NEUROPSYCHOPHARMACOLOGY

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Summary

Neuropsychopharmacology is a broad and growing field that is related to several disciplines, including neuropharmacology, psychopharmacology and fundamental neuroscience. It comprises research on the action of psychoactive drugs on different levels. This ranges from molecular and biochemical characterization, to behavioral effects in experimental animals, and finally to clinical application. Over the years, the developments in the neuropsychopharmacological field have led to advances in our

understanding of the brain and how it (dys)functions. In addition, technological advances have led to interesting discoveries that give more insight into the underlying neuropathologies of psychiatric and neurological diseases.

The basis of neuropsychopharmacology is the principle of neurotransmission; in other words the way information within the brain is transferred from one neuron to another. This process underlies everything we feel, think, know and do. Abnormal neurotransmission in the brain will cause us to feel, think and act differently. These changes in behavior or mood can be so severe that the individual is diagnosed as suffering from a psychiatric disorder. Unfortunately, in the majority of these disorders the actual 'defect' in neurotransmission is unknown. Nonetheless, the ground-breaking work of researchers in the past, together with great discoveries of today's scientists, have increased our knowledge about the neural circuitries involved in hallucinations, the signal transduction pathways implicated in depression and the neurotransmitter deficiencies in obsessive compulsive disorders. In the end, the clinicians will be pleased to prescribe effective pharmacological treatment devoid of side effects. The present chapter will emphasize the concepts of action of psychoactive medical drugs prescribed for psychiatric disorders. The following classifications are used: antipsychotics, antidepressants and mood stabilizers, and anxiolytics. The reader should consult other sources for more information on psychotropics used for neurological disorders and for recreational mind-altering drugs.

1. Introduction

In the 1950s, the first set of psychotropic drugs introduced consisted of two structurally different neuroleptics (reserpine and chlorpromazine), two structurally and functionally distinct antidepressants (iproniazid and imipramine), a moodstabilizer (lithium) and an anxiolytic (amobarbital). These drugs were the first therapeutically effective treatments for psychiatric patients. Before the introduction of the first generation of psychoactive drugs, morphine was one of the prevailing drugs used in the treatment of psychiatric diseases. By administering morphine subcutaneously, agitation and aggression, as well as neuralgic pain, were rapidly controlled. Because of this general 'therapeutic' effect, morphine was commonly used in psychiatric hospitals and mental institutions, mainly to sedate patients. However, in the 1950s, it became possible to symptomatically treat patients. For example, the first neuroleptics were clinically useful in controlling excitement and psychomotor agitation, symptoms seen in schizophrenic and manic patients or in the management of psychosis, whereas the antidepressants were effective in the treatment of depression, panic disorder and obsessive compulsive disease. Based upon the known structure and pharmacology of this first generation, more drugs were developed, and at the end of the 1970s there were about 65 psychotropic drugs available for clinical use. Today, second and even third generations of antipsychotics and antidepressants are available.

The development of the symptomatic treatment of psychiatric illnesses in the mid-50s coincided with the introduction of the spectophotofluorimeter. With this instrument, it was possible to measure concentrations of substrates in the brain that were involved in neurotransmission in the synaptic cleft. The neurotransmitters in the brain were discovered and in 1958, five different neurotansmitters were known: acetylcholine,

noradrenaline, serotonin, GABA (γ-aminobutyric acid) and substance P. From this time on it was possible to actually detect biochemical changes in the brain with increasingly sensitive technologies, which was fundamental for the therapeutic effects of psychotropic drugs. Moreover, biochemical disturbances in the brain underlying psychiatric diseases were detectable, setting the stage for the development of theories about the pathophysiological mechanisms of psychiatric diseases and new effective treatments for schizophrenia, depression and anxiety disorders. However, despite the progress in neuropsychopharmacological research and in pharmacotherapy of mental illnesses, there are still many obstacles. To date, no psychopharmacological treatment is without adverse side-effects. Moreover, the heterogeneity of psychiatric populations within the diagnostic categories is hindering the improvement in the therapeutic effects of drugs. In addition, most, if not all, treatments today are symptomatic rather than disease-modifying or curing. There is still a long way to go before we really can control psychiatric disorders with psychopharmacological treatment.

2. Chemical Synaptic Transmission in the Central Nervous System

Within the central nervous system, communication between neurons occurs by transforming the electrical signal (i.e. an action potential) of one neuron into a chemical message that is then released by this neuron. The receiving neuron cell detects this signal and this modulates its own activity by either increasing or decreasing the probability of an action potential, and hence communication with surrounding neurones. The site for this neurotransmission is the chemical synapse and the specific chemical messengers are the neurotransmitters and neuromodulators. For detailed information on neurotransmission see *Neurons, action potentials, and synapses*.

In the central nervous system, there are a large number of neurotransmitters and neuromodulators. By definition, a neurotransmitter is a chemical that directly relays, amplifies, inhibits or modulates electrical signals between neurons, whereas a neuromodulator is a chemical substance that is also released by a neuron (or glial cell), but conveys its information to other neurons in a local region of the central nervous system by modulating the response of a neurotransmitter. Although it has generally been accepted for a long time that one neuron releases only one neurotransmitter, it is nowadays more obvious that neurons release more than one neurotransmitter and/or –modulator. This phenomenon is called co-transmission and we are only just beginning to understand the functional implications of this. Neurotransmitters may broadly be divided into fast neurotransmitters (glutamate, GABA, acetylcholine) or slow neurotransmitters and neuromodulators (monoamines and neuropeptides). For an overview of the neurotransmitters and neuromodulators see *Neurotransmitters and modulators*.

The essential processes of chemical neurotransmission, i.e. the synthesis, release, reuptake and breakdown of neurotransmitters and their interaction with receptors on the target cells (postsynaptic receptors) or on the presynaptic terminal to modulate subsequent transmitter release (presynaptic receptors), have been described in *Neurons, action potentials, and synapses* . In this section some general characteristics of chemical neurotransmission relevant to psychopharmacology are considered.

The targets for psychoactive drugs are one of four types of target proteins, namely receptors, ion channels, enzymes and transport proteins. Targeting a specific protein leads to alteration in neurotransmission and thereby to more widespread changes in physiological and psychological functioning. For example, cocaine blocks the reuptake of dopamine, leaving this neurotransmitter longer in the synaptic cleft. The result is a stimulation of dopaminergic systems in the brain leading to, for instance, a feeling of euphoria or repression of fatigue. Cloning the genes of the target proteins for drugs has revealed a great diversity in receptors, ion channels and other target proteins. All of the known receptors and ion channels appear to be expressed in at least three of more subtypes with quite characteristic distributions in different brain regions. For instance, the serotonin family consists of 14 identified subtypes, most with a similar architecture but with significant differences in their sequence, localization in the brain and often in their pharmacological properties. Although our present state of knowledge about receptor subtypes and their functional role is quite high, the clinical application of this knowledge lags behind. Many of the drugs nowadays used to treat patients with psychiatric disorders are often not very selective for receptor subtypes or brain areas, thereby causing unwanted, adverse side effects. For example, antipsychotics are dopamine antagonists that decrease psychotic symptoms, mainly by blocking the dopamine D_2 receptor in mesolimbic brain areas. However, by blocking D_2 receptors also in the striatum, antipsychotics cause severe motor side effects. Another example, fluoxetine, an antidepressant, selectively blocks the re-uptake of serotonin (5-HT) in the brain. This increases the presence of 5-HT in the limbic system, stimulating 5-HT_{1A} receptors and decreasing depressive symptoms. However, the increased amount of 5-HT in the brain can also stimulate the remaining 13 subtypes of 5-HT receptors in different brain areas, theoretically causing many adverse side effects. Therefore, it seems logical to develop more selectively-acting drugs affecting a particular subtype of receptors only, or being active in a particular brain region only. However, others favor the view that a broad active profile is needed to control psychiatric disorders.

The effect of a drug can gradually diminish when it is given continuously or repeatedly. Desensitization is a term to describe this phenomenon. Clinically, the term tolerance is used to describe this loss of effectiveness of a drug. Many different mechanisms can give rise to this type of phenomenon; one of them is loss of receptors. Prolonged exposure to an agonist or to the endogenous neurotransmitter can result in a gradual decrease in the number of receptors expressed on the cell surface, often called downregulation. This type of adaptation is generally an unwanted complication when drugs are used clinically, but can also be exploited. For example, classical antidepressants by increasing the amount of endogenous 5-HT, and newer antidepressants by directly stimulating the 5-HT receptor, cause a down-regulation of 5-HT receptors which is thought to underlie the therapeutic effects of the drugs. The opposite, a gradual increase in receptors takes place when a receptor is denervated from its neurotransmitter for a longer time. The receptor will up-regulate and becomes supersensitive. Also, long-term blockade of a receptor by receptor antagonists causes receptors to proliferate, leaving the cell supersensitive. This phenomenon is also clinically of importance (see also ‘Antipsychotics’ below).

As synaptic neurotransmission in the brain is thought to be the basis of (normal) physiological and psychological functioning of organisms, it is assumed that the basis of

psychiatric diseases or the occurrence of psychiatric symptoms may lie in an adaptation of, or changes in, the transmission in one or more neurotransmitter systems in the brain. This abnormal functioning of neurotransmission may be due to a combination of inherited vulnerability to a disease (genes) or to individual life events or stressors (environment). Examples of malfunctioning can be absence, excess or altered rate of neurotransmission, imbalance between neurotransmitters, loss of neuronal plasticity, excitoxicity or changed neuronal firing. Treatment with psychopharmacological agents can redirect or overcome the malfunctioning of the brain, thereby reducing the behavioral abnormalities in the patient suffering form a particular psychiatric disease.

3. Psychopharmacology and Psychotropic Drugs

Psychotropic drugs are defined as drugs that affect mood and behavior. As mentioned in the former section, it is hypothesized that a specific psychiatric disease or specific psychiatric symptoms have their origin in a neurochemical defect in the brain. Based on this assumption, conventional psychopharmacology classifies psychotropic drugs according to their beneficial effects in the clinic, i.e. according to the disorders they are believed to treat or the symptoms they are thought to relieve through counteracting or compensating abnormal neurofunctioning. For example, antipsychotics decrease psychotic symptoms in patients by blocking dopamine overactivity in the brain. In the present chapter we use this classification as a basis for discussing three different psychotropic drugs: the antipsychotics, the antidepressants and mood stabilizers, and the anxiolytics.

4. Antipsychotics

Antipsychotics are drugs that are used to treat psychosis. Psychosis itself is not a specific disorder, but it represents a syndrome with a mixture of symptoms that can be associated with different psychiatric disorders. Schizophrenia or schizo-affective diseases are psychoses, but psychoses can also result from the chronic use of stimulant drugs or sudden withdrawal from depressant drugs. Besides being linked to diseases where psychosis is one of the core symptoms, a psychotic episode can also occur in other psychiatric diseases like (bipolar) depression, mania or Alzheimer's. People experiencing a psychotic episode may suffer from hallucinations and delusions. Alongside these symptoms the patient may demonstrate personality changes and exhibit disorganized thinking and speech (thought disorder) and cognitive deficits. They lack insight in their abnormal behavior and have difficulties with social interactions. Often a psychosis is referred to as 'a loss of contact with reality'.

4.1. Schizophrenia

Although antipsychotics can be used to treat any form of psychotic illness, they are conventionally used to treat schizophrenia. Schizophrenia affects about 0.5-1% of the population, its onset is mid to late adolescence through early adulthood, and its prevalence is higher in males than females. Schizophrenia can follow a relapsing and remitting course or be chronic and progressive. The main clinical features can be categorized in the positive and the negative symptoms. Positive symptoms, also known as psychotic symptoms, are defined as an excess of normal functions. Most

characteristic are hallucinations (usually in the form of voices), delusions (often paranoid) and thought disorder. The negative symptoms are characterized by a decrease or shortage of normal functioning. Schizophrenics with negative symptoms show lack of emotional reactivity (blunted affect), emotional withdrawal, passive behavior, social withdrawal, and apathy. Finally, deficits in cognitive functioning – attention and memory – are often present. Together with aggressive and depressive symptoms this can lead to suicide in some schizophrenic patients. The number and severity of symptoms vary between affected persons, particularly with respect to balance between positive and negative symptoms. This variation in clinical phenotype has an impact on the efficacy of antipsychotics in individual cases.

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Free Online Neuropsychopharmacology Textbook (link: http://www.acnp.org/Default.aspx?Page=5thGenerationChapters) [The American College of Neuropsychopharmacology has put a massive 134 chapter textbook online covering everything from neurotransmitters to functional imaging in psychiatry, all with free access.]

Biographical Sketches

Mirjam A.F.M. Gerrits (1967) received her PhD in 1995. The topic of her thesis was 'Initiation of drug addiction; the role of dopamine and endogenous opioids'. In 2000 she was appointed as staff member of the Rudolf Magnus Institute of Neuroscience, Department of Pharmacology and Anatomy, University Medical Center Utrecht, The Netherlands. As Assistant Professor, she is teaching and performing research in the fields of neuropsychopharmacology and neuroscience.

Jan M. van Ree (1945) was appointed as staff member of the Rudolf Magnus Institute of Pharmacology in 1969. He specialized in pharmacology and received his PhD in 1975 after defending his thesis, "Self-administering behavior of drugs in rats". He was appointed as Professor of Psychopharmacology at the Utrecht University in 1987. He has been the Director of the Rudolf Magnus Institute of Neuroscience since 2001, in which the research in neurology, neuroscience, neurosurgery, pharmacology and psychiatry of the Utrecht University and the University Medical Center Utrecht is integrated. He is also Manager, Science and Education, of the Division of Neuroscience at the University Medical Center Utrecht, Director of the Rudolf Magnus Graduate School of Neuroscience, and Director of the Master of Neuroscience and Cognition at the Utrecht University.