

THE NEUROBIOLOGY OF SCHIZOPHRENIA: A MINI-REVIEW

C.W.LO

SUMMARY

Some recent advances in schizophrenic research are summarized. The theories on the pathogenesis of schizophrenia are discussed.

Key words: schizophrenia, neurobiology

INTRODUCTION

In this decade of the brain advances on the neurobiology of schizophrenia have been going on rapidly. Since my last review 6 years ago (Lo, 1991) we have seen new developments in various aspects of schizophrenic research. In this mini review I shall concentrate on four recent themes that have been at the centre of efforts to understand this disease: the neuropathology of schizophrenia, functional imaging in psychiatric applications, the etiological theories of schizophrenia and the novel antipsychotics in the treatment and understanding of the underlying mechanisms.

NEUROPATHOLOGY

Johnston's discovery (Johnston, 1976) on ventricular enlargement remains the most consistent finding in schizophrenia. Other findings are more controversial. (Chua & McKenna, 1995; Deakin, 1996)

Recent postmortem studies point to the limbic system as one major focus of pathology. Reduced volume of hippocampus, amygdala and parahippocampal gyrus are found, as well as left temporal horn enlargement. It may be related to reduced cell number or cell size in hippocampus/parahippocampal gyrus/entorhinal cortex. White matter in hippocampal/parahippocampal gyrus is also reduced. The cytoarchitecture is disturbed, there being increased vertical axon numbers and deficits in small interneurons in the cingulate gyrus and abnormal cell arrangements in the hippocampus or entorhinal cortex. (Falkai & Bogerts, 1995)

In the cortex, contradictory results are reported in whether there is reduction of cortical volume. There appears to be shape abnormalities in the corpus callosum in that the sex difference in anterior and posterior callosal thickness in normal controls seem to be reversed in schizophrenics, and the mean curvature in corpus callosum is more marked in schizophrenia, with the corpus callosum being thicker in female and thinner in male.

In the basal ganglia, it is reported that caudate volume might increase under the influence of continuous neuroleptic treatment. In the thalamus, there is volume and cell number reductions in the medio-dorsal nucleus of the thalamus, or

smaller whole thalamic volume. In the brain stem, a reduced nigral volume, and a trend for reduced locus coeruleus volume are taken as an indication of a dopaminergic/noradrenergic underactivity.

Although postmortem studies give equivocal results in the brain size and weight, the majority of CT and MRI studies dismiss the idea of reduced brain size in schizophrenia.

UNDERLYING MECHANISM

What are the mechanisms underlying the neuropathological changes? Recent findings favour a static, non-progressive subtle brain abnormalities resulting from disturbed prenatal brain development.

LACK OF GLIOSIS IN LIMBIC STRUCTURES

Astrocytes show changes in response to almost every type of injury or disease in the CNS. The capacity of astrocytes to react with proliferation and hypertrophy develops during the last trimester of gestation. The majority of studies involving glial cell counts, neuron-glial ratios and glial cell nuclei volumes found no difference in temporo-limbic structures, thalamus and cingulate gyrus. Most studies dismiss a chronic progressive disease, but support the idea of a static lesion occurring prior to the 20th week of gestation.

CYTOARCHITECTURAL ABNORMALITIES

The cytoarchitectural abnormalities, cellular disarray, lower neuronal density, smaller cell size etc., recently described in different limbic structures, prefrontal and temporal cortex of schizophrenics are very subtle and will easily be missed using classical neuropathological methods. It is likely that the subtle differences are due to disturbances in the late migration or final differentiation of neurons that takes place in the second and third trimester of pregnancy.

CORTICAL LATERALISATION.

The two hemispheres are asymmetrical, being most marked in the temporoparietal region. Postmortem, MRI and CT studies indicate an absence of normal cerebral asymmetry in cortical and limbic areas of schizophrenics which suggests disturbed brain lateralisation at early stages of brain development.

LACK OF PROGRESSIVE VENTRICULAR ENLARGEMENT

Four out of five prospective CT and MRI studies show no progressive ventricular enlargement in schizophrenia, suggesting a neurodevelopmental etiology.

In summary, when looking for possible mechanisms underlying the pathomorphological changes in the brains of schizophrenics, a neurodevelopmental model is presently favoured. Lack of a significant degree of gliosis, the presence of neurohistological indicators of disturbed prenatal brain development, reduced normal cortical lateralization and the lack of progressive ventricular enlargement rather dismiss the idea of a chronic progressive brain lesion.

FUNCTIONAL IMAGING

Functional Imaging tries to find out the pattern of cerebral activity, sometimes when associated with specific symptom profile or neuropsychological tasks.

FUNCTIONAL IMAGING METHODS

There are four main types of functional imaging methods.

Positron Emission Tomography (PET)

Radioactive substances that emit positrons are introduced into the cerebral circulation, through IV injection or inhalation and the positron emitted from tissue in turn cause the emission of (radiation through positron electron interactions. Each positron causes the simultaneous release of (radiation in 2 opposite directions. Computed measurement of simultaneous dual (photons travelling in opposite directions is used to produce brain slice images which can demonstrate metabolic changes, regional cerebral blood flow and ligand binding.

Single photon emission computerised tomography (SPECT)

The radioactive substances introduced into the cerebral circulation in SPECT, such as Xenon-133 and technetium-99m, emit single (photon (not dual photons). Computed tomographic techniques allow the measurement of the (photons to yield regional cerebral blood flow images and, through the use of radiolabelled receptor binding ligands, ligand binding images.

Functional Magnetic Resonance Imaging (fMRI)

Increase in neural activity is associated with a fall in the concentration of deoxyhaemoglobin, because the increase in rCBF exceeds metabolic demand. Deoxyhaemoglobin is paramagnetic and a change in its concentration produces a measurable change in MRI signal. It allows noninvasive regional estimation of changes in regional cerebral blood flow and, therefore, activation, which can be statistically mapped onto structural MRI scans. Both PET and SPECT are invasive and fMRI has a greater spatial resolution than PET, and in turn, has a greater resolution than SPECT.

Magnetic Resonance Spectroscopy (MRS)

MRS is a safe and non invasive tool which can be used to study aspects of brain chemistry and metabolism. It is based on the principle that atomic nuclei within molecules behave like

tiny magnets in the presence of an externally applied magnetic field and resonate at a characteristic frequency. (Frangou, 1996)

The proton number (1H) in the hydrogen atom is the most commonly observed nucleus in MRS experiment. In MRI, one collects the signal from H atom in water and fat molecules, whereas in MRS, the concentration is placed on other H bearing neurochemicals such as amino acids, neurotransmitters and their metabolites.

Another commonly observed endogeneous nucleus is the stable isotope of phosphorus. ³¹P MRS provides information about compounds involved in energy utilization, such as phosphocreatinine, ADP and ATP and membrane phospholipids, including phosphomonoesters (PME) and phosphodiester (PDE) which are respectively, precursors and breakdown products of membrane phospholipids and provide information about neuronal membrane metabolism.

The finding of increase in phosphodiester (PDE) in dorsolateral prefrontal cortex in schizophrenia may indicate abnormal membrane phospholipid metabolism and may relate to structural changes such as excessive synaptic pruning.

RECENT FINDINGS

Functional imaging reveal the following findings:

Hypofrontality

Some studies found hypofrontality in schizophrenia, others not, especially in acute, unmedicated patients. Thus, hypofrontality does not occur in all patients at all phases of illness, only depend on mental activity at the time of scanning. There is strong evidence that resting hypofrontality is characteristic of schizophrenic patients with marked psychomotor poverty, while patients with a different symptom profile might actually exhibit abnormally high frontal activity. Studies of cerebral activity during performance of neuropsychological tasks indicate that a degree of impairment of ability to activate frontal lobe probably occurs in all patients with schizophrenia.

Cerebral Function associated with the experience of symptoms

Liddle (1996) studied the relationship between symptom profile and cerebral activity. He found that each of the three syndromes of characteristic schizophrenic symptoms is associated with a different pattern of cerebral activity. In each instance, the pattern included regions of increased rCBF and regions of decreased rCBF, suggesting the existence of *dynamic imbalance* between activity in different cerebral areas, rather than an isolated local deficit or increase in activity. In the psychomotor poverty syndrome, which is characterised by poverty of speech, flat affect, and decreased movement, there was underactivity of prefrontal cortex and left parietal cortex, and overactivity of bilateral caudate nuclei. In the disorganisation syndrome, (formal thought disorder, inappropriate affect) there was underactivity of right ventral prefrontal cortex and insula, and overactivity in the anterior cingulate gyrus. In the reality distortion syndrome, characterised by delusions and hallucinations, there was underactivity of the posterior cingulate cortex, left lateral temporal cortex and

adjacent parietal cortex, and overactivity in the medial temporal lobe and left lateral frontal lobe.

These findings indicate that patients with different symptom profile have different patterns of cerebral activity, and there are imbalances between neuronal activity at diverse interconnected brain sites, rather than abnormal function at a single location.

Neuropsychological challenge studies

These studies aim to delineate the pattern of cerebral activity associated with a specific neuropsychological task (it is necessary to compare cerebral activity during the performance of the task with that during an appropriate reference condition).

1. WISCONSIN CARD SORTING TEST (WCST)

Weinberger demonstrated that schizophrenics exhibit lesser degree of prefrontal activation during WCST, which demands flexibility in problem solving.

The degree of diminution of prefrontal activation correlates inversely with CSF HVA (dopamine metabolite), implying a relationship with decreased cortical dopaminergic activity.

2. WORD GENERATION

During word generation, schizophrenic patients exhibited less activation of the prefrontal cortex and displayed greater activity in superior temporal gyrus (Liddle, 1996).

3. INNER SPEECH

Schizophrenic patients prone to auditory hallucinations fail to activate areas concerned with the monitoring of inner speech.

4. MEMORY

Schizophrenic patients show attenuated activation of hippocampal formation during memory tasks.

5. HALLUCINATIONS

PET scans were acquired from patients while hallucinating. Activity was maximal in the bilateral thalamus, left hippocampal formation and right ventral striatum. A lack of frontal activation was thought to indicate the possibility of abnormal connectivity. Similar studies by the same group of workers on verbal fluency, verbal imagery and inner speech yielded same conclusion of aberrant connectivity between fronto-temporal region (Travis, 1997).

In summary, schizophrenia is characterised by disorder of the connections between cerebral areas.

ETIOLOGICAL THEORIES

The best established etiological component in schizophrenia continues to be the substantial genetic liability. In most individuals, this is likely to be caused by the collective action of multiple genes. In addition, one or more major genes may be inherited in a proportion of families. If an environmental factor is clearly delineated, obstetric complications for example, it is likely to be of relatively small effect and to interact with the genetic liability. (Cardno, 1996)

THE NEURODEVELOPMENTAL THEORY

This is the prevalent theory and many findings support this view; e.g. the non-progressive brain abnormalities present in first onset patients; the absence of gliosis; and the presence of premorbid abnormalities such as minor physical anomalies, subtle neurological abnormalities, and social and cognitive deficits in schizophrenic patients. To add weight to it, a sample

of people born in the week 3-9 March 1946 was collected. The premorbid function of the 30 individuals who developed schizophrenia was compared with the rest. The schizophrenic group showed later walking, more speech problems and poorer performance on educational achievement. This result shows that structural brain abnormalities precede the onset of symptoms in at least a proportion of individual with schizophrenia and is suggestive of abnormalities beginning before birth, although they may be a consequence of genetic factors. (Jones, 1994)

The neurodevelopmental model can further be divided into two schools of thought. The early lesion hypothesis by Weinberger proposed that a fixed 'lesion' occurring in foetal life that interacts with normal neurodevelopmental processes leading to the expression of schizophrenic symptoms later in life. The Late "Lesion" hypothesis states that schizophrenia results from a deviation in the maturational process that occur in the brain during adolescence and early adulthood.

THE GLUTAMATE THEORY

Olney (1995) proposed that schizophrenia is a complex multineural disturbance in which hypofunction of the NMDA receptor may play a part. This proposal is based on two findings: (a) Phencyclidine non-competitively blocks the ion channel of the NMDA receptor. It produces schizophrenia like psychotic symptoms. (b) NMDA antagonists (CPP etc.) that cause psychotic reactions in humans cause neurodegenerative changes in corticolimbic regions of the rat brain (post cingulate and retrosplenial cortex). However, therapeutic trials with glutamatergic agonists so far have not yielded any striking results. It is also difficult to imagine how a natural glutamatergic antagonist could exist and work in a diseased brain to produce psychotic symptoms.

Carlsson (1995) proposed a complex interaction between the dopaminergic and glutamatergic systems and that a deficiency in glutamatergic stimulation of striatal gabaergic neurons would result in an increased responsiveness of these neurons to variations in dopaminergic tone. Such variations occur normally in response to external stimuli of various kinds, e.g. stress. Hence an important pathogenetic factor in psychosis may be an increased responsiveness to dopamine, depending on a deficient glutamatergic function.

CONNECTIVITY

Neuropsychological as well as the imaging and postmortem data suggest that in schizophrenia the connectivity of the prefrontal and temporo-limbic areas is abnormal. This connectivity mishap may account for the failure to activate the correct cortical regions in response to a task demand. However, it does not lead to understanding the presumed connectivity abnormality as pathognomic for schizophrenia. Neither does this abnormality explain characteristic hallucinations nor does it appear to account for the response to antipsychotic drugs.

AN INTEGRATIVE MODEL

The theory (Ereshefsky, 1995) states that schizophrenia is associated with disturbances of the systems for glutamate, NE

and GABA. Symptoms of schizophrenia may result from the disruption of excitatory amino acid transmission via the NMDA receptors in the cortex, limbic system and hippocampus. In the normally functioning brain, excitatory glutaminergic neurotransmission in the prefrontal cortex sends signals that maintain normal sensitivity and function of dopamine receptors in the limbic system by stimulating tonic dopamine 'leak' from the neuron into the presynaptic space. This background, low level constant output of dopamine regulates receptor sensitivity under normal conditions.

The presence of frontal cortex dysfunction in schizophrenia interrupts glutamate transmission, diminishes dopamine function in the cortex, and decreases tonic signal in the limbic dopamine system, leading to the simultaneous finding of prefrontal dopamine hyperactivity (receptor sensitization). Limbic and cortical dopaminergic neurons are regulated by different mechanisms, which helps to explain the divergence in dopamine system function.

5HT₂ blockade may enhance glutamate transmission to the limbic system.

Clozapine and risperidone improve cortical function by blocking 5HT₂ receptors and thus increasing dopamine release in the frontal cortex (densities of 5HT₂ are lower in midbrain structures) It is hypothesized that improved cortical function via 5HT₂ blockade leads to normalization of descending innervation (glutamate) of the midbrain, thereby improves positive as well as negative symptoms.

NEW ANTIPSYCHOTICS

GOALS FOR DRUG DEVELOPMENT

While developing new antipsychotic drugs, workers should aim to have drugs that can have increased effectiveness for positive and/or negative symptoms. They should be effective for patients refractory to standard drugs. There should be minimal or no extrapyramidal side effects at clinically effective dose, be highly acceptable to patients and have reduced risk of tardive dyskinesia.

SEROTONIN-DOPAMINE ANTAGONISTS (SDA)

This group including clozapine, risperidone, olanzapine and sertindole may improve positive symptoms as well as negative symptoms. The neurophysiological cognitive deficits may also be improved. Extrapyramidal side effects, if present, are mild.

RISPERIDONE

This drug produces blockade of both cortical 5HT₂ receptors and limbic D₂ systems. More dopamine is released in cortical regions as a result of relatively selective 5HT₂ blockade in these areas, ameliorating the core negative symptoms. From the distribution of 5HT₂ receptors, DA transmission is enhanced in basal ganglia as well, resulting in diminished EPS.

PARTIAL DOPAMINE AGONISTS

This is a new type of medication under development. Partial agonist can exist for any neurotransmitter. It has the property of being either an agonist or antagonist depending on the amount of naturally occurring agonist present. Thus, a DA partial agonist would be a net agonist in the absence of DA and

simultaneously would be a net antagonist when dopamine is in excess (such as postulated for the mesolimbic dopamine pathway and relating to the positive symptoms of schizophrenia). Also, where normal dopamine activity may exist (such as nigrostriatal neurons), a partial agonist may not generate EPS as easily as would the full antagonist typical neuroleptics.

FUTURE DIRECTIONS

It is proposed that the development of new antipsychotic drugs should be aimed at regulating intracellular messenger pathways and gene expression, and possibly at modifying connectivity of specific cell populations. Although, at present, it is difficult to envisage how a drug could improve the aberrant connectivity of the miswired cortex implicated in the disease. (Beerport,1996)

DISCUSSION

In reviewing a vast subject as the neurobiology of schizophrenia, this article is necessarily limited in depth and scope. I have not cited the original sources in describing the findings. Interested readers may look up the papers in the review articles given in the reference section. Instead of a simple review, I venture to discuss some of the limitations in the current directions of research, which I think may not be sufficient for a thorough understanding of the disease process.

From a clinician's point of view, it is known that there are several characteristics of the schizophrenic illness that cannot be dismissed in explaining the pathogenesis simply by a neurodevelopmental theory, which perhaps act only as a predisposing factor for the disease process. It has failed to consider the on-going processes and the dynamic aspect of the disease.

● **The effect of neuroleptic drugs on the course of illness**

With neuroleptic treatment, schizophrenia is still a progressive disorder. Impairment acquired earlier cannot be dissipated by later neuroleptic treatment. The greater the number of admissions, the less the likelihood of a successful therapeutic outcome. The more episodes a patient had, the more insidiously developing and longer lasting these have been, the more likely it is that some residual damage will remain.

Recent studies suggest that timely pharmacological or psychosocial interventions can alter the natural history of schizophrenia and have rekindled interest in early detection and prevention (Fenton,1997). This cannot be explained by the neurodevelopmental theory which claims that the course of the illness, once started, is non-progressive.

● **Positive symptoms usually precede negative symptoms**

The reverse would be true if the primary defect lies in the prefrontal cortex.

● **Only about 35% of the patients remain in the defect state.**

● **Rate of progression of illness varies.**

In schizophreniform disorder there is remission in between episodes with insignificant or mild residual negative defect.

More commonly, positive symptoms progress to negative symptoms and defect state within weeks or months but the progression usually becomes static after a few episodes. Sometimes positive and negative symptoms exist together. Individual patients could show either deterioration, improvement or, occasionally recovery, many years after onset. Negative symptoms, in contrary to previous thinking, are not untreatable. Recently, investigators tend to support the possibility of a modest but direct effect of newer antipsychotic drugs on primary negative symptoms. (McPhillips,1997)

CONCLUSION

Base on the above argument, the author favours a dynamic imbalance of the neurotransmitter systems, mainly involving the interaction between glutamate and dopamine, to be the cause of the pathogenesis. The connection problem found in recent studies may not be "disconnection" but rather "isconnection" due to a proliferation and mis-directed re-wiring during the compensatory process. It does not favour the structural damage to a specific brain region or a transmitter system. Rather, the interaction and dynamic imbalance when one structure or one region is at fault can explain the symptoms which may be over-compensations. A "challenge - response" model is proposed. Adolescent development is a challenge, as are psychosocial stressors and the use of psychotropic medications. These would lead to response by the brain through chemical neurotransmission, synapse formation, gene expression etc. The therapeutic methods should aim not at enhancing or antagonising one neurotransmitter system, but the restoration of the imbalance or regulating the maladaptive mechanism.

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