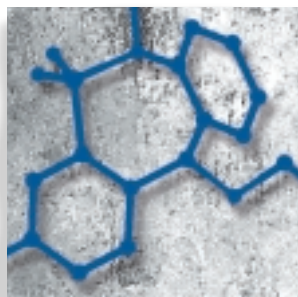


Pharmacological aspects

Developments in antipsychotic therapy with regard to hypotheses for schizophrenia

Manfred Ackenheil, MD; Klaus Weber, MPharm



The typical antipsychotic drugs like chlorpromazine and haloperidol were discovered by serendipity in the 1950s. A number of so-called “me too” drugs with similar chemical structures and modes of action were marketed in the subsequent years. The first atypical antipsychotic, clozapine, was an exception because it lacked some of the pharmacological properties of the typical antipsychotics related to the extrapyramidal motor system. This unique feature of clozapine significantly broadened understanding of the mode of action of antipsychotics, and created new hypotheses for schizophrenia. Hypothesis-orientated development of new drugs was only recently initiated. Abnormalities of the immune system in schizophrenia are being increasingly discussed: shifts in the levels of T helper cells subsets 1 and 2 (Th1 and Th2) have been observed, and studies with risperidone and the cyclooxygenase (COX2) inhibitor celecoxib as an add-on therapy have provided very promising results. The glutamate N-methyl-D-aspartate (NMDA) receptors have also been investigated in relation to neuropathological abnormalities in prefrontal areas of the brain of patients with schizophrenia. This may lead to new technologies like artificial networks related to the glutamate NMDA receptor system. New molecular biological techniques used in pharmacogenomics and proteomics offer new and exciting directions for future drug developments.

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Modern psychopharmacology began in the 1950s with the discovery of chlorpromazine and later haloperidol, drugs that were mainly discovered by serendipity. A vast number of similar phenothiazine- and butyrophenone-structured “me too” drugs with similar receptor binding profiles and therapeutic benefit were developed in the subsequent years (the so-called typical antipsychotics). The first real alternative to these drugs, in terms of mode of action and therapeutic outcome, became available with the introduction of clozapine (an atypical antipsychotic). The discovery of clozapine, and drugs like it, led to the dopamine hypothesis of schizophrenia,¹ which had a high impact on the search for neurotransmitter functions. However, the pathophysiology of schizophrenic symptoms and the related mechanism of action of antipsychotics could not be fully explained. It became increasingly evident that schizophrenia is both a complex disease, in which numerous factors contribute to the symptomatology, and a heterogeneous disease, most probably resulting from many different pathological causes. To underline this, no convincing evidence of abnormal biological findings valid for all or most of the patients with schizophrenia could be found. However, most clinical studies could demonstrate that antipsychotics were an effective treatment in schizophrenia and that they considerably ameliorated the outcome of the disease. The disadvantage of these drugs are their major side effects, such as parkinsonian symptoms, dyskinesia, and akathisia, due to the extrapyramidal motor system, and sometimes depressive effects.

Keywords: *schizophrenia; new treatment; immunology*

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Current knowledge suggests that the antipsychotic effect of the typical antipsychotics is mediated by the ability to reduce mesolimbic dopaminergic activity, whereas the side effects related to the extrapyramidal motor system are caused by a decreased dopaminergic activity in the nigrostriatal system.²

The introduction of clozapine with its unique pharmacological profile pointed to various theories. The unique effect of clozapine contributed to the relative preponderance of clozapine in the mesolimbic system. Other biochemical features have been related to its pharmacological profile. Clozapine has different affinities for the different dopamine receptor subtypes. There are two major types of dopamine receptor: D₁ and D₂ receptors. The D₁ receptor family includes D₁ and D₅, which are positively coupled to G-proteins, whereas the three D₂-like receptors, D₂, D₃, and D₄, inhibit the G-protein adenylate cyclase system. Clozapine has relatively stronger effects on the D₁ and D₂ receptors than other classic neuroleptics, which predominantly block the D₂ receptors; *o*-benzamides like sulpiride and amisulpride have a relatively strong effect on the D₃ receptors. In the case of clozapine, the ratio of D₄ to D₂ receptors is also crucial. In the last few years, this limited thinking focused on dopamine receptors has been abandoned in favor of a broader approach including other neurotransmitter systems in neuronal circuits. Clozapine and the new atypical antipsychotics also influence other neurotransmitter systems, notably the serotonin (5-hydroxytryptamine) 5-HT_{2A} receptor, the α_1 and α_2 adrenergic receptors, and sometimes the histaminic and muscarinic receptors.

Since biochemical and molecular genetic studies have failed to prove the dopamine hypothesis of schizophrenia and the broader view of other related neurocircuits, other theories of schizophrenia have been hypothesized (Figure 1).³

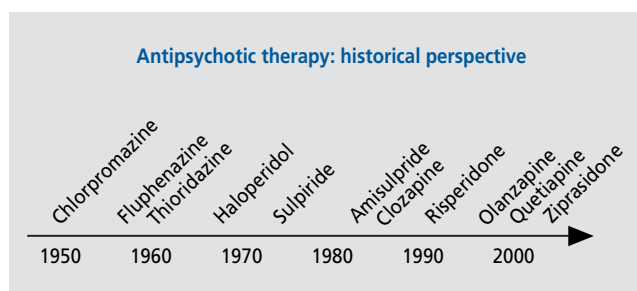


Figure 1. Historical development of major antipsychotic substances.³

Immunology and schizophrenia

In addition to hypotheses surrounding the classic neurotransmitters, the glutamate hypothesis and the immunological and neurodevelopmental theories for schizophrenia came into play. Abnormalities of the immune system are being increasingly discussed, and there is much evidence that abnormalities of the immune system play a major role in the development of schizophrenia. Links with seasonality of birth, influenza epidemics during gestation, pathological findings in cerebrospinal fluid (CSF), and genetic findings on the chromosomes with genes for immune response have been reported. We found an imbalance of the T helper subset 1 and 2 immune cells, Th1 and Th2, in schizophrenia.⁴ Th2 preponderance leads to a higher expression of humoral responses, which can be measured by the immunoglobulins, interleukin (IL) 4, and IL-6. The Th1 cells responsible for cellular response are related to IL-2 and IL- γ , which have lower levels in blood and CSF in schizophrenia (Table I). In relation to this theory, new treatment strategies may soon be available for patients with schizophrenia.

The question is whether it is possible to produce a reduction in the Th2 shift and an induction of the Th1 shift in schizophrenia. One of the current treatments for diseases of the immune system, like in rheumatology, is cyclooxygenase-2 (COX2) inhibitors. Interestingly, there is a negative correlation between the occurrence of schizophrenia and rheumatoid arthritis.⁵ COX2 enhances production of IL-6⁶ and IL-10⁷ via prostaglandin E₂, and inhibition of COX2 leads to a decrease in production of IL-10.

On the basis of these theories, we carried out a clinical trial with a COX2 inhibitor, celecoxib, as an add-on therapy versus placebo.⁸ In this double-blind, placebo-controlled, randomized trial with a parallel-group design, patients were treated with risperidone 2 to 6 mg/day plus celecoxib (400 mg/day) or risperidone 2 to 6 mg/day plus placebo. Twenty-five patients were included in each group. It was shown that the add-on therapy of COX2 inhibition significantly reduced the total score on the Positive and Negative Syndrome Scale (PANSS) compared with the risperidone-placebo group. Simultaneous measurement of plasma levels of risperidone did not show a difference. Further studies in a greater number of patients, which are currently underway, will hopefully support these preliminary results.

Pharmacological aspects

Glutamate and schizophrenia

Possible links between abnormalities of the immune system and another neurotransmitter system, the glutamate system may exist, according to animal models of autoimmune diseases. Transgenic mice lacking IL-2 are susceptible to autoimmune diseases. Cytokines can influence the activity of the glutamate system.⁹ The glutamate system is closely connected to dopaminergic and serotonergic neurons. Hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor leads to increased dopaminergic activity in the frontal cortex. The NMDA glutamate hypothesis offers a possible link between the various theories surrounding the immune system and the hypothesis related to neurotransmitters. The growing importance of amino acid transmitters like glutamate was recognized from neuroimaging studies and neuro-pathological findings showing an involvement of the cerebral cortex (in which the major neurons are glutamatergic) in the neuropathology of schizophrenia. Further support came from the psychotomimetic effects of the NMDA-receptor antagonists phenylcyclidine (PCP), dizocilpine (MK-801), and ketamine. The theo-

ries focused on these NMDA receptors because of the psychomimetic effects of NMDA antagonists. Most notably, PCP and ketamine can induce symptoms related to schizophrenic symptomatology in healthy human subjects. Positive symptoms like grandiose paranoid delusions, bizarre ideation, and hallucinations have been described, as have negative symptoms like blunted affect and psychomotor retardation. Furthermore, cognitive deficits related to circuits in the frontal cortex have been observed, like distractibility, reduced verbal fluency, and working memory deficits. Cognitive deficits related to temporal hippocampal circuits have also been reported, like the disruption of new learning and reduced prepulse inhibition of the startle response. In the so-called revised dopamine hypothesis, Carlsson underlined the central role of glutamate- γ -aminobutyric acid (GABA) in neuronal circuits, which are closely connected to other neurotransmitters, eg, dopamine, norepinephrine, serotonin, acetylcholine, and glycine. The glutamate receptor system offers multiple targets for pathogenesis and pathophysiology in schizophrenia, and is rather complex. Four classes of glutamate receptors, the NMDA, the amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), the kainate, and the metabotropic receptors, each of which has a wide variety of subunits, form various receptor combinations, and can be differentiated on this basis (Figure 2).¹⁰ These NMDA antagonistic drugs lead to NMDA receptor hypofunction, which is due to the connections with the other neurotransmitter systems, producing an excessive release of excitatory trans-

Site of cytokine expression	Th1	Th2
In vitro production	IFN- γ ↓↓	IL-10 ↑
	IL-2 ↓↓	IL-3 ↑
Peripheral levels	IFN- γ ↔	IgE ↑↑
	IL-2 ↔	Antibodies against several antigens ↑↑
	sIL-2R ↑↑	IL-6 ↑↑
After remission:		
		IL-6 ↓↓
CSF levels	IL-2 ↓↑	IgG ↑
	IFN- γ ↓	IL-4 ↑
		TGF- β 1 ↔
		TGF- β 2 ↔
Hypothesis	A Th2 shift in schizophrenia with predominant negative symptoms and treatment resistance	

Table 1. Markers of Th1/Th2 responses in schizophrenia. Alterations of immunologic parameters in schizophrenic patients: the Th2 shift.⁴ CSF, cerebrospinal fluid; IFN- γ , interferon gamma; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; sIL, soluble interleukin; TGF, transforming growth factor; Th1, T helper cell subset 1; Th2, T helper cell subset 2.

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Glutamate receptors					
		Ionotropic			Metabotropic
		NMDA	AMPA	Kainate	
Subunits	NR ₁	GluR ₁	GluR ₅	Receptors	mGluR ₁
	NR _{2A}	GluR ₂	GluR ₆		mGluR ₅
	NR _{2B}	GluR ₃	GluR ₇		
	NR _{2C}	GluR ₄	KA ₁		mGluR ₂
	NR _{2D}		KA ₂		mGluR ₃
	NR ₃				
Binding sites	Glutamate		AMPA		mGluR ₄
	Glycine			Kainate	mGluR ₆
	Polyamines				mGluR ₇
	PCP, MK-801, or ketamine				mGluR ₈

Figure 2. Glutamate receptor subunits and binding sites. AMPA, amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; PCP, phenylcyclidine; NMDA, *N*-methyl-D-aspartate.

mitters in the cerebral cortex, and with other transmitters like dopamine. It is of interest that these psychotomimetic effects are only seen in adults, and not in children or young adolescents.¹¹ It is therefore postulated that the effects depend on the maturation of the brain and that an intact wiring of all neurons is necessary to produce such effects, and that this is only finalized during adolescence.

Animal experiments show that, depending on the severity or grade of NMDA receptor hypofunction, the first psychotomimetic effects occur later than the neurotoxic effects, which lead to neurodegeneration of cells. Chronic treatment with certain drugs like olanzapine, clozapine, lamotrigine, α_2 -adrenergic agonists, and perhaps antimuscarinic agents could prevent these neurotoxic effects. The NMDA receptor is, in addition to the L-glutamic acid-responsive recognition site, also modulated via the glycine-B receptor, indicating that the inhibitory amino acid glycine could have antipsychotic properties. Animal models have been developed to test antipsychotic agents on the basis of the reduced prepulse inhibition of the startle response, which can be observed in schizophrenic patients.¹² Prepulse inhibition is used as a model for attentional processes, and NMDA antagonists can disrupt prepulse inhibition. This disruption in prepulse inhibition can be prevented by atypical antipsychotics like clozapine, risperidone, quetiapine, and olanzapine.¹³ Most recently, artificial neuronal networks have been cultured on microelectrode arrays to evaluate new drugs in a very effective manner. For example, primary embryonic rat spine neurons have been cultured on microelectrode arrays. These neuronal networks display in vitro complex spatiotemporal spike and burst patterns, which are highly sensitive to their chemical environment and allow precise pharmacological manipulations free of homeostatic interference.¹⁴ Preliminary results have been reported with the cannabinoid agonists anandamide and methanandamide. Anandamide and methanandamide reversibly inhibited spike and burst production in these neuronal networks. Similarly, a dose-dependent stimulatory effect of glutamate on extracellular neuronal potentials has been recorded. First, an increased frequency of spikes was observed with serial elevations of the glutamate concentration; exposure to higher levels resulted in functional neurotoxicity. This new methodology allows a very rapid test-

ing of new drugs, to determine which interfere with the glutamate system. In this way, complex and expensive animal experiments can be drastically reduced.

Future directions

The reported theories can be tested in humans with new molecular biological techniques related to the pharmacogenetics and pharmacogenomics of drugs.¹⁵ According to the recently completed draft sequence, the human genome comprises about 30 000 to 35 000 genes. At least half of them are expressed in the brain. These could be targets for psychotropic drugs and therefore be related to the pathophysiology of mental disorders. An important challenge for pharmacogenetic studies is to choose candidate genes that may be relevant to drug response. There are three ways to achieve this goal:

- Knowing the mechanism of action of the drugs.
- Identifying the genes that are switched on or off, using expression studies.
- Identifying the susceptibility loci for the psychiatric disorders, using linkage or association studies.

Since the genes are expressed by messenger RNA and this is translated into proteins that will determine the functioning of the brain, the method of proteomics offers another route to new drug targets.¹⁶ The essence of proteomics is the identification of proteins that are uniquely expressed in brain tissues. Protein expression profiles in disease are compared with known disease tissues. This can be done in postmortem brains, CSF, and peripheral blood cells like lymphocytes. This can be a powerful approach to overcome the problem of genome-based technologies that do not consider differences between DNA structure, gene expression, and the functions of the proteins. Preliminary results have already been reported, but so far in an inconsistent manner.^{17,18} The major difficulty is the collection of representative tissue samples. Most sample brain tissue comes from postmortem brains and suicide victims, but it must be representative so as to avoid pitfalls due to different times after death and different unknown treatments.

With the help of pharmacogenomics and proteomics, an individualized therapy can be offered to each patient, to overcome the problem of heterogeneity of the disease and heterogeneity of therapeutic response. □

Pharmacological aspects

Desarrollos en la terapia antipsicótica basados en las hipótesis para la esquizofrenia

Los fármacos antipsicóticos típicos como la clorpromazina y el haloperidol fueron descubiertos en forma casual en la década de 1950. Un número de fármacos de los así llamados "yo también" con estructuras químicas y mecanismos de acción similares fueron puestos en el mercado en los años siguientes. El primer antipsicótico atípico, la clozapina, fue una excepción por el hecho de carecer de algunas de las propiedades farmacológicas de los antipsicóticos típicos relacionadas con el sistema motor extrapiramidal. Esta característica singular de la clozapina amplió significativamente la comprensión acerca del mecanismo de acción de los antipsicóticos y dio origen a nuevas hipótesis para la esquizofrenia. Sólo recientemente se ha iniciado un desarrollo de nuevos fármacos en base a dichas hipótesis. Las anomalías del sistema inmune en la esquizofrenia están siendo cada vez más discutidas: se han observado cambios en los niveles de los subtipos 1 y 2 de las células T helper (Th1 y Th2), y se han obtenido resultados muy promisorios en estudios con risperidona y celecoxib, un inhibidor de la ciclooxigenasa (COX2), como una terapia combinada. Los receptores de glutamato del tipo NMDA (N-metil-D-aspartato) también han sido investigados en relación con las alteraciones neuropatológicas en las áreas prefrontales del cerebro en pacientes con esquizofrenia. Esto puede conducir a nuevas tecnologías como las redes artificiales que se relacionan con el sistema receptor de glutamato NMDA. Las nuevas técnicas de biología molecular utilizadas en farmacogenómica y proteómica ofrecen nuevas y excitantes perspectivas para los futuros desarrollos de fármacos.

Avancées dans le traitement des psychoses et implications relatives aux hypothèses sur la schizophrénie

Les neuroleptiques typiques tels que la chlorpromazine et l'halopéridol ont été découverts fortuitement dans les années 1950. Un certain nombre de médicaments appelés « me too (moi aussi) » de même structure chimique et de même mode d'action ont été mis sur le marché au cours des années suivantes. Le premier antipsychotique atypique, la clozapine, était une exception parce qu'il lui manquait quelques propriétés pharmacologiques des antipsychotiques classiques liées au système moteur extrapyramidal. Cette caractéristique unique de la clozapine a élargi de façon significative la compréhension du mode d'action des neuroleptiques, et a permis de nouvelles hypothèses sur la schizophrénie. Le développement de nouveaux médicaments basé sur des hypothèses pharmacologiques a débuté récemment seulement. Des anomalies du système immunitaire au cours de la schizophrénie sont de plus en plus évoquées : des déviations dans les niveaux des sous-populations 1 et 2 (Th1 et Th2) de cellules T amplificatrices ont été observées, et des études de traitements additionnels avec la risperidone et un inhibiteur de la cyclooxygénase (COX2), le célécoxib, ont fourni des résultats très prometteurs. Les rapports entre récepteurs du glutamate N-méthyl-D-aspartate (NMDA) et les anomalies neuropathologiques des aires préfrontales du cerveau de patients atteints de schizophrénie ont également été étudiés. Ceci pourrait conduire à de nouvelles technologies comme les réseaux artificiels liés au système des récepteurs du glutamate NMDA. Les nouvelles techniques de biologie moléculaire utilisées en pharmacogénomique et protéomique offrent des voies nouvelles et passionnantes pour le développement de futurs médicaments.

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