in: Psychopharmacology Drugs, the Brain and Behavior?
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Long-term outcome depends on pharmacological treatment

Before the advent of drug therapy, the history of treatment for schizophrenia was rather dismal (Figure 18.2A). The mentally ill were maintained in huge mental hospitals where treatment was limited to isolation or restraint, "shock" therapy using insulin-induced seizures or electric current, or surgery such as prefrontal lobotomy. Figure 18.2B shows a steady increase in the number of hospitalized psychiatric patients in the United States from 1900 to 1956 because such patients were usually permanently hospitalized. In 1956, the number of hospitalized patients began a sudden and steady decline despite a continued increase in initial admissions. This reduction coincided with the introduction of drug therapy, in particular the use of chlorpromazine (Thorazine). Chlorpromazine, a drug in the phenothiazine class, was initially used to enhance surgical anesthesia because it produces a sense of calmness and reduced awareness of environmental stimuli when administered before surgery. When tried with schizophrenic patients, chlorpromazine was especially effective because it calmed the excited patient and activated the patient who was profoundly withdrawn. Many modifications of the chlorpromazine molecule have already been made, and the development of new compounds to reduce symptoms with fewer side effects continues today.

Figure 18.2 Treatment of the mentally ill (A) Drawing depicting one of the available methods of "treatment" of the mentally ill during the early 1800s. (B) Patient populations in public mental institutions in the United States increased from 1900 to 1956. At that point a dramatic decline occurred in the number of institutionalized patients following the introduction of antipsychotic drugs. (After Bassuk and Gerson, 1978.)

Preclinical Models of Schizophrenia

Animal models of schizophrenia are important for identifying the neurochemical and genetic basis for the disorder. They are also vital for screening new antipsychotic drugs. Developing such models is difficult, however, because the primary symptom is profound thought disorder, a cortical process not found in lower animals.

The toxic reaction to high doses of central nervous system (CNS) stimulants is a model that is still considered among the best. It was found quite accidentally when clinicians realized that people who abuse CNS stimulants (amphetamine and cocaine) frequently show signs of thought disorder. Addicts hospitalized with stimulant toxicity often have well-formed paranoid delusions; various stereotyped, compulsive behaviors; and either visual or auditory hallucinations. Even trained clinicians find the symptoms to be indistinguishable from those of paranoid schizophrenia. Also, when amphetamine is administered to patients with schizophrenia, the patients report that their existing symptoms get worse, not that new symptoms are produced. Finally, amphetamine-induced psychosis can be treated with the same drugs that are most effective in treating schizophrenia.

In animals, high doses of amphetamine produce a characteristic stereotyped sniffing, licking, and gnawing. Because stereotyped behavior also occurs in response to high doses of amphetamine in humans and is similar to the compulsive repetitions of meaningless behavior seen in schizophrenia, the **amphetamine-induced stereotypy** is used in the laboratory as an animal model for schizophrenia. For many years it has been a classic screening device to identify effective antipsychotic drugs. Because high doses of amphetamine release dopamine, the abnormal behaviors produced by the

drug support the dopamine hypothesis of schizophrenia (see the section on this hypothesis later in the chapter).

A second screening procedure compares the dose–response curve for the antipsychotic drug's inhibition of motor activity induced by apomorphine (a dopamine agonist) with the curve for the drug's effectiveness in producing catalepsy (maintenance of abnormal postures). Although the animal models for measuring drug-induced running and the peculiar posturing of catalepsy may not seem to reflect psychotic behavior and extrapyramidal symptoms, respectively, they have provided consistent preclinical results. Drugs that are effective in reducing psychotic symptoms in humans quite consistently also reduce apomorphine-induced running as well as amphetamine-induced stereotyped behaviors. Likewise, neuroleptics that do not produce catalepsy in rats have low incidences of motor side effects. Figure 18.3 shows that for the classic antipsychotic haloperidol, the dose–response curves for inhibiting apomorphine-induced locomotion and producing catalepsy are very similar, suggesting that doses that are effective in reducing the locomotion are almost identical to those that induce catalepsy. In contrast, the dose–response curves for the atypical antipsychotic remoxipride show a much larger difference in doses required to inhibit hyperactivity and induce catalepsy. This type of preclinical screening predicts a lower incidence of motor side effects with the atypical drugs, and clinical evaluation with patients supports that conclusion.

Another drug-induced syndrome produced in humans by high doses of phencyclidine (PCP; "angel dust") forms the basis for the dopamine–glutamate hypothesis of schizophrenia (see the section on this hypothesis later in the chapter). At low doses, PCP produces symptoms of drunkenness and mild stimulation, which progress to loss of body boundaries and withdrawal from social interaction. The symptoms of severe PCP intoxication include disorientation, muteness, profound cognitive impairments, various motor symptoms (e.g., agitation, grimacing, rigidity, catalepsy, tremors), and occasionally paranoid delusions (see Chapter 14). PCP-induced psychosis in normal individuals closely resembles an acute episode of schizophrenia. Repeated use of PCP may produce long-lasting psychotic symptoms. Furthermore, PCP intensifies the primary symptoms of schizophrenia. The usefulness of studying PCP's action stems from its ability to produce both positive and negative symptoms of schizophrenia (Javitt and Zukin, 1991), unlike toxic doses of amphetamine, which produce only the more dramatic positive symptoms of paranoid schizophrenia. Note that both amphetamine and PCP enhance dopamine release and block reuptake, while PCP in addition antagonizes glutamate transmission (Lahti et al., 1995).

One very different type of model is based on evidence that schizophrenics fail to "gate," or filter, most of the sensory stimuli they receive. Such a defect may lead to sensory overload and fragmented thinking, because schizophrenics are overwhelmed by sights and sounds and odors in the environment that they cannot filter out. The acoustic startle response is one of the most reliable and generalizable models used to study sensory-filtering deficits, and it can be utilized easily in both animals and human subjects. Box 18.2 describes the technique called prepulse inhibition of startle (PPI) and demonstrates the elegance of this model.

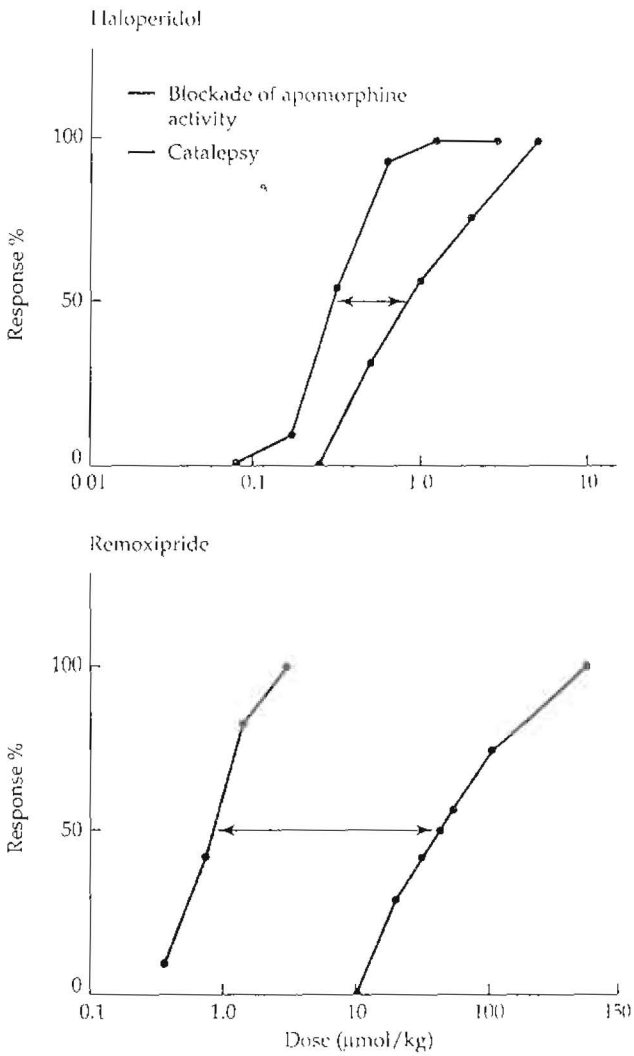


Figure 18.3 Dose–response curves for haloperidol and remoxipride for blocking apomorphine-induced hyperactivity and producing catalepsy in rats The horizontal distance between the curves on each graph represents the difference in potency of the drug required to produce both of the effects. The wider the separation of the curves, the lower the likelihood that the effective antipsychotic dose will produce motor side effects in humans.

BOX 18.2

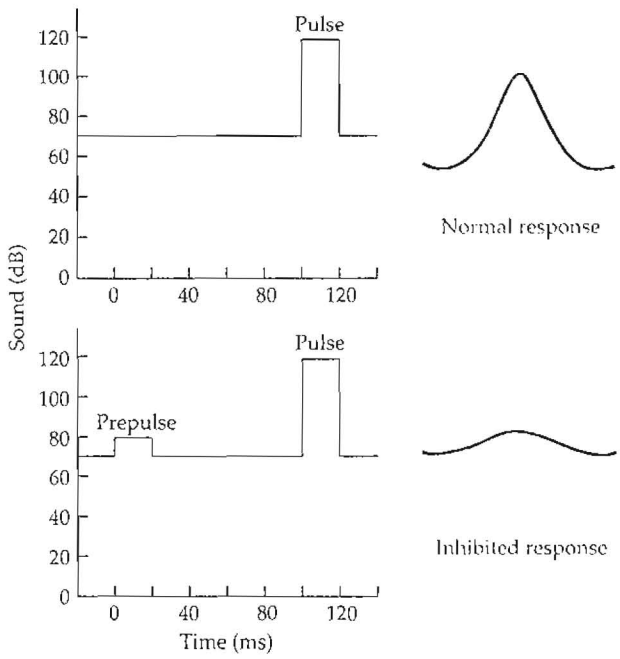
Pharmacology in Action

Animal Model—Prepulse Inhibition of Startle

No single animal model can mimic the complex symptomatology of schizophrenia, so each one tends to focus on one aspect of the disorder and experimentally induce homologous (similar) changes in animal behavior. It is assumed that subsequent attempts to manipulate the experimental response both neurochemically and neuroanatomically should provide evidence for the neurobiological basis of human behavior.

Animal models are used to screen new therapeutic drugs for effectiveness. These models may not resemble the psychiatric condition at all and may depend on neurochemically induced behaviors that are known to respond to currently useful drugs. The disadvantage, of course, is that such screening devices often fail to identify drugs with novel mechanisms of action, which may be of greatest importance to the researcher.

Of the available models for schizophrenia, one in particular meets many of the objectives of conventional testing. Among the symptom clusters characteristic of schizophrenia, the information-processing abnormalities that contribute to the illogical thinking and disorganized behavior has been modeled effectively. The model called prepulse inhibition (PPI) of startle focuses on the failure of individuals with schizophrenia to "gate," or screen out, irrelevant stimuli. By failing to screen out incoming information, they are bombarded by stimuli, causing sensory overload, fragmented thinking, and thought disorder. Prepulse inhibition refers to a reduction in the reflex startle response to a strong, rapid-onset stimulus (either a sudden loud tone or sudden bright light) when it is preceded by a prepulse (occurring 30 to 500 milliseconds before) that is too weak to elicit a startle response itself. The experimental design is shown in Figure A. Apparently, under normal conditions the prepulse activates a neural circuit that inhibits the reflex to the second stimulus. Although the startle response itself is a relatively simple reflex, the inhibition of the reflex is exerted by a neuroanatomical circuit involving the limbic cortex, striatum, globus pallidus, and pontine reticular formation. Abnormalities in each of these brain areas have been implicated in the etiology of schizophrenia; therefore, failure of the prepulse to inhibit the startle response would be anticipated. Many studies have shown that PPI is diminished in schizophrenia, which means that patients do not inhibit the startle as effectively as normal subjects, as shown in Figure B. Deficits in PPI occur in other clinical conditions that involve some part of the cortical–striatal–pallidal–pontine circuit, such as obsessive–compulsive disorder, attention deficit disorder, Huntington's disease, and others. Thus, PPI deficiency is associated not with a



(A) Demonstration of prepulse inhibition of startle for a normal subject The graphs on the left show the stimulus presentation; the graphs on the right, the response. The normal startle response follows the single pulse. The inhibited response occurs in a normal subject when a prepulse occurs shortly before the major pulse.

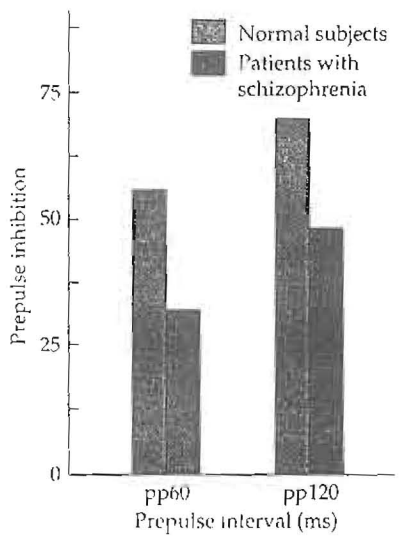
BOX 18.2 (continued)

specific psychopathology but with deficits in gating resulting from abnormalities in a particular brain circuit.

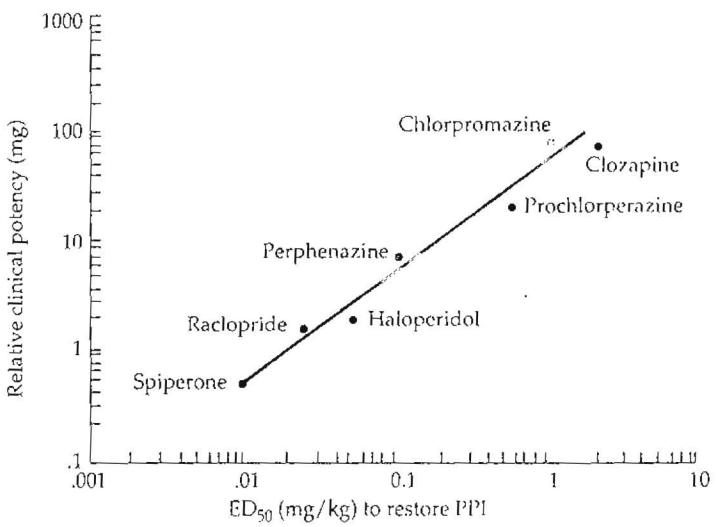
PPI has several advantages that make it an appealing animal model. First, the reflex is simple to measure and produces reliable results. PPI is exhibited in virtually all mammals, including primates, and requires no training. In human studies the eyeblink reflex is measured, while in rats the whole-body flinch is evaluated.

Support for the dopamine hypothesis comes from findings that PPI is disrupted by systemic administration of dopamine agonists and reinstated by dopamine receptor–blocking antipsychotic drugs. That is, treatment with apomorphine or other dopaminergic drugs interferes with the normal gating function. The ability of antipsychotics, including the atypical antipsychotic clozapine, to restore PPI in apomorphine-treated rats at doses that strongly correlate with clinical potency further validates this model (Figure C). However, PPI is also disrupted by systemic administration of serotonin agonists and glutamate antagonists and by a variety of surgical or neurochemical manipulations of the cortical–striatal–pallidal–pontine circuit. Since structural or functional abnormalities in schizophrenic patients have been reported at every level of the gating circuit as well as in glutamate and serotonin function, the PPI model may provide unique information on the pathology underlying schizophrenia.

This chapter describes the interaction of factors that contribute to the occurrence of schizophrenia: genetic, anatomical, and environmental. The PPI model is especially appealing because it also responds to each of these factors. First, genetically distinct rat strains differ significantly in the dopaminergic modulation of PPI. Also, rats that have been bred for apomorphine sensitivity or lack of sensitivity show parallel differences in PPI. Thus, if genes control susceptibility to apomorphine-induced gating disruption, such a model may provide information about genetic-mediated susceptibility to schizophrenia. Second, some evidence exists to suggest that early brain lesioning may have an impact on apomorphine-induced disruption of PPI in the adult animal. Third, developmental influences such as isolation stress early in life significantly reduce PPI (impaired gating), and this effect is reversed by both typical and atypical antipsychotic drugs (Varty and Higgins, 1995). Such parallels make PPI modeling of schizophrenia a particularly appealing design and one that may provide a good deal of new information. A more detailed description of these experiments and the PPI model can be found in Swerdlow and Geyer (1998).



(B) Failure of prepulse inhibition in schizophrenia at two different prepulse intervals



(C) Antipsychotic drugs that are clinically effective at low doses also restore the prepulse inhibition at low doses. High-dose antipsychotics also require higher doses to restore the prepulse inhibition.