Pharmacological Treatment of Schizophrenia

by Richard H. Hall, 1998

Drugs

The primary theory of schizophrenia at the neurotransmitter level, the dopamine hypothesis, was formed as the result of an accidental, yet dramatic event in the history of the treatment of schizophrenia. In the 1940s a French surgeon, Henri Laborit, began using a drug in an effort to reduce post operative shock in his patients. Laborit found that the drug reduced patients' anxiety without impairing cognitive functioning. This finding lead French drug companies to explore similar drugs, and as a result **Chlorpromazine** was developed. This drug was tested on a variety of mental disorders and did not seem to have much affect on disorders such as depression, but had dramatic effects on schizophrenia. As a result the "drug revolution" in the treatment of schizophrenia was born, and the result was profound. Schizophrenic patients who had been "out of touch" from consensus reality for years, were suddenly able to function effectively in society. As we'll discuss below, the effects do not occur for all schizophrenics, and there were side effects. Nevertheless, the introduction of drugs like chlorpromazine increased practitioners' ability to treat schizophrenia more dramatically than anything before, or anything that has come sense. Like all anti-schizophrenic drugs that have since been introduced, chlorpromazine was a **dopamine (DA) antagonist**.

Since the introduction of chlorpromazine, anti-schizophrenic drugs have improved. Primarily they have become more specific in their effect, and, as a result, the side effects have decreased. One of the first widely used drugs introduced after Chlorpromazine is called Haloperidol (that goes by the commercial name, *Haldol*), and it is also a dopamine antagonist. However, it has it's primary effect on one principal type of dopamine receptor, **DA_2** receptors. Recently another class of drugs has been introduced for the treatment of schizophrenia, the so called atypical anti-schizophrenic drugs, the main representative being **Clozapine**. Clozapine is called "atypical" because it's primary effect is on, recently discovered, **DA_3** and **DA_4** receptors. In addition, the effect of Clozapine is primarily on neurons in the **Mesolimbic** pathway, while the earlier drugs also effected Dopamine in the **Nigrostriatal** pathway. The Mesolimbic pathway, which begins in the **Ventral Tegmental Area** and terminates in the **Nucleus Accumbens**, has been implicated as an important pathway in reinforcement. The Nigrostriatal pathway, beginning in the **Substantia Nigra** and ending in the **Neostriatum**, on the other hand, is important in movement and motor learning. Parkinson's disease results from the break down of neurons in this pathway. (Figure 1 illustrates the difference between these two pathways). The fact that the older schizophrenic drugs effected the Nigrostriatal system is one of the reasons that a primary side-effect of these drugs was motor disturbance, and the fact that Clozapine has a minimal effect on this pathway is why the motor side effects are significantly less.

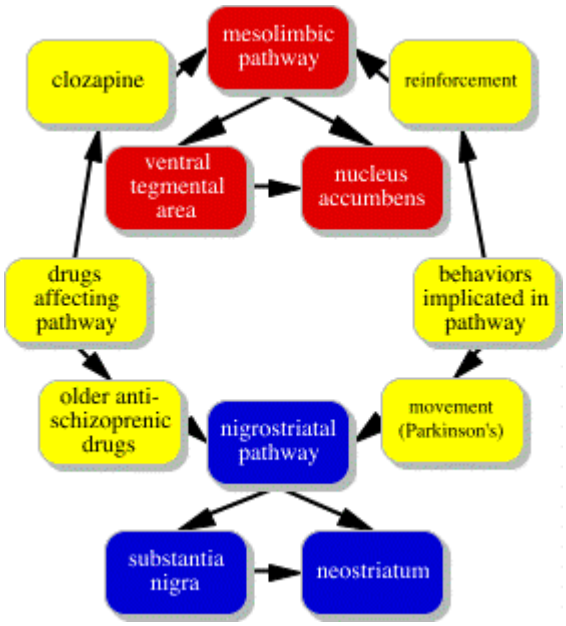

Figure 1. Comparison of Mesolimbic and Nigrostriatal pathways

Side Effects/Limitations

Although anti-schizophrenic drugs significantly increased the practitioner's ability to effectively treat the symptoms of schizophrenia, they were not, and are not, perfect by any means. First, approximately one-third of the patients who take the drugs for schizophrenia do not see significant improvement in their symptoms. Second, the drugs, especially those before Clozapine, often produced Parkinson's-like side effects in their patients, such as jerky and stiff movements. Clozapine also has one, somewhat rare, but very important side effect. **Agranulocytosis** is a syndrome that can result from Clozapine, which is a dramatic decrease in white blood cells, which can cause death in a small percentage of patients. A pretty significant side effect! For this reason, the blood of patients who are taking Clozapine is constantly monitored, and the patient is immediately taken off the drug if there is any sign of Agranulocytosis. Even with newer anti-schizophrenic drugs, another important limitation is that they have no effect on negative symptoms, they simply decrease the delusions, hallucinations, and other positive symptoms. This is one of the reasons why many researchers believe that the positive symptoms are more associated with neurotransmitter abnormalities, while the negative symptoms are more associated with brain damage.

Another dramatic side of anti-schizophrenic drugs, which is again most associated with pre-Clozapine drugs and only occurs in a small percentage of patients, is referred to as **Tardive Dyskinesia**. Tardive Dyskinesia is characterized by behaviors such as facial tics, gestures, tongue protrusion, and the pursing of lips. Interestingly enough, these behaviors are much the opposite of the Parkinson'-like side effects that usually occur. This side effect usually occurs when a patient has been taking anti-schizophrenic drugs for many years, and strangely becomes more pronounced when the drug is withdrawn. The most popular explanation for this perplexing phenomenon is a **supersensitivity hypothesis**. The idea is that dopamine neurons may become

"super sensitive" to dopamine because of being deprived of dopamine via antagonists for so many years, and, as a result, increase their response dramatically (supersensitivity as it applies to Tardive Dyskinesia, is illustrated in Figure 2). This general tendency of neurons to adapt to being deprived of a neurotransmitter is important with respect to the effect of drugs on behavior in many cases. This illustrates an important point that drugs which dramatically increase or decrease the levels of a neurotransmitter, will often instigate a compensatory effect in the nervous system.

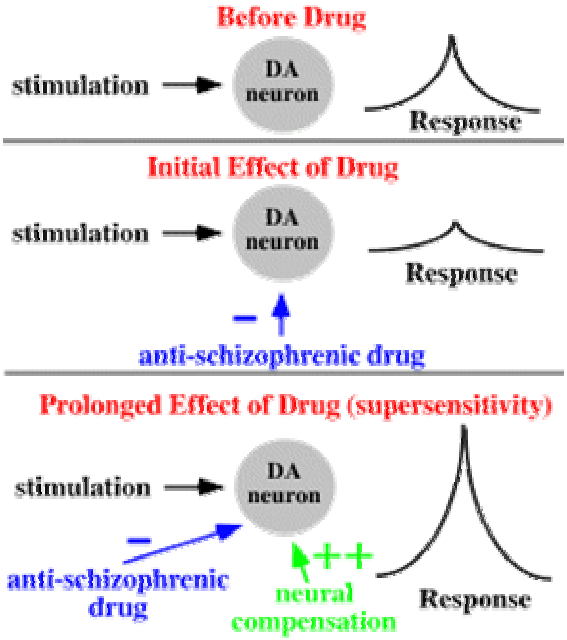

Figure 2. Supersensitivity as it Applies to Tardive Dyskenesia