tr>
<td>Klippel and Lhermitte (1909)</td>
<td>Cell loss in layers V &amp; VI</td>
</tr>
<tr>
<td>Southard (1914, 1915, 1919)</td>
<td>Left cerebral atrophy or aplasia</td>
</tr>
<tr>
<td>Vogt and Vogt (1952)</td>
<td>Focal cell loss, dwarf cells, lipid sclerosis</td>
</tr>
<tr>
<td>Coln (1952)</td>
<td>Cortical thinning</td>
</tr>
<tr>
<td>Bruetsch (1952)</td>
<td>Cortical degeneration &amp; obliterated endarteritic cerebral vessels</td>
</tr>
<tr>
<td>Benes and Bird (1987)</td>
<td>Increased interneuronal space in layers II, III &amp; V of anterior cingulate</td>
</tr>
<tr>
<td>Jakob and Beckmann (1986)</td>
<td>Decreased cell numbers &amp; heterotopic arrangements in entorhinal cortex</td>
</tr>
</tbody>
</table>
ventricular structures and hypothalamus (Nieto and Escobar 1972; Stevens 1982). An attempt to confirm these findings using glial fibrillary acidic protein as a measure was unsuccessful (Casanova et al. 1987). Whether this technique is a reliable measure of gliosis, however, is itself debatable (Roberts et al. 1986, 1987a, 1987b; Casanova et al. 1987). Further attempts to replicate these findings and to determine their significance are obviously needed.

A second promising series of studies of the hippocampus has emerged over the last decade. The highlights of these studies involve reports of disarray of hippocampal pyramidal cells (Scheibel and Kovelman 1981; Kovelman and Scheibel 1984) and reduced hippocampal volume (Bogerts et al. 1985). Unfortunately, the former was not replicated using a different staining technique (Weinberger et al. 1980; Altshuler et al. 1987; Christison et al. 1988). Reduced hippocampal volume has not yet been replicated or refuted, but the finding also includes the amygdala and the hippocampal formation (Bogerts et al. 1985), an area where another study had similar findings (Brown et al. 1986).

Cerebral Cortex. Neuropathological abnormalities in cerebral cortex of schizophrenic patients predate Alzheimer (1897) and are summarized in Table 4. A lack of a consistent neuropathological change has characterized cortical studies. The recent work of Benes and Bird (1987) is a novel new approach that appears promising.

Brainstem and Other Structures. Again there have been reports of neuropathological findings in thalamus (B. Pakkenberg, and H. J. G. Gunderson, unpublished data), midbrain tegmentum (Stevens 1982), substantia nigra (Bogerts et al. 1983), reticular formation (Fisman 1975), brainstem (Fisman 1975), and substantia innominata (Von Buttlar-Bentano 1952). Unfortunately, there has been a failure to replicate some of these findings (Hankoff and Peress 1981; Kirch 1988).

One finding of brain “pathology,” ventriculomegaly, has been reported in numerous computed tomographic brain studies (Shelton and Weinberger 1986). Although edema obliterates ventricles acutely post-mortem, a satisfactory assessment can be made after standard fixation (Pakkenberg 1987). To date, several post-mortem studies have confirmed ventriculomegaly in schizophrenic patients, especially in association with deficit symptoms (Pearlson et al. 1984; Williams et al. 1985).

New Approaches

The inability of traditional neuropathology and post-mortem neurochemistry to unravel the mysteries of schizophrenia suggest the need for new approaches. Fortunately, autoradiography, immunocytochemistry, and neuronal morphometrics are now available as new techniques in neuropathology. Thus far, they have been applied only rarely in schizophrenic research (Ko et al. 1986). Difficulties in dissecting small nuclei and poorly defined structures, as well as the magnitude of the problem (billions of neurons), make these approaches attractive. They offer some hope for an answer to the simple question: Where to look?

Discussion

Perhaps the single most significant post-mortem neurochemical study to date has been the discovery that there is reduced dopamine in the caudate and putamen of patients with Parkinson’s disease (Ehringer and Hornykiewicz 1960). This finding ultimately led to a major treatment for this syndrome, namely, l-dopa. Insofar as this is a model for post-mortem neurochemical studies, it is probably worthwhile to remember that pigment loss of the substantia nigra gave a valuable clue as to where one should look.

The question that arises is whether there are any similar clues in the dozens of post-mortem studies reviewed to date. Although there is clearly no pathognomonic lesion, the most replicable findings to date involve D2 receptor increases. Although it is unclear whether this “finding” is primary to the syndrome or a byproduct of treatment, it is, at least, suggestive that the basal ganglia (caudate, putamen) and nucleus accumbens are one place to look.

It seems unlikely that schizophrenia is “just” a basal ganglia or nucleus accumbens disorder. But if these structures are involved, then perhaps their connections are important. The afferents to the caudate and putamen include the cerebral cortex, amygdala, substantia nigra, ventral tegmentum, and the thalamus. The efferents include the globus pallidus, substantia nigra, and cerebral cortex. Perhaps the way to proceed with further neuropathological studies is to study the input and the output of the basal ganglia with the new techniques of autoradiography, immunocytochemistry, and neuronal morphometrics. We hope that this approach will teach us something about the regulation of dopamine receptors and the significance of increases in these receptors in schizophrenic brains. If it
does, then we may be able to develop new and improved treatments.

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