International Journal of Pharmacognosy and Pharmaceutical Sciences

ISSN Print: 2706-7009
ISSN Online: 2706-7017
IJPPS 2021; 3(2): 28-30
www.pharmacognosyjournal.net
Received: 09-10-2021
Accepted: 08-11-2021

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Psychopharmacology of schizophrenia

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DOI: https://dx.doi.org/10.33545/27067009.2021.v3.i2a.88

Abstract
The revolution in psychopharmacology and biological psychiatry started by the introduction of chlorpromazine provided the first effective treatment for schizophrenia, as well as ideas and evidence about the pathophysiology of the illness. Brain imaging studies of receptor densities in young adults and children, or in patients with first-episode schizophrenia may be helpful in identifying early vulnerability factors.

Keywords: Brain imaging studies, psychiatry, psychopharmacology, schizophrenia

Introduction
The revolution in psychopharmacology and biological psychiatry started by the introduction of chlorpromazine provided the first effective treatment for schizophrenia, as well as ideas and evidence about the pathophysiology of the illness. There is evidence for a variety of neurochemical abnormalities, ranging from excessive to deficient concentrations of dopamine, serotonin, and glutamate, in studies comparing patients with schizophrenia and controls [1].

Dopamine
The leading hypothesis for schizophrenia is based upon the neurotransmitter dopamine. Dopaminergic neurons utilize the neurotransmitter dopamine (DA), which is synthesized in dopaminergic nerve terminals from the amino acid tyrosine after it is taken up into the neuron from the extracellular space and bloodstream by a tyrosine pump, or transporter. Tyrosine is converted into DA first by the rate-limiting enzyme tyrosine hydroxylase (TOH) and then by the enzyme DOPA decarboxylase (DDC) [2]. DA is then taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission. The DA neuron has a presynaptic transporter (reuptake pump) called DAT, which is unique for DA and which terminates DA's synaptic action by whisking it out of the synapse back into the presynaptic nerve terminal; there it can be restored in synaptic vesicles for subsequent reuse in another neurotransmission [3, 4]. DATs are not present in high density at the axon terminals of all DA neurons [5]. For example, in prefrontal cortex, DATs are relatively sparse and DA is inactivated by other mechanisms. Excess DA that escapes storage in synaptic vesicles can be destroyed within the neuron by the enzymes monoamine oxidase (MAO)-A or MAO-B, or outside the neuron by the enzyme catechol-*O*methyl- transferase (COMT). DA that diffuses away from synapses can also be transported by norepinephrine transporters (NETs) as a false substrate, and DA action will be terminated in this manner [6].
The DA transporter DAT and the vesicular transporter VMAT2 are both types of receptors. A plethora of additional dopamine receptors exist, including at least five pharmacological subtypes and several more molecular isoforms. Perhaps the most extensively investigated dopamine receptor is the dopamine 2 (D2) receptor, as it is stimulated by dopamine agonists for the treatment of Parkinson's disease, and blocked by dopamine antagonist antipsychotics for the treatment of schizophrenia. Dopamine 1, 2, 3, and 4 receptors are all blocked by some atypical antipsychotic drugs, but it is not clear to what extent dopamine 1, 3, or 4 receptors contribute to the clinical properties of these drugs [7-10].
Dopamine 2 receptors can be presynaptic, where they function as autoreceptors. Presynaptic D2 receptors thus act as gatekeepers, either allowing DA release when they are not occupied

by DA or inhibiting DA release when DA builds up in the synapse and occupies this gate keeping presynaptic autoreceptors. Such receptors are located either on the axon terminal or on the other end of the neuron in the somatodendritic area. In both cases, occupancy of these D2 receptors provides negative feedback input, or a braking action upon the release of dopamine from the presynaptic neuron [11]

The early 1960s implicated monoamines in the effects of the antipsychotic drugs and in the pathophysiology of schizophrenia and related drug side effects. Dopamine was one of the approximately 10 neurotransmitters distributed diffusely throughout the brain considered for pathophysiology of schizophrenia. The strongest support for a connection between dopamine function and schizophrenia came from studies showing that the clinical efficacy of drugs depends on their ability to block dopamine receptors, especially the dopamine D2 receptor subtype. These studies, carried out in the 1970s, used post-mortem brain tissue samples. The studies of dopamine metabolites in the cerebrospinal fluid and dopamine receptor binding that used *in vivo* functional neuroimaging provided additional evidence for dopamine abnormalities in schizophrenia [12-13].

Serotonin

In 1943, Swiss chemist Albert Hoffman ingested a new chemical compound—an ergot derivative called lysergic acid diethylamide (LSD). He experienced psychotic delusions and vivid hallucinations. That experience led him to the studies of drugs that produce psychotic symptoms. LSD seemed to enhance and potentiate the effects of serotonin in the brain. This finding initiated interest in the role of serotonin in schizophrenia, which was rekindled in the late 1980s and early 1990s with the development of atypical antipsychotic drugs, starting with clozapine and risperidone. These compounds appeared to work by blocking both dopamine D2 and serotonin 5HT2 receptors. This dual activity distinguished these newer, atypical antipsychotics from the older, typical antipsychotics that only blocked dopamine receptors. The serotonin-blocking action seemed to be an important part of the demonstrated efficacy for positive and, to some extent, negative symptoms of schizophrenia, as well as a reduction in the risk of tardive dyskinesia with atypical compared with typical antispychotics. Other, newer atypical antipsychotic agents developed since then, such as olanzapine, quetiapine, ziprasidone, and aripiprazole, share this dual neurotransmitter action. However, direct evidence for a primary role of serotonin in the pathophysiology of schizophrenia remains less convincing compared to that for dopamine [14].

Glutamate [15]

The search for other altered neurotransmitter systems involved in the pathophysiology of schizophrenia continues. Glutamate is a principal excitatory neurotransmitter distributed in the brain structures implicated in schizophrenia, such as the frontal cortex, hippocampus, and entorhinal cortex. Dopamine antagonizes the glutamate system, reducing glutamate release. The most suggestive evidence for the role of glutamate comes from the effects of a drug of abuse, phencyclidine (PCP), which serves as one of the putative neurochemical models for schizophrenia (Kornhuber, 1990). PCP binds to a specific site on the *N*-methyl-D-aspartate (NMDA) receptor and blocks the action of glutamate, which is considered to be responsible for its analgesic, anesthetic, and physiological effects. Supportive evidence comes from postmortem neuropathological studies reporting reduction in the glutamate transmitter binding in brains of people with schizophrenia. Deficient glutamate neurotransmission may be a primary or secondary, underlying mechanism in schizophrenia.

Other candidate neurotransmitters include aspartate, glycine, and gamma-aminobutyric acid (GABA), collectively dominating excitatory and inhibitory neurotransmission. Eventually, we might discover that dysregulation of several neurotransmitter systems is the unifying underlying mechanism of the disease [16-18].

Conclusion

Brain imaging studies of receptor densities in young adults and children, or in patients with first-episode schizophrenia may be helpful in identifying early vulnerability factors.

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