Indian Journal of Clinical Biochemistry, 2008 / 23 (4) 307-327

REVIEW ARTICLE

THE BIOCHEMICAL WOMB OF SCHIZOPHRENIA: A REVIEW

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ABSTRACT

The conclusive identification of specific etiological factors or pathogenic processes in the illness of schizophrenia has remained elusive despite great technological progress. The convergence of state-of-art scientific studies in molecular genetics, molecular neuropathophysiology, in vivo brain imaging and psychopharmacology, however, indicates that we may be coming much closer to understanding the genesis of schizophrenia. In near future, the diagnosis and assessment of schizophrenia using biochemical markers may become a "dream come true" for the medical community as well as for the general population. An understanding of the biochemistry/ visa vis pathophysiology of schizophrenia is essential to the discovery of preventive measures and therapeutic intervention.

KEY WORDS

Schizophrenia, Neurobiology, Biochemical markers

INTRODUCTION

Schizophrenia is a relatively common, chronic, and frequently devastating neuropsychiatric disorder, affecting about one percent of the world's general population (1). It imposes a disproportionately large economic burden in terms of hospitalization, chronic treatment and rehabilitation, and lost productivity (2). The full syndrome is characterized by positive symptoms (delusions and hallucinations), negative symptoms (impaired cognition, volition and emotion) and substantial functional deterioration (e.g., work, interpersonal relationships, or self care) typically occurs, especially during the first five to ten years and then clinical deterioration reaches a plateau (3).

There is as yet no accepted biological validation of or laboratory test for the diagnosis of schizophrenia. The human suffering, family tragedies and financial burden caused by schizophrenia represent a tremendous challenge for the scientific community (4). Although some insights into the etiology of schizophrenia have been developed, an understanding of the illness on the molecular level remains elusive. Molecular genetics, neuroanatomy, neurophysiology, brain imaging and psychopharmacology thus represent important avenues for current research efforts (5).

Many researchers over the years had the general aim of finding a specific neurochemical deficiency in schizophrenia. Almost all of the known neurotransmitters in the brain have been considered as candidates for defective and/or altered neurotransmission systems in schizophrenia (6). This review summarizes the evidence so far regarding various biochemical alterations in neurotransmission systems in schizophrenia.

THE NEUROTRANSMITTER HYPOTHESIS OF SCHIZOPHRENIA

Several theories of schizophrenia are in prevalence; most of them implicating aberrant neurotransmission systems—in particular, aberrant dopaminergic, serotoninergic and glutamatergic systems. It is not clear however that to what extent any neurochemical findings reflect primary rather than secondary pathology, compensatory mechanisms, or

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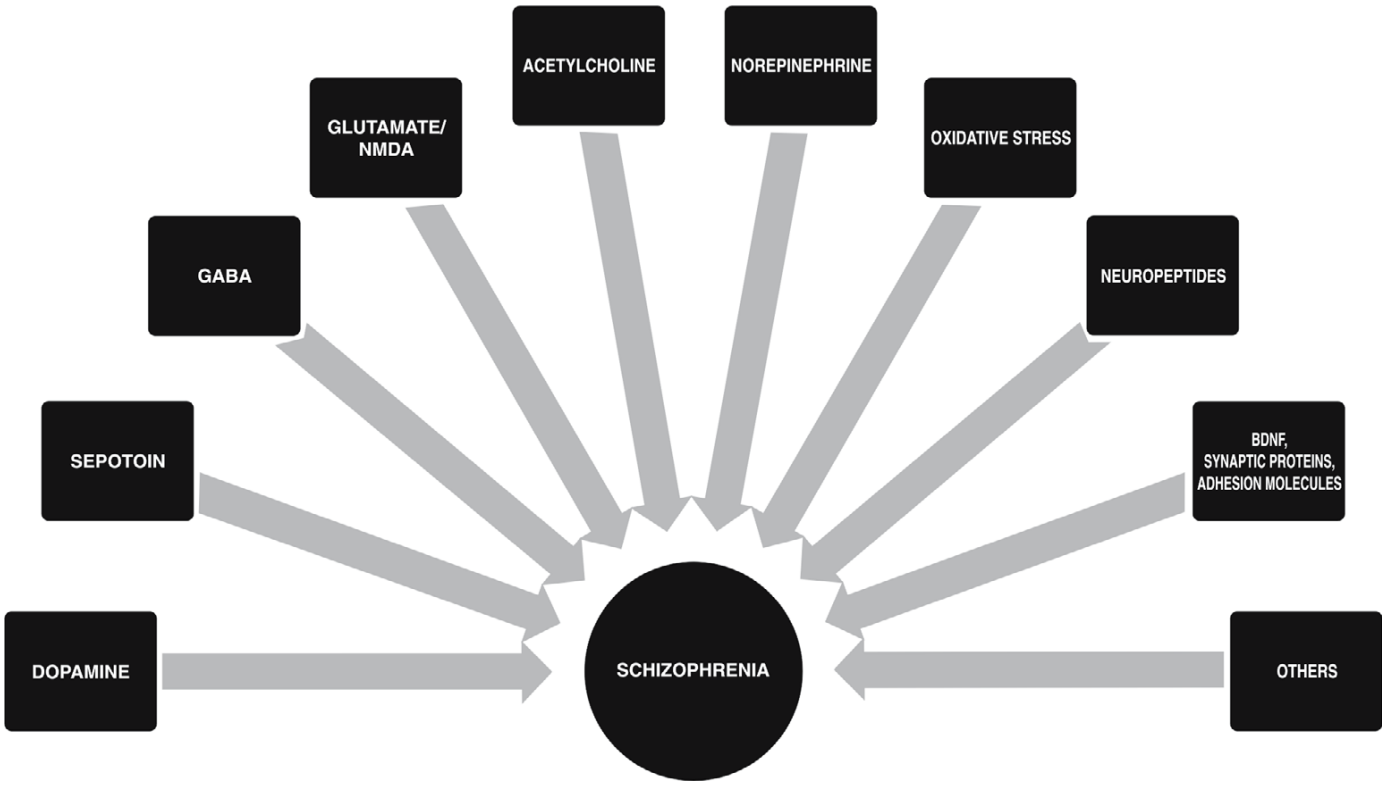

Figure 1. The Neurotransmitter Spectrum of Schizophrenia

environmental influences. The figure below summarizes the intriguing complicacies involved in the etiopathogenesis of schizophrenia.

THE DOPAMINE (DA) HYPOTHESIS

Dopaminergic neurons arising in basal ganglia have widespread projections to different areas of the brain. Five different types of dopamine receptors are now known to be present in human brain:

- D_1- prefrontal cortex, striatum
- D_2 – striatum, low concentration in medial temporal structures (hippocampus, entorhinal cortex, amygdala), thalamus, prefrontal cortex
- D_3 – striatum and ventral striatum
- D_4 - prefrontal cortex and hippocampus (have not been detected in the striatum)
- D_5 - hippocampus and entorhinal cortex

The classical "dopamine hypothesis of schizophrenia" postulates a hyperactivity of dopaminergic transmission at the dopamine D_2 receptor in the mesencephalic projections to the limbic striatum especially in the etiology of positive symptoms (8-10). Negative symptoms and EPS have been postulated to be related to deficits in dopaminergic activity in the mesocortical and nigro-striatal systems, respectively (10,11).

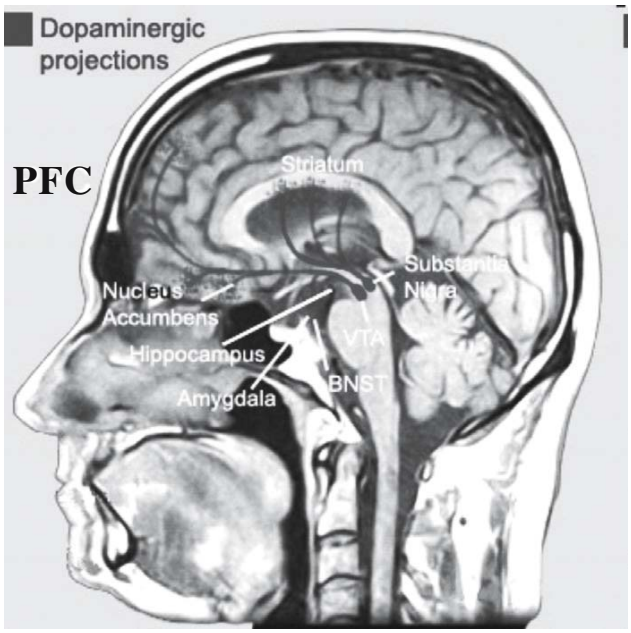

Figure2 : From: Guillin O & Laruelle M. Cellscience Reviews 2005; 2:79-107

The dopaminergic hypothesis of schizophrenia reposes on the major following facts: the therapeutic efficiency of neuroleptics (dopaminergic antagonists); a positive correlation between plasma homovanillic acid (metabolite of dopamine) concentration and the severity of schizophrenic illness; a higher density of dopaminergic D_2-receptors revealed by Positron Emission Tomography (PET), particularly in the striatum; and an abnormal plasmatic growth-hormone response to apomorphine (dopaminergic agonist) (12,13).

Psychopharmacological evidence supports the fact that all clinically useful antipsychotic medications are dopamine antagonists (14). Positron Emission Tomography (PET) studies suggest that an antipsychotic effect is obtained when D_2 receptor occupancy is between 60-70% and higher occupancy results in extrapyramidal side effects (15).

Several studies with plasma homovanillic acid (HVA), which is the major metabolite of dopamine, have also attempted to assess dopamine function in schizophrenia. It has been shown that 11-35% of plasma HVA comes from the brain (16-18). Other studies noted that the behavioral response to antipsychotic drugs (i.e., a decrease in psychosis levels) parallels a decrease in plasma HVA levels in schizophrenic patients over time (19-20). However, plasma HVA derives from both central and peripheral areas and from both noradrenergic (NA) and dopaminergic transmissions. The results from these studies would presumably be insensitive to counterbalanced changes in dopamine turnover in cortical and subcortical regions (21).

A model has been proposed that shows that the association between HVA and MHPG in plasma or urine under varying rates of NA metabolism can be used to obtain an estimate of the central DA neuronal contribution of HVA to plasma or urine. This estimate is called the central dopaminergic index (CDI) and suggests that only about 30 percent of the total plasma HVA concentration in schizophrenic patients is derived from central DA neurons. Since the CDI of plasma HVA is not likely to be confounded by NA activity, this tool may prove useful in disentangling the roles played by the DA and NA systems in schizophrenia (22). Overall, studies support the notion that although patterns of association exist between dopamine metabolite levels and psychosis individual effects and methodological constraints may make them more difficult to define (23).

Indirect dopamine agonists (e.g., L -dopa, cocaine, and amphetamines) can induce psychosis in healthy subjects and, at very low doses, provoke psychotic symptoms in schizophrenics (9). The dopamine hypothesis has received support from postmortem and PET indications of increased dopamine D_2 receptor levels in the brains of schizophrenic patients (24). However, it has been suggested that upregulation of D_2 receptor expression may be the result of adaptation to antipsychotic drug treatment rather than a biochemical abnormality intrinsic to schizophrenia. In fact, some PET studies show no significant difference in D_2 receptors densities between neuroleptic-naive schizophrenics and healthy controls (25).

Dopamine build-up may be caused by a faulty gene that code for the enzyme Dopamine-β-hydroxylase, which converts dopamine to norepinephrine. Blocking this enzyme with the drug disulfiram results in psychosis indistinguishable from schizophrenia in alcoholics who overdosed on disulfiram (26).

There is emerging evidence for a presynaptic dopaminergic abnormality in schizophrenia, implying dysfunction in presynaptic storage, vesicular transport, release, reuptake, and metabolic mechanisms in mesolimbic dopamine systems (27). It has been further hypothesized that dysregulation and hyper-responsiveness of presynaptic dopamine neurons could lead to lasting consequences through the induction of sensitization and/or oxidative stress (3,28). On the contrary, the functional activity of dopamine may be decreased in the neocortex in schizophrenia, which could be, at least partially, associated with negative symptoms (e.g., emotional or cognitive impairment) (3). Whether a dopamine hyperfunction or hypofunction occurs under minimal stress thus remains an open question.

A number of promising partial agonists of the D_2 receptor are currently in clinical trials (29). Drugs of this class, including 3-(3-hydroxyphenyl)-*N* -propylpiperidine, could stabilize dopaminergic tone, that is, they are capable of alleviating signs of hyperdopaminergia without reducing dopaminergic function below the baseline level (30). Aripiprazole is a dopamine autoreceptor partial agonist and postsynaptic D_2 receptor antagonist, and has modest affinity for 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and 5-HT_7 receptors (31).

The molecular characterization of other dopamine receptor families has changed the number of potential sites of dysfunction and the mechanism by which it might occur in schizophrenia. There are reports of altered D_1, D_3 and D_4 receptors but these are either unconfirmed or contradicted by other studies (32-35).

Considerable data suggest that heritable prefrontal dopamine function abnormalities are prominent features of schizophrenia that may relate to a unique role for catechol-o-methyl transferase (COMT) in dopamine-mediated prefrontal information processing in working memory (36). COMT inhibitors can improve working memory in both rodents and humans (37-38). Interestingly, studies of COMT-deficient mice have demonstrated that dopamine levels are increased in the prefrontal cortex but not in the striatum, and that memory performance is enhanced (39).

Recently it was demonstrated that a COMT polymorphism (a valine residue at a position of methionine residue), which results in a COMT enzyme that is four times more active, occurs at higher rates in both schizophrenics and their unaffected siblings. Moreover, these subjects performed relatively poorly on a neuropsychological test of working memory and manifested inefficient brain activation as assessed by functional magnetic resonance imaging (FMRI) suggesting that the high-activity allele impairs prefrontal cognition and physiology, and thus, may increase the risk for schizophrenia (40).

But a recent study of 2800 individuals and a major review concludes that no robust conclusions about the relationship between *COMT* and schizophrenia can be drawn and virtually exclude a simple relationship between schizophrenia and the Val/Met variant previously thought to dominate COMT function (41-42).

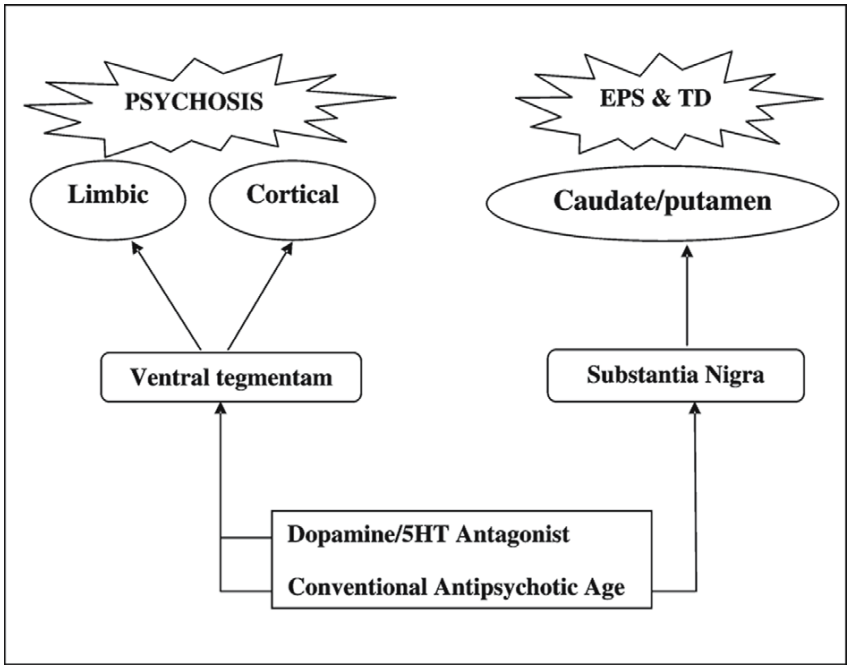

Figure 3. Comparative actions of atypical and conventional antipsychotic medications

The intricacies of dopaminergic neurochemical wiring in the brain still remain fully unearthed but in spite of this ongoing debate on the exact status of dopamine in the etiopathogenesis of schizophrenia, dopamine hypothesis continues to occupy the central seat of neurochemical theory.

The Serotoninergic System

A great deal of attention has been focused on the involvement of serotonin (5-HT) in the pathophysiology of schizophrenia (43). The major breakthrough restoring interest in the role of 5-HT in schizophrenia is the identification of 14 distinct 5-HT receptor subtypes and their extensive impact on multiple neurotransmitters and behaviors (44).

The "serotonin hypothesis of schizophrenia" is informed by several observations: a) serotonin receptors are involved in the psychotomimetic and psychotogenic properties of hallucinogens [e.g., lysergic acid diethylamide (LSD)]; b) a number of direct and indirect 5-HT agonists (fenfluramine, 5-hydroxytryptophan [5-HTP], mCPP, and tryptophan) sometimes exacerbate symptoms of schizophrenia; c) the number of cortical 5-HT_{2A} and 5-HT_{1A} receptors is altered in schizophrenic brains; d) 5-HT_{2A} and 5-HT_{1A} receptors play a role in the therapeutic and/or side-effect profiles of atypical antipsychotics (e.g., clozapine); e) certain polymorphisms of the 5-HT_{2A} receptor gene are associated with schizophrenia; f) the trophic role of serotonin in neurodevelopment may be usurped in schizophrenia; g) 5-HT_{2A} receptor–mediated activation of the prefrontal cortex may be impaired in some schizophrenics; and h) serotoninergic and dopaminergic systems are interdependent and may be simultaneously affected in schizophrenia (43, 45-49).

Many studies of schizophrenia have also demonstrated alterations in: 1) serotonergic neurotransmission as measured by the concentration of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HI_{AA}) and the density of 5-HT_{1A} or 5-HT_{2A} receptors in post-mortem brain specimens; and 2) abnormalities of 5-HT and its metabolites in blood or CSF (50).

The maximum number of platelet 5-HT_{2A} receptors is increased in drug-naïve schizophrenic patients that return to normal following treatment with antipsychotic medications (51). In addition, the alteration of serotonin transporters has been reported (52).

The notion that 5-HT receptors play a role in mediating atypical antipsychotic effects has increasingly gained widespread acceptance. The ability of atypical neuroleptics such as clozapine to achieve an antipsychotic effect with lower rates of extrapyramidal symptoms is said to be because of their robust antagonism at 5-HT receptors and weak antagonism at D_2 receptors (53). Of the other 5-HT receptors with which these drugs directly interact, the 5-HT_{1a} and 5-HT_{2c} receptors are the strongest candidates for contributing to their antipsychotic action and low EPS profile. The 5-HT_6 and 5-HT_7 receptors may also be of some importance. Stimulation of the 5-HT_{1a} receptor appears to produce many of the same effects as antagonism of the 5-HT_{2a} receptor while antagonism of the 5-HT_{2c} receptor appears to diminish some of the actions of 5-HT_{2a} receptor antagonism (54).

The fact that many atypical antipsychotic agents are potent 5-HT_{2A} antagonist is interesting in light of the evidence that stimulation of 5-HT_{2A} or possibly 5-HT_{2C} receptors is the basis for the hallucinogenic action of indoleamines such as LSD or psilocybin (55). Clozapine and other potent 5-HT_{2A} antagonists such as olanzapine and mianserin ameliorate the psychosis due to levodopa or direct-acting DA agonists such as bromocriptine and pergolide in patients with Parkinson's disease. This conclusion is supported by the evidence that two potent D_4 antagonists were ineffective antipsychotic agents in controlled clinical trials of schizophrenics (56).

CSF 5-HI_{AA} levels, at best, provide an integrated measure of serotonergic activity in multiple brain regions. They cannot distinguish between selective changes in different regions or provide any index of the necessary integration between serotonergic activity and that of other neurotransmitters (50).

Neuroendocrine challenge studies are consistent with an altered sensitivity of 5-HT_{2A} receptors, since: 1) most investigators have found blunted responses to indirect-acting 5-HT agonists (e.g., fenfluramine) and cimetidine or 5-$HT_{2A/2C}$ agonists; and 2) atypical antipsychotic agents block the neuroendocrine responses to serotonergic agonists. Among the serotonergic drugs that have been studied in schizophrenia are: 1) fenfluramine (which induces the release of 5-HT), 2)m-chlorophenylpiperazine (mCPP a full or partial agonist at multiple 5-HT receptors); 3) L-tryptophan (a precursor of 5-HT, and thus, a potential agonist at all 5-HT receptors); and 4) MK-212 (a potent 5-HT_{2A} and 5-HT_{2C} agonist, and a weak agonist at 5-HT_{1A} receptors). Common findings of these studies include blunted prolactin (PRL), cortisol or temperature response (50).

A number of authors have measured 5-HT receptor density in post-mortem brain tissue from patients with schizophrenia. There is strong evidence for a down regulation of 5-HT_{2A} receptors in the cortex of schizophrenics. Since 5-HT_{2A} receptor density is decreased by 5-HT_{2A} receptor stimulation, this may be the result of increased 5-HT_{2A} receptor activity. Blockade of this activity by drugs such as clozapine and other atypical antipsychotic agents that are 5-HT_{2A} receptor antagonists may contribute to their clinical profile (57-59). There is some evidence in support of 5-HT_{1A} receptor density increase in specific cortical areas in schizophrenia (60-62). It is noteworthy that the dorsolateral prefrontal cortex had both decreased 5-HT_{2A} and increased 5-HT_{1A} receptor binding sites. This is the area of the brain that has been most implicated in schizophrenia. The resulting imbalance of the 5-HT_{1A} to 5-HT_{2A} receptor ratio could contribute to abnormalities in the function of cortical association pathways (50).

There is strong evidence indicating that the 5-HT system modulates dopaminergic activity and vice versa. This interaction occurs at the level of the cell bodies in the ventral tegmentum, substantia nigra and medial and dorsal raphe, as well as at various terminal areas of these three nuclei. According to this new found "serotonin-dopamine hypothesis" there might be enhanced dopaminergic and serotonergic neurotransmission in subcortical areas in schizophrenia, leading to positive symptoms, and decreased dopaminergic and serotonergic activity, perhaps in the prefrontal cortex, which led to negative symptoms. 5-HT activity has an overall inhibitory effect upon dopaminergic function (63-68).

Thus, it can be said about the role of 5-HT in schizophrenia that the functional alterations in the serotonergic system affect other neurotransmitter system/s and cause the various behavioral disturbances in schizophrenia. Future studies examining the role of multiple 5-HT receptors in the etiopathology and/or treatment of schizophrenia are likely to yield productive results (50).

Glutamatergic Hypothesis

Excitatory amino acid Glutamate is said to be intimately associated with brain growth and development of schizophrenic illness. Several aspects of brain development and functions of excitatory amino acids have been linked to the pathology of schizophrenia. First, glutamate receptors stimulate neurite outgrowth, synaptogenesis and maturation of synapse in the developing brain. Second, the excitatory amino acids also play a critical role in neurotoxicity. Third, several neural tracts and circuits have glutamate as their

neurotransmitter along with synaptic glutamate receptors and can result in some of the clinical findings of schizophrenia. Finally, glutamate and dopaminergic systems are known to modulate each other's activity levels in a reciprocal fashion (69-75).

Finding of reduced concentrations of glutamate in the CSF of patients with schizophrenia in eighties led to the proposition that decreased glutamatergic activity may be an etiologic factor in the disorder. This finding was replicated by some but not all subsequent studies (76).

An alteration in glutamate receptor density in several brain areas has been reported including prefrontal and left temporal cortex (77-79). A decrease in mRNA of all non-NMDA receptors has been demonstrated in the hippocampus and a reduction in NR_1 mRNA levels has been reported in the superior temporal cortex of a subgroup of patients with schizophrenia showing significant cognitive deterioration (80-81).

It has been observed that competitive antagonism of NMDA-receptors has psychotomimetic effects (82). Phencyclidine (PCP) and ketamine, that are potent non-competitive antagonists of the NMDA subtype of glutamate receptor (NMDA-R) induce schizophrenia-like symptoms in healthy individuals and worsen some symptoms in schizophrenia (5). One of the features that distinguish NMDA-R antagonists from other psychotogenic drugs such as amphetamine and LSD is the degree to which they produce frontal cognitive deficits that mimic schizophrenia (83). Partial deletion of the gene encoding a form of the NMDA receptor causes the same behavioral abnormalities as phencyclidine (84).

Decreased NMDA-R function may thus be a predisposing or causative factor in schizophrenia (85-87). Postmortem studies of schizophrenics additionally indicate abnormalities in pre- and postsynaptic glutamatergic indices. NMDA-R hypofunction in the cortical association pathways could be responsible for a variety of cognitive and other negative symptoms and, in mice, partial deletion of the NMDA-R1 (NR1) subunit causes the same behavioral abnormalities as PCP (30, 84). In addition, the NR1 hypomorphic animals manifest reduced [^{14} C]-2-deoxygluose uptake in the medial prefrontal and anterior cingulate cortices, as is observed in chronic schizophrenic patients (88).

The existence of anatomical and functional interrelationships between dopamine and glutamate systems in the central nervous system suggests that inhibition of the NMDA-R would enhance dopamine neurotransmission (89-91). In humans, PET studies of dopamine receptor occupancy after acute administration of ketamine suggest that the NMDA-R antagonists increase dopamine release in the striatum. In contrast, chronic administration of NMDA-R antagonists elicits decreased dopamine release (92-93).

It has been recently shown that both PCP and ketamine have direct effects on D_2 and 5-HT_2 receptors. It has also been proposed that NMDA-R antagonists can cause an excess compensatory release of glutamate that can overactivate unoccupied non-NMDA glutamate receptors, including α-amino-3-hydroxy-5-methy-isoxazole-4-propionic acid (AMPA) and kainate receptors. The release of glutamate in response to NMDA-R antagonists might in part be responsible for their behavioral effects (94-95).

The role of metabotropic glutamate receptors (mGluRs) is also under consideration. The mGluRs levels were found increased in the orbitofrontal cortex but not in prefrontal cortex (96). Excitatory amino acid transporters (EAATs) may also be the markers of glutamatergic synapse abnormalities as a decrease in the EAAT3mRNA expression has been found in the striatum of schizophrenic subjects (97). Further studies are required to confirm whether this decrease reflects a loss of glutamatergic cortico-striatal pathways or not.

If schizophrenia involves diminished NMDA receptor activity, then one would predict that drugs activating the receptor might be therapeutic. The glutamate theory has been bolstered by several studies establishing that treatment of schizophrenic patients with glycine, D-serine or cycloserine causes symptomatic improvement (76).

A number of agents that interact directly with the glutamatergic system are currently in various stages of development. Examples of the new "glutamate-based" agents are the glycine site agonists, glycine reuptake inhibitors, glutamate release inhibitors, AMPA agonists and antagonists, ampakines and drugs acting on different subtypes of metabotropic glutamate receptors (76, 83, 90).

Amino Acid Disturbances: Glycine, Serine and Homocysteine

Amino acid disturbances may contribute significantly to the pathophysiology of schizophrenia. Glutamatergic dysfunction has already been discussed and associated with this are those that act through NMDA-glutamate receptors - glycine, serine and homocysteine.

NMDA receptors in brain are regulated by glycine, acting via a strychnine-insensitive regulatory site, and by glycine (GlyT1) transporters that maintain low glycine levels in the immediate vicinity of the NMDA receptor complex. Clinical studies with the NMDA/ glycine-site agonists glycine and D-serine indicate significant improvements in negative and cognitive symptoms of schizophrenia, supporting the concept that reduced activation of the glycine binding site of the NMDA receptor contributes substantially to ongoing symptoms. In several glycine trials in schizophrenia, low pretreatment plasma glycine levels predicted treatment response, suggesting that reduced glycine concentrations may be of particular importance (98).

Two recent studies demonstrated low glycine levels, low serine levels and lower glycine-serine ratios in schizophrenics, and even predicted higher levels of negative symptoms. Low glycine levels persist even in medicated patients with schizophrenia, although levels may differ by medication types. In particular, glycine levels may be higher among patients receiving clozapine, potentially explaining the differential effectiveness of NMDA modulators when used in combination with clozapine or with other antipsychotics (99-101).

In addition to being associated with lower levels of positive NMDA modulators, schizophrenia may also be associated with higher levels of endogenous NMDA antagonists, in particular homocysteine. Homocysteine, a sulfur-containing amino acid, acts as a partial antagonist at the glycine site of the NMDA receptor when glycine levels are in the physiologic range. Homocysteine has been shown to act as an *N*-methyl-D-aspartate (NMDA) receptor agonist when glycine levels are pathologically elevated. At high concentrations, homocysteine may activate the NMDA receptor glutamate site, leading to increased susceptibility to excitotoxicity. However, at lower concentrations homocysteine also has the ability to act as a competitive antagonist at the NMDA receptor co-agonist glycine site. Neurodevelopment studies indicate that most adverse homocysteine effects are significantly blocked by glycine, reflecting reversal of the inhibitory actions of homocysteine (102-103).

Homocysteine is neurotoxic and it has been shown that stress can open the blood-brain barrier to some neurotoxic substances. Homocysteine may elicit DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. An oral methionine load has classically been reported to exacerbate schizophrenia and is of course converted to homocysteine (104-106).

Probable mechanisms by which homocysteine might cause developmental perturbations that increase risk for schizophrenia is through partial antagonism of the NMDA receptor and the induction of placental vasculopathy and other obstetric complications, which may lead to fetal hypoxia and adverse consequences for fetal development, including impaired brain growth and disturbances of neurotransmitter systems (107).

Deficiencies of several nutrients may give rise to maternal hyperhomocysteinemia. Folate is a prime candidate because this B vitamin donates a methyl group to homocysteine, permitting its transformation to methionine, and folate levels are inversely related to homocysteine levels. Human pregnancy is a period of increased maternal folate requirement and thus, of increased susceptibility to folate deficiency (108-110).

Other nutritional deficiencies that may be responsible for elevated homocysteine levels include vitamin B_{12}, which acts as a cofactor in the conversion of homocysteine to methionine, and vitamin B_6, a cofactor in the conversion of homocysteine to cystathionine and cysteine(108). Elevated homocysteine levels also result from genetic influences. One of the more promising candidates is the C677T polymorphism in the gene for methylenetetrahydrofolate reductase (*MTHFR*). Homozygosity for this thermolabile mutation causes a deficiency in methylenetetrahydrofolate, with a consequent reduction of the re-methylation of homocysteine to methionine and elevated homocysteine levels. This mutation has been associated with schizophrenia in some but not all studies (111).

Deficiencies of other enzymes, such as methionine synthase and cystathionine β-synthase, may also disrupt the metabolism of homocysteine and lead to an accumulation of homocysteine. Folic acid, cobalamin, and pyridoxine supplementation can markedly lower plasma homocysteine. Thus, if future studies support a causal link, then daily supplementation with these vitamins could prevent clinical deterioration in some patients with schizophrenia and continuation of folic acid supplementation into the second and third trimesters would merit evaluation as a strategy for prevention of schizophrenia in offspring (111).

Gabaergic System

One hypothesis concerning the neurobiological substrate of cognitive deficits in schizophrenia highlights the role of inhibitory cortical interneurons that use γ-aminobutyric acid (GABA) as their main neurotransmitter (112-114). There is abundant histopathological evidence of abnormalities in GABA

neurons and their postsynaptic receptors in the prefrontal and anterior cingulate cortices of schizophrenic patients (115-116).

The GABA interneurons are increasingly recognized as important for coordinating synchronized oscillations in sparse assemblies of pyramidal neurons; such oscillations are a plausible physiological substrate for perception, memory, and cognition and show alterations in schizophrenia (117-120). These observations predict that drugs modulating inhibitory transmission via GABA-A receptors could be relevant in treating cognitive deficits in schizophrenia (113, 121).

Schizophrenic brains exhibit a thirty to fifty percent reduction in the expression of reelin, a trophic glycoprotein that acts as a "stop" signal for neuronal migration during development in the prefrontal cortex and hippocampus (122). In adult brains, reelin is secreted preferentially by cortical GABAergic interneurons that binds to integrin receptors located on dendritic spines of pyramidal neurons or on GABAergic interneurons expressing the disabled-1 gene product (DAB1), a cytosolic adaptor protein that mediates reelin action (123).

It is intriguing that the uptake and release of GABA, the density of GABA transporter, the level of a major enzyme in GABA biosynthesis glutamic acid decarboxylase, and its mRNA expression have been reported to be reduced in the brain of schizophrenic patients (124-126).

Thus, if schizophrenic patients have reduced GABAergic function, their ability to inhibit increased glutamatergic activity might be deficient, thus making them more susceptible to excitotoxicity (83).

Cholinergic System

Although the above discussed altered neurotransmission hypotheses retain considerable theoretical strength, they do not explain all features of this disorder. Despite the limited experimental evidence for abnormal cholinergic neurotransmission in psychiatric disorders, increased understanding of the role of acetylcholine in the human brain and its relationship to other neurotransmitter systems has led to resurgence of interest in the cholinergic system in schizophrenia (127).

Impairments in attentional functions and capacities are central to the cognitive symptoms of schizophrenia and these depend on the integrity and activity of cortical cholinergic inputs. The neurobiological, behavioral, and cognitive effects of repeated exposure to psychostimulants (e.g., amphetamine) model the importance of cholinergic aspects of schizophrenia (128).

There is enough anatomical and pharmacological evidence indicating that cholinergic muscarinic receptors may modulate dopamine and glutamatergic neurons. Moreover, the fact that schizophrenics have sensory gating and cognitive dysfunction suggests a role for the cholinergic system in the etiology and therapy of these deficits. Research evaluating the effects of partial agonists of muscarinic receptors (e.g., Xanomeline) on cognitive and psychotic-like symptoms had shown promising results and may find utility in the treatment of schizophrenia in near future (129-131).

Adrenergic System

While the evidence for the importance of norepinephrine physiology in the etiology and treatment of depression is well known, the importance of norepinephrine in the pathophysiology and treatment of schizophrenia is relatively obscure. With the cognitive and behavioral activities of norepinephrine including focusing attention, working memory, and coping with challenges, the potential relevance of norepinephrine to the pathophysiology of schizophrenia is reasonable.

Norepinephrine is said to be an important player in the regulation of dopamine and serotonin (132). Locus ceruleus activity regulates midbrain dopamine neuron activity via increased norepinephrine and that this effect can be blocked by the alpha-1 antagonist prazosin, thereby indicating that regulation of midbrain dopamine neurons is via alpha-1 receptors (133). Animal models of schizophrenia, like conditioned avoidance and catalepsy, have shown that alpha-2 antagonist produce beneficial effects when added to a D_2 antagonist by indirectly activating alpha-1 receptor through increased norepinephrine release (134). Also, double-blind placebo-controlled studies have shown that adding alpha-2 antagonist idazoxan to fluphenazine leads to improvement in both positive and negative symptoms (135).

There is evidence that alpha-2 antagonism of risperidone may play a significant role in producing its atypical effects by regulating frontal cortex serotonin levels (136). However, studies of alpha-2 antagonists using other animal models of schizophrenia, like prepulse inhibition, do not share this view (137).

Central noradrenergic dysfunctions are also suggested by higher cerebrospinal fluid levels of norepinephrine, and a failure of suppression of its metabolite levels (3-methoxy-4-

hydroxy-phenylglycol (MHPG)) in plasma after administration of an alpha-2-adrenergic agonist (13).

The toxic effects of dopamine metabolites on norepinephrine neurons can also be a deciding factor in the etiopathogenesis of schizophrenia. Some of the dopamine is auto-oxidized to 6-hydroxydopamine and cause degeneration of peripheral sympathetic nerve terminals that results in a marked and long-lasting depletion of norepinephrine. Evidence supporting 6-hydroxydopamine as a neural degenerative agent of noradrenergic nerve endings comes from the isolation and identification of an odorous substance (known as trans-3-methyl-2-hexenoic acid, a metabolic product of 6-hydroxydopamine) found in the sweat of schizophrenics. Phenylethylamine derivatives with the same 2,4,5- substitution pattern as 6-hydroxydopamine were found to have high hallucinogenic activity in humans (138).

Considering all these possible mechanisms, it does appear that norepinephrine may provide a significant contribution to the understanding of schizophrenia and its treatment.

Neuropeptides

There is no longer any doubt that neuropeptide-containing neurons are altered in several neuropsychiatric disorders because of the fact that a variety of neuropeptides occur ubiquitously in brain regions. Efforts are now focused to determine the alternations in neuropeptide systems that are associated with schizophrenia, mood disorders, anxiety disorders, alcoholism and various neurodegenerative disorders (139). Targeting of neuropeptide neuromodulator systems, capable of concomitantly regulating several transmitter systems, represents a promising approach for the development of increasingly effective and side effect-free antipsychotic drugs (140).

a) N-Acetylaspartylglutamate / N-Acetyl Aspartate

N-acetylaspartylglutamate (NAAG) is an acidic dipeptide located in glutamatergic neurons and acts as an antagonist at NMDA receptors. Its metabolite N-acetyl aspartate (NAA) is considered a marker of neuronal function. The concentration of NAAG has been seen increased in the hippocampus, and the activity of glutamate carboxypeptidase II (GCP II), the enzyme that cleaves NAAG to produce glutamate and NAA, was selectively reduced in the frontal cortex, temporal cortex, and hippocampus in the schizophrenia brains (141-142).

Similarly, reduced NAA concentrations were found in frontal and temporal regions of schizophrenic patients on magnetic resonance spectroscopy (MRS) and altered NAA/creatine and NAA/choline ratios are also reported (143-146).

b) Somatostatin

Alterations in the inhibitory circuitry of the dorsolateral prefrontal cortex (DLPFC) in schizophrenia include a reduced expression of the messenger ribonucleic acid (mRNA) for somatostatin, a neuropeptide present in a subpopulation of GABA neurons. This alteration appears to be a downstream consequence of impaired neurotrophin signaling through the trkB receptor (147).

c) Neurotensin

Neurotensin is a tridecapeptide which fulfills many of the requisite criteria for a role as a central nervous system (CNS) neurotransmitter. Neurotensin is co-localized with dopaminergic neurons in the hypothalamus and midbrain and has been shown to interact with dopamine at physiological, anatomical and behavioral levels (148).

Because of its close association with the dopamine system, the role of neuropeptide Neurotensin (NT) in clinical disorders hypothesized to involve DA circuits such as schizophrenia, Parkinson's disease, and drug abuse has been closely scrutinized. In addition, NT neurotransmission has been implicated in regulation of the stress response, stress-induced gastric ulcers, temperature regulation, food consumption, and analgesia. NT also acts as a growth factor in a variety of human cancer cell lines derived from lung, colon, prostate, and pancreas (149).

Considerable evidence also exists concordant with the involvement of NT systems in the mechanism of action of antipsychotic drugs. The behavioral and biochemical effects of centrally administered NT remarkably resemble those of systemically administered antipsychotic drugs, and antipsychotic drugs increase NT neurotransmission. These interlaced findings led to the hypothesis that NT functions as an endogenous antipsychotic. Clinical studies in which CSF NT concentrations have been measured revealed a subset of schizophrenic patients with decreased CSF NT concentrations that are restored by effective antipsychotic drug treatment (150).

Increased nucleus accumbens NT neurotransmission, via the NT_1 receptor, can decrease the effects of activation of the mesolimbic dopamine system and disruption of the glutamatergic input from limbic cortices,

resembling the action of clozapine (151). There are reports that typical and atypical antipsychotic drugs differentially alter NT neurotransmission in nigrostriatal and mesolimbic regions affecting the side effect liability and efficacy, respectively (140).

Thus, it is reasonable to assume that drugs that directly modify the activity of NT systems, particularly NT receptor agonists, could plausibly represent a novel class of neuroleptics (150).

d) Cholecystokinin

Cholecystokinin (CCK) is involved in the physiologic modulation of pain perception and modulation of dopaminergic activity. Dopaminergic pathways are involved in the antidepressant-type responses triggered by both enkephalin catabolism inhibitors and CCKb receptor antagonists (152). Studies have evaluated the role of CCK in the pathogenesis of schizophrenia. Significant decreases in immunoreactivity and binding sites for CCK have been shown in the frontal cortex and hippocampus at necropsy of schizophrenic patients (153). Polymorphism of CCK-A receptor has been shown to be associated with presence of auditory hallucinations in schizophrenia (154).

e) Other Neuropeptides

Research is on for the search of other plausible neuropeptides that could have an influence on the disease of schizophrenia. Various polypeptides, viz., Antidiuretic hormone (ADH), Corticotropin, Endorphins and chromgranin are in focus of researchers but further studies are required to confirm their status in the neurochemistry of schizophrenia (155-158).

Hypothalamic-Pitutory-Adrenal (HPA) Axis

There is evidence suggesting dysfunction in the HPA axis in schizophrenia (159-160) that is demonstrated using the dexamethasone suppression test (DST). Nonsuppression, due to the lack of glucocorticoid secretion feedback mechanisms, occurs frequently in schizophrenia, with percentages varying between 11 and 55% (161-163). Moreover, several studies showed that basal cortisol levels are significantly higher in schizophrenic (schizophrenia) patients compared to normal controls, although these findings have not been consistent between studies (159, 164-165).

Studies also suggest a relationship between HPA activity and symptomatology in schizophrenia. Cortisol secretion has been associated with more severe positive symptoms in some (166-167), while in others it was associated with higher ratings of negative symptoms especially with DST nonsuppression (168-169).

Stressors, such as 2-deoxyglucose that is a glycopyruvic stressor, result in increased dopamine release in schizophrenic brains as reflected in increased plasma HVA, ACTH and cortisol levels in comparison to normal subjects suggesting that patients with schizophrenia may have a greater susceptibility to subcortical dopaminergic release under stress (170-171). Taken together, these results suggest that HPA axis dysregulation/activation and hypercortisolemia are frequently present in schizophrenic patients.

The Immunological Markers

New insights into the complex functioning of immune system have improved our understanding of its role in the pathogenesis of schizophrenia. Growing evidence suggests that immune system functioning may be impaired in schizophrenia. A recent theory postulates that schizophrenia may primarily be a consequence of vascular inflammation in the brain. The theory proposes that abnormalities arise because genetically modulated inflammatory reactions damage the micro-vascular system in response to environmental agents such as infections, hypoxia, and physical trauma (172-173).

Both innate and specific cellular arms of the immune system seem to be involved in the dysfunction of the immune system in schizophrenia. Findings such as alteration in inflammatory proteins, lymphocytes populations (T_4/T_8, CD_5), antibrain auto-antibodies, abnormal lymphocytes responses to mitogens, altered production of interleukins, changes in cytokine levels in blood and CSF of drug-resistant as well as drug-naïve patients have lead to two main hypotheses: autoimmunity and immunologic incompetence (174-179, 13).

Acute Phase Proteins (APP) like ceruloplasmin, C_3, C_4, etc., is a group of proteins whose plasma levels increase in response to inflammation (180). Most of the investigations that studied the relationship between ceruloplasmin and schizophrenia have found elevated levels of ceruloplasmin in schizophrenic patients, although decreased levels or normal levels have also been found (181-184). In a recent study, Ceruloplasmin, C_3 and C_4 blood levels were found as useful peripheral biological markers of negative acute paranoid schizophrenic symptoms (185). An upregulation of APP genes has been found in schizophrenia, especially in the prefrontal cortex, and that that these genes overlap in the schizophrenia

susceptibility loci. It has been suggested that acute phase reaction may be an aetiological agent in the pathophysiology of schizophrenia, but not just an accompanying symptom (186-188).

Cytokines too have their inputs. In addition to providing communication between immune cells, specific cytokines play a role in signaling the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioral changes (189-190). Altered levels of IL-6, TNF-α, IL-2 and IFN-γ are widely reported (191-193).

Cytokine IL-2 exerts numerous effects within the immune as well as the central nervous system and is thought to serve as a humoral signal in their communication at different levels of regulation (194). The data indicate that IL-2 and IL-6 are potent activators of the HPA axis, which provide additional evidence to support the hypothesis that hypercortisolemia in schizophrenia may be mediated by the elevated cytokines (195). All these alterations may reflect a genetic background or a non-specific stress response. Several reports on other cytokines await confirmation (191, 196).

It has recently been shown that inflammation can modify myelination levels on transplanted oligodendrocyte precursors and that oligodendrocyte precursor responses are dependent on the presence of cytokines. Thus, increased expression of inflammatory genes in schizophrenic subjects may affect myelin producing cells, offering a possible link between the inflammatory and the myelin hypothesis of the disease (173).

The relationship between schizophrenia and immunological factors is further supported by the existence of psychotomimetic effects that cytokines produce in non-psychiatric patients (197). Antipsychotic medications have been found to at least partially normalize abnormal immune alterations in schizophrenia and may be useful for predicting the neuroleptic response (193,198). Based on the immunology-inflammatory hypothesis of schizophrenia, some authors have treated schizophrenic patients with a combination of antipsychotics and anti-inflammatory drugs, obtaining a positive effect on psychopathology (199). Further research is still needed before use of anti-inflammatory drugs can be recommended in the treatment of schizophrenia.

Neurosteroid system

Because Neuroactive steroids (NASs) modulate neurotransmitter systems that are implicated in the pathology of schizophrenia, recent research has focused on examining the role that NASs play in the illness. Although research in this area is relatively new, it appears that NASs may potentially be implicated in the pathophysiology of the illness (200). Classical steroid hormones (for example, cortisol, dihydrotestosterone, and aldosterone) exert their effects via genomic mechanisms. The term “neuroactive steroids” was later coined to describe those steroids that exhibit rapid, nongenomic (but may produce genomic effects) effects on neuronal excitability by interacting with, and modulating the activity of, cell surface ligand-gated ion channel receptors, including $GABA_A$ and NMDA receptors (201-202).

NASs can be synthesized in the brain and in the periphery from cholesterol. NAS synthetic enzymes are present in peripheral endocrine glands and in glia and nerve cells in the brain. Examples of NASs include Pregnenolone (PREG) and its sulfate (PREGS), dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), 3a-hydroxy ring A-reduced pregnane steroids (3a, 5a-tetrahydroprogesteroneTHP and 3a, 5a-tetrahydrodeoxycorticosteroneTHDOC), androsterone, progesterone (PROG), testosterone, cortisol and estrogen.

NASs play a modulatory role in the central nervous system and affect many neurotransmitter systems. PREG and DHEA may be memory enhancing, and 3a-hydroxy ring A-reduced pregnane steroids exhibit sedative, hypnotic, anesthetic, and anxiolytic properties. Neuroactive steroids modulate other neurotransmitter receptors, including nicotinic acetylcholine, AMPA, kainite, oxytocin, sigma, glycine, and serotonin receptors (203-204). NASs synthesized in the brain and the periphery are among the most selective, potent, and efficacious allosteric modulators of the $GABA_A$ receptor complex or NMDA receptors (205-206).

Research examining the effects of NASs in schizophrenia is a relatively new field with many unknowns and sometimes seemingly contradictory findings. However, altered circulating DHEA, DHEAS, testosterone, cortisol, PROG, and estrogen levels have been reported in patients with schizophrenia, and these NASs correlate, to varying degrees, with symptom severity (207-209).

Interestingly, animal studies show that NAS concentrations may be affected by atypical but not typical antipsychotic treatment and may be a contributing factor in the efficacy of antipsychotic medication (210-211). In extension to this, NASs, such as DHEA and DHEAS, may also possess intrinsic antipsychotic properties (212).

Because of the lack of studies investigating NASs in drug-naive individuals with schizophrenia, it is unclear at this point whether altered steroid plasma levels are due to the disease process or to comorbid symptoms or are the result of treatment itself. Following NASs over time and during treatment would help to establish the precise changes in steroid concentrations and their relation to symptom domains in schizophrenia. The precise pharmacokinetic and pharmacodynamic profile of NAS is not yet known and thus, warrants further investigations.

Intracellular Ca^{++} signalling

Ca^{2+} is capable of inducing structural and cognitive deficits seen in schizophrenia. Evidence of the ability of antipsychotic drugs to affect Ca^{2+} signaling is also present. Based on these data, a hypothesis has been proposed that altered Ca^{2+} signaling may constitute the central unifying molecular pathology in schizophrenia. According to this hypothesis schizophrenia can result from alterations in multiple proteins and other molecules as long as these alterations lead to abnormalities in certain key aspects of intracellular Ca^{2+} signaling cascades (213).

Other neurochemical changes

The GABAergic system has been repeatedly postulated to mediate an inhibitory deficit as a central pathophysiological mechanism in schizophrenia, but the findings are controversial, at least in some areas, and mostly negative regarding treatment with drugs enhancing GABAergic activity. Although the GABAergic system should be further studied, especially in sensory gating model in humans, researchers recommend that an emphasis on other inhibitory mechanisms may prove useful and provide more effective treatment. The neuromodulator adenosine has been proposed as a candidate for this purpose. A state of adenosinergic hypoactivity in schizophrenia is suggested to be compatible not only with the inhibitory deficit but also with symptoms, clinical response to antipsychotics, impaired sensory gating, deteriorating course, increased smoking and sleep alterations reported in schizophrenia (214-215).

Changes in adhesion molecules (e.g., neural cell adhesion molecule), cytoskeletal proteins, neurotrophins (e.g., brain-derived neurotrophic factor, trkB), and other cell–cell signaling molecules have been observed in the brains of schizophrenic patients (216-217).

The suggestion that schizophrenia may be associated with synaptic malfunction or damage has led to studies of synaptic-associated proteins in post-mortem brains with conflicting results. Reduced levels of synaptophysin, mRNAs coding for synapsin 1A and 1B, synaptophysin, synaptic vesicle protein rab3a and synaptosomal associated protein SNAP-25 have been reported. Levels of the neural cell adhesion molecule N-CAM and syntaxin, non-phosphorylated MAPs and GAP-43 were found raised (218-225). Considering the early state of this work it would be premature to try and draw any conclusions. However it is clearly a field of great promise.

CONCLUSION

Central nervous system is one of the most complicated areas to understand in human physiology, guiding us to strive for perpetual revision of our understanding of the pathophysiology of mental illnesses and their treatment. Current data suggest that schizophrenia may represent a spectrum of phenotypic consequences that involve the dynamic gene–environment–development interactions posing a tremendous challenge for the clinical elaboration of mechanisms operative in schizophrenia.

Given the not so good treatment outcomes, we are reminded of the fact that our current understanding of the disease process in schizophrenia is far from complete. The need of the hour is to conclusively identify specific etiological factors and pathogenic processes in schizophrenia. In addition to improving prognoses, studies of the illness may more generally deepen our understanding of the working of the normal human brain. Search for biological markers may allow for early identification and proactive intervention in the disease process. Evidence ranging from neuroanatomy, neurophysiology, brain imaging, genetic analysis and psychopharmacology, is promising to provide a host of new insights into the etiology and treatment of schizophrenia. Thus, it is reasonable to expect major breakthroughs in our understanding of the pathophysiology of schizophrenia and in the development of effective therapeutic measures of curative potential in times to come.

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