Neurochemical Abnormalities in Schizophrenia

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Summary

This article reviews the findings focusing on neurochemical abnormalities of several brain areas in schizophrenia. Almost all of the known neurotransmitters in the brain have been considered to be candidates for altered neurotransmission systems in schizophrenia. The first hypothesis is originated from the overactive dopaminergic neurotransmission which can induce changes of other neurotransmitters such as GABA, serotonin, and glutamate. The abnormalities of these neurotransmission have been observed as the response to symptoms or pathology of the disease.

Keywords: schizophrenia, dopamine, gamma-aminobutyric acid, glutamate, serotonin

Introduction

Schizophrenia is a severe mental disorder in which there is impaired judgement and loss of contact with reality. The lifetime prevalence of schizophrenia is approximately 0.5% to 1% worldwide (American Psychiatric Association, 1994). The fourth Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) (1994) is at present perhaps the most widely used for diagnosis of schizophrenia. Symptoms such as delusions, thought disorder, perceptual disturbances, incongruous mood, and increased motor function are referred to as positive symptoms, whereas poverty of speech, loss of emotional responsiveness, reduced motor function, and social withdrawal are referred to as negative symptoms. Schizophrenia has alternatively been categorized into Type I (primarily acute) and Type II (primarily chronic) groups by Crow (1980, 1985). These are considered distinct but potentially overlapping syndromes; patients with an acute disorder show mainly positive symptoms (Type I syndrome) and chronic patients with mainly negative symptoms (Type II syndrome). In this theory the cerebral atrophy of schizophrenia might underlie the negative symptoms (schizophrenia Type II) whereas the psychotic symptoms might involve dopamine neuronal systems (schizophrenia Type I) (Strange, 1992).

Many researches over recent years have 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 or altered neurotransmission systems in schizophrenia. The movement of research for considering particular neurotransmitters has been inspired by the ability of certain psychotic drugs such as amphetamine, lysergic acid diethylamide (LSD) or phencyclidine to induce in normal individual symptoms resembling more or less closely those seen in schizophrenics. Given that a particular drug is known to affect a particular neurotransmitter system, then it has been suggested that neurotransmission is altered in schizophrenia. This review illustrates the abnormalities of neurotransmissions in schizophrenia. The clinical profiles and antipsychotic drug treatment of schizophrenia will also be discussed in terms of pharmacological properties of the drugs.

Abnormal dopaminergic neurotransmission in schizophrenia

The classical dopaminergic hypothesis of schizophrenia proposes that hyperactivity of dopamine transmission is responsible for the symptoms of the disorder (Carlsson, 1988; Carlsson and Lindqvist, 1963). This hypothesis originated with the discovery that all effective antipsychotic

and that dopamine-releasing agents such as amphetamine can produce a paranoid psychosis (Randrup and Munkvad, 1965).

With regard to clinical presentation, the positive psychotic symptoms (i.e., hallucinations, delusions, thought disorganisation) are more easily elicited by dopamine agonist treatment than negative symptoms (i.e., blunted affect, social withdrawal, decreased cognitive function) and may be better treated with D2 antagonist drugs (Crow, 1980). Thus the overactive dopamine hypothesis of schizophrenia may be more applicable to positive than to negative psychotic symptoms.

There is emerging evidence for a presynaptic dopaminergic abnormality in schizophrenia, with positron emission tomography (PET) and single photon emission tomography displacement studies indicating an elevated dopamine release in response to amphetamine (Breier et al., 1997; Laruelle et al., 1992). This implies a dysregulation and hyperresponsiveness of dopaminergic neurones. Additionally, several studies with plasma homovanillic acid (HVA), which is the major metabolite of dopamine, have also attempted to assess dopamine function in schizophrenia; however, plasma HVA derives from both central and peripheral areas and from both noradrenergic and dopaminergic transmissions. The results from these studies have been variable, and would presumably be insensitive to counterbalanced changes in dopamine turnover in cortical and subcortical regions (Soares and Innis, 1999).

The molecular characterisation of other dopamine receptor families has changed the number of potential sites of dysfunction and the mechanisms by which it might occur in schizophrenia. There are reports of altered D1 (Okubo et al., 1997) and D3 (Gurevich et al., 1997) receptors in schizophrenia but these are either unconfirmed or contradicted by other studies (reviewed by Harrison, 1999). The D4 receptor has proven particularly controversial following a report that its density was increased several-fold in schizophrenia, seemingly independently of medication (Seeman et al., 1993). However, it appears that the result was due to a 'D4-like site' rather than the true D4 receptor (Reynolds, 1996; Seeman et al., 1995).

Abnormal GABAergic neurotransmission in schizophrenia

Schizophrenia also seems to involve a component of gamma-aminobutyric acid (GABA) transmission dysfunction. Post-mortem studies have reported a loss of GABAergic terminals, using ^{3}H-nipecotic acid binding to GABA uptake sites, in the hippocampus, amygdala, putamen and left temporal cortex, in schizophrenia (Reynolds et al., 1990; Simpson et al., 1989, 1992). However, this marker of GABA uptake sites has been found to be unchanged in the frontal cortex (Simpson et al., 1998). An increase in GABA-A receptor binding has been found in several brain regions, including the prefrontal cortex (Hanada et al., 1987; Benes, Vincent et al., 1996), the cingulate gyrus (Benes et al., 1992) and the hippocampus (Benes, Khan et al., 1996) in schizophrenia. Morphometric studies have found abnormalities in local circuit neurones within the schizophrenic cingulate cortex (Benes et al., 1991), and this alteration may actually represent increased cell packing density in the absence of changes in GABA neurone number which is indicative of reduced neuropil (Selemon et al., 1995).

Furthermore, schizophrenic prefrontal cortex show reduced levels of glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis (Akbarian et al., 1995) and altered axonal terminals of GABAergic chandelier cells (Woo et al., 1998). A reduction in parvalbumin-containing GABAergic interneurones has been observed in the prefrontal cortex (Beasley and Reynolds, 1997) and hippocampus (Zhang and Reynolds, 2002) in patients with schizophrenia.These studies have provided strong evidence that neurochemical abnormalities in the GABAergic system are implicated in the pathophysiology of schizophrenia.

Serotonergic dysfunction in schizophrenia

Abnormalities in serotonergic neurotransmission may also be involved in the pathophysiology of schizophrenia (Abi-Dargham et al., 1997; Bleich et al., 1988; Kapur and Remington, 1996). This idea has long been advocated because the hallucinogen LSD is a 5-HT agonist. 5-HT dysfunction in cortical areas in patients with schizophrenia has been supported by post-mortem studies which showed a decrease in 5-HT2A/C receptor density (Arora and Meltzer, 1991; Dean and Hayes, 1996; Gurevich and Joyce, 1997) and an increase in 5-HT1A receptor density in schizophrenic patients compared to controls (e.g. Hashimoto et al., 1993; Joyce et al., 1993; Simpson et al., 1996). An increase in maximum number (B_{max}) of platelet 5-HT2A receptors has been found in drug-naive schizophrenic patients, which declined to normal level after neuroleptic drugs treatment (Govitrapong et al., 2000). In addition, the alteration of serotonin transporters has been reported to be involved in schizophrenia. An increase in [3H]imipramine binding was seen in platelets of drug-naive schizophrenic patients (Govitrapong et al., 2002).

Moreover, 5-HT receptors play a role in mediating atypical antipsychotic effects. The ability of atypical antipsychotic drug is to achieve an antipsychotic effect with lower rates of extrapyramidal symptoms compared to conventional antipsychotic drug. It has been proposed that potent 5-HT2A receptor antagonism together with weak dopamine D2 receptor antagonism are the principal pharmacologic property of atypical antipsychotic drugs (Meltzer et al., 1989; Meltzer et al., 2003). Moreover, 5-HT receptor genes have received much investigative attention in schizophrenia. It has been reported a positive association between A and C polymorphism at position 102 of the 5-HT2A receptor gene and schizophrenia (Berry et al., 2003; Ohara et al., 1999) and the various mutations in human 5-HT receptor variants (Gothert et al., 1998). These results provide evidence to support the involvement of 5-HT receptor genes in schizophrenia.

Abnormal glutamatergic neurotransmission in schizophrenia

Glutamatergic neurotransmission has been demonstrated to be involved in a variety of normal CNS functions (e.g. Collingridge, 1987; Tocco et al., 1992). There are many aspects of brain development and function of excitatory amino acids that have been linked to the pathology of schizophrenia. First, glutamate receptors stimulate neurite outgrowth, synaptogenesis and maturation of synapse in the developing brain (Court et al., 1993; McDonald and Johnston, 1990). Second, the excitatory amino acids also play a critical role in neurotoxicity (Choi, 1988; Coyle and Puttfarcken, 1993). Third, connecting tracts, a dysfunction of which has been implicated in schizophrenia, including corticostriatal, thalamocortical, and corticocortical association fibres, utilize glutamate as a transmitter and exhibit clusters of glutamate receptors at sites of synaptic contact (Huntley et al., 1994). Abnormalities of glutamatergic transmission in these connecting pathways could produce some of the clinical findings of schizophrenia (Egan and Weinberger, 1997). Finally, glutamatergic and dopaminergic systems are closely integrated, as each modulates activity levels of the other (Grace, 1991). Models positing abnormalities in glutamatergic function are quite compatible with dopaminergic models of schizophrenia, since reciprocal changes in dopaminergic activity might occur in response to glutamatergic dysregulation (Carlsson and Carlsson, 1990; Goff and Wine, 1997).

The idea of glutamatergic neurotransmission involvement in the pathophysiology of schizophrenia is interesting. The first observation of reduced glutamate levels in spinal fluid of schizophrenic patients was used to suggest reduced glutamatergic function in the illness (Kim et al., 1980) although this was not replicated successfully by other studies (Gattaz et al., 1985; Korpi et al., 1987; Macciardi et al., 1990). The hypothesis remains interesting because of the study involving phencyclidine (PCP), a drug that can block glutamate at N-methyl-D-aspartate (NMDA) receptors. The demonstration that PCP antagonises glutamate is the basis of the hypothesis that

antiglutamatergic actions might be associated with the mechanism of endogenous psychosis. Moreover, it has recently been observed that other pharmacological strategies for antagonising NMDA-sensitive glutamate transmission (i.e., competitive NMDA antagonists) also appear to be psychotomimetic (Kristensen et al., 1992). The abnormalities in presynaptic and postsynaptic glutamatergic neurotransmission in schizophrenia have also provided evidence to support the dysfunction of glutamatergic system in this disease (Eastwood et al., 1995, 1997; Kerwin et al., 1990; Porter et al., 1997).

An alteration in glutamate receptor density has been reported for several distinct brain areas in schizophrenia. An increase in 3H-kainate binding was seen in the prefrontal cortex of schizophrenic individuals (Nishikawa et al., 1983). Toru et al. (1988) reported the same increase and an inverse correlation between the increased kainate receptors in the prefrontal cortex and glutamic acid concentrations in related brain areas. Deakin and colleagues also reported an increase in kainate and aspartate receptor binding in the orbitofrontal cortex and a decrease in aspartate binding (putatively a marker for presynaptic glutamate reuptake sites) in the left temporal cortex (Deakin et al., 1989; Simpson et al., 1992). Increased N-[1-(2-thienyl)cyclohexyl]piperidine (TCP) binding (presumably at the PCP receptor) was also observed in the cortex (Simpson et al., 1992). A decrease in the mRNA of all non-NMDA receptors was demonstrated in the hippocampal cortex (CA3) (Harrison et al., 1991); consistent with this, a reduction in kainate receptors was also observed in this area of brain, without a change in NMDA or quisqualate sites (Kerwin et al., 1990). Increased MK-801 binding was found in several brain regions in schizophrenia, including the hippocampus and entorhinal cortex (Kornhuber et al., 1989). Moreover, an increase in radioligand binding to the glycine site on the obligate NR1 subunit of the NMDA receptor has been identified in the superior temporal cortex in schizophrenia (Nudmamud and Reynolds, 2001; Nudmamud-Thanoi and Reynolds, 2004). These results indicate a possible compensatory response to glutamatergic deficits in schizophrenia. A reduction in NR1 mRNA levels has been reported in the superior temporal cortex of a subgroup of patients with schizophrenia showing significant cognitive deterioration (Humphries et al., 1996). However, the study of Le Corre et al. (2000) was found an increase in the expression of NR1 mRNA, as measured with the NR1 pan probe which does not distinguish NR1 isoforms, in the superior temporal gyrus of patients with chronic schizophrenia. Morever, the validity of the finding has also been supported by the specificity of alterations in the level of the mRNA coding for the carboxy-terminus NR1-1 splice variant (Le Corre et al., 2000). This may provide further insight into the involvement of NR1 isoforms in schizophrenia. However, the basis and functional consequences of a specific alteration of the NR1 isoforms in patients with schizophrenia remain to be elucidated.

There are a few studies published which examine the involvement or role of the metabotropic glutamate receptors (mGluRs) in schizophrenia. The mGluR3 mRNA was not changed in schizophrenia in several areas of the prefrontal cortex, whereas mGluR5 mRNA levels were increased in the orbitofrontal cortex (Brodmann area 11), but not in areas 9 or 10 (Ohnuma et al., 1998).

Based on the finding of alteration in glutamate receptor expression in the striatum, the components of the glutamate synapse may be abnormal in this area of schizophrenia. Excitatory amino acid transporters (EAATs), a group of molecules essential for normal glutamatergic neurotransmission, may be markers of such an abnormality of glutamatergic synapse. A decrease of EAAT3 mRNA expression was found in the striatum of subjects with schizophrenia (McCullumsmith and Meador-Woodruf, 2002) and the report of decreased saturable [^{3}H]D-aspartate binding in striatal and accumbens tissues in schizophrenia which has been interpreted as reflecting effects on glutamatergic neuronal innervation (Aparicio-Legarza et al., 1997). Decreased EAAT3 in striatum

in schizophrenia also suggest deficits of cortico-striatal innervation and may contribute to the cognitive dysfunction in this disease. However, further studies of EAAT3 and other glutamatergic markers in the frontal cortex would be valuable to determine if changes of EAAT3 expression seen in striatum in the present study reflect from loss of glutamatergic cortico-striatal pathways.

Deficits of N-acetylaspartylglutamate and N-acetylaspartate in schizophrenia

N-acetylaspartylglutamate(NAAG), a neuropeptide found in glutamatergic neurones, and its metabolite N-acetylaspartate (NAA) have also been proposed in schizophrenia. Magnetic resonance spectroscopy (MRS) has been used to demonstrate deficits in the concentration of NAA in the frontal cortical and temporal lobe structures in schizophrenia. NAA is considered a marker of neuronal function and is metabolite of NAAG, a neuroactive peptide found in neurons (Neale et al., 2000). There are few post-mortem studies of NAA or NAAG in schizophrenia. Tsai and colleagues (1995) have reported increases in NAAG in hippocampus in schizophrenia but no significant changes in NAA. However, deficit of NAA and NAAG has been found in the superior temporal cortex in schizophrenic subjects, providing further evidence for neuronal dysfunction or neuronal loss in this region in schizophrenia (Nudmamud et al., 2003).

Antipsychotic drug treatment of schizophrenia

Psychopharmacological evidence supports the fact that all clinically useful antipsychotic are antidopaminergic (Reynolds and Czudek, 1995). Most antipsychotic drugs bind strongly to D2 receptors, and this action appears to account for both their antipsychotic activity and their propensity to cause movement disorders. Positron emission tomography (PET) studies suggest that an antipsychotic effect is obtained when D2 receptor occupancy is between 60 and 70%. However, higher levels of D2 receptor occupancy are associated with extrapyramidal movement disorders (Farde et al., 1992). Many antipsychotic drugs not only antagonise dopamine receptors but they also have a variety of effects on other receptors in the CNS such as adrenergic, serotonergic, muscarinic and histaminergic receptors which are discussed below.

There are two main types of antipsychotic drugs, which have been used for treatment of schizophrenia; typical or conventional (e.g. haloperidol and chlorpromazine) and atypical (e.g. clozapine, risperidone, olanzapine, quetiapine) antipsychotic drugs. The observation that typical antipsychotic agents are primarily dopamine antagonists was first made by Carlsson in 1963 (Carlsson and Lindquist, 1963). As mentioned above, typical antipsychotics possess the ability to cause extrapyramidal and other side effects such as weight gain, sexual dysfunction, galactorrhoea, sedation and postural hypotention (reviewed by Lieberman et al., 2000). Although these antipsychotic drugs are generally effective in alleviating positive symptoms (e.g., delusions and hallucinations) and reducing patient disability (Kawanishi et al., 2000), they do not fully alleviate negative symptoms (e.g., apathy, withdrawal and flattened affect) (Coffey, 1994).

Several antipsychotics have high affinity for several neurotransmitter receptors apart from the dopamine D2 receptor, and these pharmacological features can be related to the behavioural properties of the drugs. For example, chlorpromazine has an antagonist action at the α1-adrenoceptor, histamine H1-receptor and muscarinic cholinergic receptor. Blockade of α1-adrenoceptors and histamine H1-receptors give chlorpromazine a sedating profile, while α1-adrenoceptors blockade also causes hypotension. The anticholinergic activity may cause dry mouth, urinary difficulties, and constipation, while on the other hand offsetting the liability to produce extrapyramidal effects. Haloperidol and thioxanthenes such as flupenthixol and clopenthixol are potent dopamine receptor antagonists with few effects at other neurotransmitter receptors. They are not sedating but have a high propensity to cause extrapyramidal side effects (reviewed by Lieberman et al., 2000; Miyamoto et al., 2005).

In response to extrapyramidal side effect problems, atypical antipsychotic agents have been introduced in recent years. Atypical antipsychotics are associated with a significantly lower incidence and severity of treatment-emergent extrapyramidal symptoms and tardive dyskinesia than conventional agents (Meltzer, 1995). Atypical antipsychotic agents target other neurotransmitter receptors, most notably serotonin as well as dopamine (Jibson and Tandon, 1998; Meltzer, 1995). Meltzer and associates (1989) suggested that a high affinity for 5-HT2 receptors, relatively to that for D2 receptors, is a correlate of atypicality in many drugs. Certainly, acute administration of 5-HT2 receptor antagonists can reduce extrapyramidal side effects induced by typical antipsychotic drugs (Castelao et al., 1989). Moreover, it has been suggested that the 5-HT2 receptor is a site at which antipsychotic drugs may alleviate the negative symptoms of schizophrenia. An action of atypical antipsychotic drugs has also been proposed at other 5-HT receptors such as the 5-HT1A and 5-HT3 subtypes, α1- and α2-adrenoceptors, and other dopamine receptors including the D1 subtype (Reynolds and Czudek, 1995). For example, clozapine, the first atypical antipsychotic agent to show definite benefit in the treatment of patients whose psychotic symptoms had failed to respond to classical antipsychotic agents, is a weak D2 receptor antagonist but has a high affinity for 5-HT2 receptors (Meltzer et al., 1989). Clozapine also binds to histamine H1, α1-adrenergic and muscarinic cholinergic receptors (Shayegan and Stahl, 2004). Risperidone, a potent antagonist at both 5-HT2 receptors and D2 receptors, also possess α1-adrenoreceptor blocking properties, which can cause mild sedation and hypotention (Shayegan and Stahl, 2004). Olanzapine is a slightly weaker D2 receptor antagonist than risperidone but has anticholinergic and histamine H1 receptor blocking activity (Bymaster et al., 1996; Remington, 2003).

Although, recent research has provide strong evidence to support that atypical antipsychotics greatly reduce the risk of extrapyramidal symptoms and tardive dyskinesia, the exact nature and extent of the clinical advantages of the atypical drugs are not known. It also appears that several of atypical antipsychotic drugs have profound effects on weight, the greatest increases found in clozapine and olanzapine treatments (Allison et al., 1999). Moreover, atypical antipsychotic drugs have also been associated with alteration in glucose metabolism (Popli et al., 1997; Wirshing et al., 1998) and with elevation of blood cholesterol and lipids (Allison et al., 1999). However, it is clear that atypical antipsychotic drugs have made a great impression on the treatment of schizophrenia by reducing the incidence of extrapyramidal symptoms and alleviating the negative symptoms of schizophrenia.

Conclusion

There have been many studies investigating the neurotransmission abnormalities of several brain areas in schizophrenia. The first neurochemical hypothesis of schizophrenia is the dopaminergic hypothesis originated from the observation of hyperactivity of dopaminergic neurotransmission. However, the overactive dopamine is responsible for the positive symptoms than negative symptoms. The GABAergic hypothesis first emerged from the reciprocal natures of the actions of GABA and dopamine in basal ganglia. There have been reported the deficits of various markers of GABAergic neurones in schizophrenia, although this may restricted to a selective deficit of certain subtypes of GABAergic neurones. Moreover, several studies have been focusing on the specific pathologic evidence of glutamatergic dysfunction in schizophrenia. These have included increases in glutamatergic synapses, as well as selective deficits in a more general indicator of neuronal function NAA. Recent attention has focused on the involvement of serotonin in the pathophysiology of schizophrenia because serotonin receptors provide a potential basis for the beneficial effects of atypical antipsychotic drugs in terms of diminishing the incidence of extrapyramidal side effects and therapeutic effects against negative symptoms. However, the current researches intend to extend the neurochemical studies better to define

the abnormalities of neuronal function in the brain in schizophrenia. Moreover, the future directions in the molecular genetics of schizophrenia would be studied further for providing a greater understanding of genetic mechanisms which lead to improvements in therapeutic interventions.

Acknowledgements

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