Psychiatric diseases represent a major cause of disability among individuals during their peak years of productivity (ages 15 to 44) and remain major causes of mortality in the developed world. Because of this, governments and pharmaceutical companies have expended many billions of dollars on understanding the underlying causes of mental illnesses, and on discovering new and more effective treatments for them (Roth and Conn, unpublished report). The budget for the National Institute of Mental Health (NIMH)—the major funding agency for mental health-related research in the US—for the financial year 2006 stood at $1.4 billion, as stated on their Web site. Despite this heavy investment, no psychiatric medications with greater efficacy than drugs discovered 50 years ago have yet appeared. Thus, for example, clozapine (which was synthesized nearly 50 years ago) continues to be the “gold standard” for treating schizophrenia.

The recent sequencing and continued annotation of the human genome and the tentative identification of a large number of schizophrenia susceptibility genes have raised the possibility that molecular biology and its associated technologies will lead to new and improved treatments for schizophrenia and related disorders. The assumption underlying this hope is that “we should finally make rapid progress identifying some of the vulnerability genes and thus critical pathways for the pathophysiology of the major mental illnesses...” The hypothesis is that if we can understand the pathophysiological basis of these diseases—based on their molecular neurobiological underpinning—we will be better able to develop curative therapeutics (or “cure therapeutics”) for schizophrenia and related disorders. Although this is a highly attractive hypothesis, it is founded on a number of assumptions, some of which are falsifiable, others of which are not (at least with the available technology). In this review, this hypothesis and its underlying assumptions will be exam-
Schizophrenia as a molecular disease

Currently, at least three overlapping paradigms drive the drug discovery effort for schizophrenia. These include, firstly, the molecular-genetic hypotheses which hypothesize strong effects of schizophrenia susceptibility genes. A corollary of the molecular-genetic hypothesis is the proposal that targeting drugs at these genes might yield novel and more effective treatments for schizophrenia. Secondly, the neuronal network hypotheses propose strong effects of altered neuronal integration in schizophrenia. The corollary of this hypothesis predicts that drugs which fundamentally reset the tone of networks of neuronal interactions will prove efficacious in treating schizophrenia. Thirdly, the signal transduction hypothesis proposes that basic alterations in receptor-mediated signal transduction (either at the receptor or post-receptor levels) induce schizophrenia-like pathology. It follows that ameliorating altered signaling via specific medications which target receptor/post-receptor molecules will prove efficacious in treating schizophrenia. This mutation results in diminished α7 expression which, in turn, leads to altered neuronal connectivity and signal transduction. These alterations in neuronal signaling and connectivity lead to some of the symptoms of schizophrenia. The corollary is the proposal that α7 agonists will improve schizophrenia symptoms—a hypothesis that is now being tested.

The critical node assumption has not (yet) yielded better drugs for schizophrenia

Based on the “critical node” assumption, a large number of potential nodes have been identified for therapeutic drug discovery. These have been identified via the three general strategies outlined above (eg, molecular genetic, neuronal network, or signal transduction) and a large number of these candidate nodes have been a theme of research over the past decade. As we have recently summarized as part of a larger study of psychiatric drug discovery, nearly 150 investigational compounds directed against many individual molecular targets (“nodes”) have been subjected to at least early-phase clinical trials (Roth and Conn, unpublished report). Representative compounds for each node are listed in Table I. In this table, antipsychotic drugs have been classified based on
molecular target (eg. “node”) and whether the compounds were validated with preclinical and clinical studies. Lastly, it is indicated whether the compounds were found, based on clinical trials, to be superior to a standard comparator medication (typically haloperidol). Based on the currently available data, we were unable to find any evidence to support the hypothesis that targeting any single molecular target (“node”) other than D₂ dopamine receptors will yield a drug which effectively treats the core symptoms of schizophrenia. Additionally, we were unable to find any support for the hypothesis that drugs targeting a single node are more effective at treating schizophrenia than drugs targeting a large number of nodes. Indeed, clozapine, which targets at least 50 nodes, remains superior to all other medications. The results obtained are consistent with the proposal that “D₂ dopamine receptors represent the critical node in schizophrenia pathogenesis.” It is unknown

Figure 1. Schizophrenia susceptibility genes are localized in overlapping neuronal pathways. Shown in diagrammatic form are the presumed localizations of various schizophrenia susceptibility gene products in a model synapse in the prefrontal cortex. As shown, a typical pyramidal neuron fiber receives inputs from dopaminergic, serotonergic, glutamatergic, and GABA-ergic neurons. The various susceptibility genes indicated may modulate pre- or postsynaptic glutamatergic functioning. Antipsychotic drugs mainly affect biogenic amine receptor activities which may be either pre- or postsynaptic in nature. GABA, γ-aminobutyric acid
whether any single molecular target of greater promise will ever be found.

There are many ways in which these findings can be interpreted, although each interpretation relies mainly on untested assertions. A typical criticism one can make of these findings is that “we have not yet found the critical node” and that once this key node is discovered, the pathway towards drugs with greater efficacy and fewer side effects will be clarified. The untested assumptions are (i) that such a special node associated with efficacy exists; (ii) that it can be discovered; and (iii) that, once discovered, using techniques of molecular biology, a drug can be designed to target it. An implicit assumption underlying this argument relates to the need for an enhanced understanding of the molecular pathogenesis of schizophrenia in order to discover and validate suitable molecular targets.1,9

Based upon our current understanding of the molecular pathogenesis of schizophrenia, no critical node other than the $D_2$ dopamine receptor has yet been convincingly and reproducibly elucidated, although a large number of candidate genes and susceptibility factors have been

| Node (molecular target) | Representative drug | Preclinical evidence of efficacy* | Results from randomized clinical trials | Efficacy > haloperidol | Side effects |
|------------------------|--------------------|----------------------------------|----------------------------------------|------------------------|-------------|
| $D_2$ dopamine antagonist | Haloperidol, amisulpride | Many | Effective | Equivalent | EPS |
| $D_2$ dopamine partial agonist | Aripiprazole | Many | Effective | Equivalent | Activation |
| Highly promiscuous antagonist (40+ nodes) | Clozapine | Many | Effective | More effective | Agranulocytosis, weight gain, sedation, seizures |
| Moderately promiscuous antagonist (20+ nodes) | Olanzapine | Many | Effective | Equivalent | Weight gain, sedation |
| Mildly promiscuous antagonist (10-20 nodes) | Risperidone | Many | Effective | Equivalent | Weight, gain, sedation, EPS with higher doses |
| Promiscuous agonist (40+ nodes; partial agonist at >3) | N-desemethyl-clozapine | Many | Unknown | Unknown | Unknown |
| 5-HT2A antagonist | SR463498 | Many | Possibly effective | Possibly equivalent | Minimal |
| NK-3 antagonist | SR142801 | Partial | Possibly effective (clinical development ceased) | Equivalent | Minimal |
| $D_2$ antagonist | Belaperidone | Partial | No | No | Worsening of psychosis? |
| $D_1$ antagonist | LU-201640 | Partial | Ongoing** | Ongoing | Ongoing |
| $D_1$ antagonist | BSF-78438 | Partial | Dropped*** | Dropped | Dropped |
| Sigma-1 antagonist | BMY 14802 | Partial | Ineffective | Ineffective | Perhaps worsening of psychosis |
| AMPA 1 glutamate modulator | Org-24448 | Partial | Ongoing | Ongoing | Ongoing |
| mGluR$_5$ glutamate agonist | LY-341495 | Partial | Ongoing | Ongoing | Ongoing |
| CB-1 cannabinoid antagonist | SR141716 | Partial | Ineffective | Ineffective | Dropped |
| NT-1 neurotensin antagonist | SR48692 | Partial | Ineffective | Ineffective | Dropped |
| $\alpha_7$-Nicotinic agonist/partial agonist | MEM-3454 | Partial | Ongoing | Ongoing | Ongoing |
| NMDA glutamate modulator | D-serine | Partial | Perhaps partially effective | Ongoing | Ongoing |
| PDE10A antagonist | Papaverine | Partial | Unknown | Unknown | Unknown |
| $\alpha_2$-Adrenergic agonist | Clonidine | Partial | Perhaps partial as augmentation | Unknown | Unknown |

Table I. Multiple candidate nodes have been subjected to testing as targets for treating schizophrenia. This shows an abstracted analysis from a recent study examining the evidence for and against various molecular-target based approaches for treating schizophrenia. *, various animal models which have been tested and for which the drug has efficacy; **, clinical trials are ongoing and information is not available; ***, dropped from development with no further data available; EPS, extrapyramidal syndrome.
described. These include neuregulin-1, dysbindin, disrupted in schizophrenia-1 (DISC-1) and many others (eg, reelin, regulator of G protein signaling-4, catechol-O-methyltransferase, mGluR3 glutamate receptor, and so on; see ref 8 for recent review). As we and others have pointed out (Figure 1) these susceptibility gene products are found in a variety of cell types (both neuronal and glial) and show differential subcellular localizations. As Figure 1 shows, the molecular targets identified are frequently found in circuits which are targeted by drugs with a “promiscuous” pharmacology (eg, clozapine). No single node is an obvious target for therapeutic drug discovery efforts, although nearly all of the identified nodes have been reported to be targets of therapeutic drug discovery (Roth and Conn, unpublished report).

Another possibility is that schizophrenia can be most effectively treated by influencing several nodes simultaneously. Indeed, based on the demonstrated superiority of clozapine for treatment-resistant schizophrenia and the relative inferiority of all other medications, there is strong support for this hypothesis. A great deal of effort has been expended to discover an optimal clozapine-mimetic devoid of the side effects of clozapine (eg, agranulocytosis, seizures, sialorrhea, weight gain, sedation, and hypotension. We, and others, have suggested that the massively parallel screening of large numbers of molecular targets allows one to efficiently discover “toxic” vs “therapeutic” targets. Antipsychotic drug-induced weight gain might be due to H1-histamine and 5-HT2C-receptor blockade, agranulocytosis to H4 histamine agonism, sedation to H1 histamine antagonist, and so on. Thus far, these molecular targets implicated in clozapine’s side effects (H1-histamine, H4-histamine, 5-HT2C serotonin) are not identical with those targets thought to be involved in its superiority as an antipsychotic drug (5-HT2A serotonin, D4-dopamine, 5-HT6 and 5-HT7 serotonin). A problem with the approach of designing selectively nonselective drugs is that it is very difficult to rationally design in new pharmacological properties during the drug discovery process. This is an emerging paradigm, however, and some successful strategies have recently been elucidated.

A systems level approach

The neuronal systems approach similarly proposes that there might be crucial nodes in the network that are amenable to target-based discovery efforts. Spedding and colleagues have cogently argued that a systems-level approach using animal models will lead to more effective treatment for psychiatric diseases. Based on a model which involves specific alterations in hippocampal-cortical circuitry, they propose testing compounds in animals in which these circuits are disrupted by phenycyclidine (PCP). In support of this systems-level approach, nearly every approved antipsychotic drug will ameliorate PCP-induced alterations in neuronal functioning. However, it is also true that drug classes with demonstrated ability to ameliorate PCP-induced deficits (eg, 5-HT2A antagonists) are only marginally effective in treating schizophrenia. Thus, in vivo systems-level screens can be highly effective tools to verify in vivo actions of putative atypical antipsychotic drugs. It does not appear that any of the available in vivo screening models are able to predict relative efficacy at treating schizophrenia, however. In addition, none of the available models appears to adequately recapitulate the entirety of the human phenotype.

One can easily provide the counterargument that a “suitable animal model will eventually be found which recapitulates the schizophrenia phenotype,” although it is also plausible that “no suitable preclinical model will ever be found which adequately recapitulates schizophrenia pathology.” Clearly, despite decades of research we have not yet discovered an adequate preclinical model, and it is within the realm of possibility that “schizophrenia is a uniquely human disease which cannot be adequately modeled in rodents.” In large measure, this is likely to be due to the fact that a number of genetic “hits” as well as nongenomic factors converge to produce the final phenotype in humans. At present, we have no way to predict either way, and continued research in this arena will be based more on untested assumptions than on data.

Is schizophrenia similar to hypertension in being complex, polygenic, and epigenetic?

Another possibility is that schizophrenia represents a complex disease with genetic and epigenetic factors and which is both chronic and progressive, resulting in irreversible end-organ damage—similar to hypertension. Indeed, there is accumulating evidence for epigenetic factors involved in the etiology of schizophrenia—particularly relating to reelin. There has also been abundant evidence accumulated over the past several decades that schizophrenia is associated with subtle but reproducibly
Pharmacological aspects

documented neurodegeneration (reviewed in refs 46, 47). Accordingly, optimal treatment of schizophrenia would be similar to that for other progressive and complex diseases such as hypertension, where individuals at risk would be identified and then treated to avoid end-organ damage. Such an approach has already been attempted, with a mixed degree of success. In this study, individuals at risk were identified and then prophylactically treated with placebo or olanzapine. Although the results were not statistically significant, there was a trend toward protection of conversion to overt psychosis among individuals treated with olanzapine.

Conclusion

As is clear from the foregoing, the tools of molecular biology can, at least theoretically, accelerate drug discovery in schizophrenia. In the main, molecular biological approaches have been more useful in providing reagents for high-throughput screening campaigns than for providing better animal models—at least to date. With the continued discovery of schizophrenia susceptibility genes, it is at least conceivable that better preclinical models will be produced. To a great degree, lack of progress in developing more effective antipsychotic drugs has stemmed mainly from the failure both to fully appreciate the pharmacological robustness of clozapine and to discover medications which reproduce the essential features without producing serious side effects. It is not clear whether any of the paradigms outlined will lead to more effective medications, although it is likely that continued molecular target-based screening will eventually yield medications with fewer side effects.

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Contribuciones de la biología molecular al descubrimiento de fármacos antipsicóticos: ¿promesas cumplidas o incumplidas?

Esta revisión resume los diversos paradigmas conceptuales que existen para el tratamiento de la esquizofrenia e indica cómo la biología molecular y las tecnologías para el descubrimiento de fármacos pueden acelerar el desarrollo de nuevos medicamentos. Aun no se dispone de información convincente acerca de la existencia de una molécula específica, que pueda transformarse en un medicamento, y que de encontrarse pueda dar origen a fármacos más eficaces que cualquiera de los actualmente disponibles. Se sugiere, en cambio, que es probable que fármacos que interactúan con una multiplicidad de blancos moleculares muestren mayor eficacia en el tratamiento de los síntomas centrales de la esquizofrenia.

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