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General Principles of Psychopharmacology

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Drug Action

Pharmacology is the science of drug action, and a drug is defined as any agent (chemical, hormone, peptide, antibody, etc.) that, because of its chemical properties, alters the structure and/or function of a biological system. Psychopharmacology is a sub-discipline of pharmacology focused on the study of the use of drugs (medications) in treating mental disorders. Most drugs used in animals are relatively selective. However, selectivity of drugs is not absolute inasmuch as they may be highly selective but never completely specific. Thus, most drugs exert a multiplicity of effects.

Drug action is typically defined as the initial change in a biological system that results from interaction with a drug molecule. This change occurs at the molecular level through drug interaction with molecular target in the biologic system (e.g. tissue, organ). The molecular target for a drug typically is a macromolecular component of a cell (e.g. protein, DNA). These cellular macromolecules that serve as drug targets are often described as drug receptors, and drug binding to these receptors mediates the initial cellular response. Drug binding to receptors either enhances or inhibits a biological process or signaling system. Of relevance to the field of psychopharmacology, the largest group of receptors are proteins. These include receptors for endogenous hormones, growth factors, and neurotransmitters; metabolic enzymes or signaling pathways; transporters and pumps; and structural proteins. Usually the drug effect is measured at a much more complex level than a cellular response, such as the organism level (e.g. sedation or change in behavior).

Drugs often act at receptors for endogenous (physiologic) hormones and neurotransmitters, and these receptors have evolved to recognize their cognate signaling molecules. Drugs that mimic physiologic signaling molecules at receptors are agonists, that is, they activate these receptors. Partial agonist drugs produce less than maximal activation of activation of receptors, while a drug that binds to the receptor without the capacity to activate the receptor may function as a receptor antagonist. Antagonists that bind to the receptor at the same site as agonists are able to reduce the ability of agonists to activate the receptor. This mutually exclusive binding of agonists and antagonists at a receptor is the basis for competitive antagonism as a mechanism of drug action. One additional class of drugs acting at physiologic receptors are inverse agonists. At physiologic receptors that

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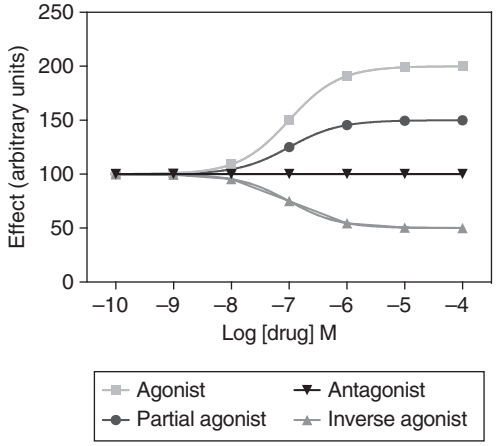

Figure 1.1 Theoretical logarithmic concentration-response relationships for agonist, partial agonist, antagonist, and inverse agonist drugs acting at a common receptor. In this theoretical set of concentration-response curves, the agonist produces a maximum response while the partial agonist is only capable of evoking a partial response. The antagonist binds to the receptor but is not capable of activating the receptor and therefore does not produce a response. Inverse agonists bind to an inactive form of the receptor and produce an effect which is in the inverse direction of that produced by the agonist.

exhibit constitutive activity in the absence of activation by an endogenous agonist, inverse agonists stabilize an inactive conformation and therefore reduce the activation of the receptor. Thus, inverse agonists produce responses that are the inverse of the response to an agonist at a given receptor. Theoretical log concentration-response curves for these four classes of drugs are depicted in Figure 1.1.

Dose Dependence of Drug Interaction with Receptors

Receptor occupancy theory assumes that drug action is dependent on concentration (dose) and the attendant quantitative relationships are plotted as dose- or concentration-response curves. Dose–response analysis is typically reserved to describe whole animal drug effects, whereas concentration-response curves describe *in vitro* drug action where the actual concentration of the drug interacting with a receptor is known. Inspection of dose–response relationships reveals that for any drug, there is a threshold dose below which no effect is observed, and at the opposite end of the curve there is typically a ceiling response beyond which higher doses do not further increase the response. As shown in Figure 1.2, these dose- or concentration-response curves are typically plotted as a function of the log of the drug dose or concentration. This produces an S-shaped curve that pulls the curve away from the ordinate and allows comparison of drugs over a wide range of doses or concentrations.

A drug-receptor interaction is typically reversible and governed by the affinity of the drug for the receptor. The affinity essentially describes the tightness of the binding of the drug to the receptor. The position of the theoretical S-shaped concentration-response curves depicted in Figure 1.2 reveals the potency of these drugs. The potency of a drug is a function of its affinity for a receptor, the number of receptors, and the fraction of receptors that must be occupied to produce a maximum response in a given tissue. In Figure 1.2, Drug A is the most potent and Drug C is least potent. The efficacy of all three drugs in Figure 1.2, however, is identical in that they all act as full agonists and produce

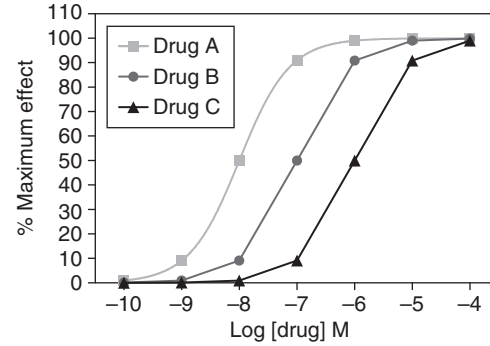

Figure 1.2 Theoretical logarithmic concentration-response relationships for three agonists which differ in relative potency. Drug A is more potent than Drug B, which in turn is more potent than Drug C.

100% of the maximal effect. As a general principle in medicine, for drugs with similar margins of safety, we care more about efficacy than potency. The comparison of potencies of agonists is accomplished by determining the concentration (or dose) that produces 50% of the maximum response (Effective Concentration, 50% = EC_{50}). In Figure 1.2, the EC_{50} values are 10^{-8}, 10^{-7}, and 10^{-6} M, respectively, for Drugs A, B and C; hence, the rank order of potency is Drug A > Drug B > Drug C, with Drug A being the most potent since its EC_{50} value is the lowest. Figure 1.3 depicts three additional theoretical concentration-response curves for drugs with identical potencies but different efficacies. In this example, Drug A is a full agonist, producing a maximum response, whereas Drugs B and C are partial agonists, producing responses, respectively, of 50% and 25% of the maximum. Similar to receptor antagonist drugs, partial agonists can compete with a full agonist for binding to the receptor. Increasing concentrations of a partial agonist will inhibit the full agonist response to a level equivalent to its efficacy, whereas a competitive antagonist will completely eliminate the response of the full agonist.

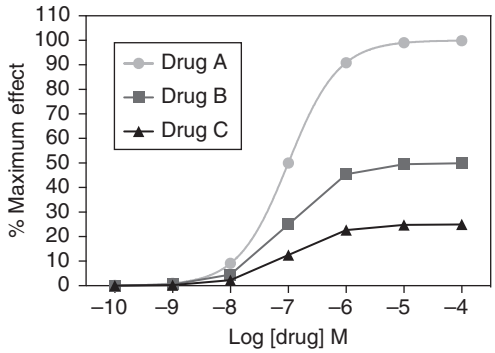

Figure 1.3 Theoretical logarithmic concentration-response relationships for three agonists with similar potency but different efficacies. Drug A is an agonist that produces a maximum response while Drugs B and C are partial agonists only capable of evoking a partial response. Drug A is therefore more efficacious than Drug B, which in turn is more efficacious than Drug C.

Structural Features of the Central Nervous System (CNS) and Neurotransmission

The cellular organization of the mammalian brain is more complex than any other biologic tissue or organ. To illustrate this complexity, consider that the human brain contains 10^{12} neurons, 10^{13} glia, and 10^{15} synapses. Understanding how this complex information processor represents mental content and directs behavior remains a daunting biomedical mystery. Recent reconstruction of a volume of the rat neocortex found at least 55 distinct morphological types of neurons (Makram et al. 2015). The excitatory to inhibitory neuron ratio was estimated to be 87:13, with each cortical neuron innervating 255 other neurons, forming on average more than 1100 synapses per neuron. This remarkable connectivity reveals the complexity of microcircuits within even a small volume of cerebral cortex.

Most neuron-to-neuron communication in the CNS involves chemical neurotransmission at up to a quadrillion of synapses. The amino acid and biogenic amine neurotransmitters must be synthesized in the presynaptic terminal, taken up, and stored in synaptic vesicles, and then released by exocytosis, when an action potential invades the terminal to trigger calcium influx. Once released into the synaptic cleft, transmitters can diffuse to postsynaptic sites where they are able to bind their receptors and trigger signal transduction to alter the physiology of the postsynaptic neuron. Just as exocytotic release of neurotransmitters is the on-switch for cell-to-cell communication in the CNS, the off-switch is typically a transport pump that mediates the reuptake of the transmitter into the presynaptic terminal or uptake into glia surrounding the synapse. A schematic of a presynaptic terminal depicted in Figure 1.4 illustrates the molecular sites that regulate neurotransmission. Once synthesized or provided by reuptake, the neurotransmitter

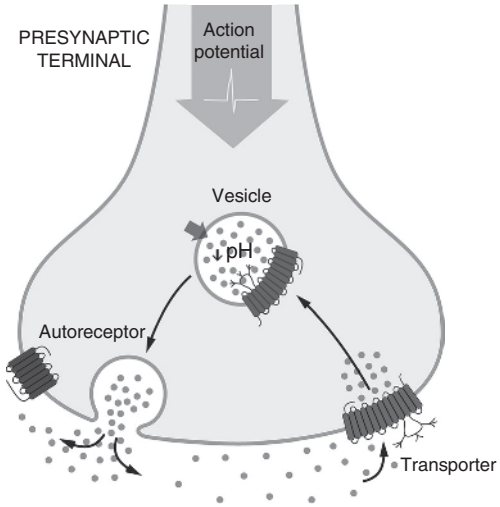

Figure 1.4 Presynaptic terminal of monoaminergic neuron, depicting sites of vesicular release, reuptake transport, and vesicular transport and storage. Monoamine transmitters are synthesized in the cytoplasm or vesicle. Transport from the cytoplasm to the vesicular compartment is mediated by the reserpine sensitive vesicular membrane transporter (VMAT2). Release into the synapse occurs by exocytosis triggered by an action of potential invasion of the terminal. Neurotransmitters are rapidly transported from the synaptic cleft back into the cytoplasm of neuron by a process termed reuptake, which involves a selective, high-affinity, Na^+-dependent plasma membrane transporter.

is transported into the synaptic vesicle for subsequent exocytosis. The pH gradient across the vesicular membrane is established by the vacuolar H^+-ATPase, which uses ATP hydrolysis to generate the energy required to move H^+ ions into the vesicle (Lohr et al. 2017). This movement of H^+ ions creates the vesicular proton gradient and establishes an acidic environment inside the vesicle (pH of ~5.5). Specific reuptake transporters are localized on the plasma membrane where they recognize transmitters and transport them from the synaptic cleft into the cytoplasm of the terminal (Torres et al. 2003). These transporters have evolved to recognize specific transmitters such as dopamine, serotonin, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA). In all cases, these presynaptic transporters regulate the extracellular concentration of transmitters and therefore a mechanism for termination of their respective synaptic actions. The monoamine transporters (dopamine, norepinephrine, and 5-hydroxytryptamine) are the pharmacological targets for antidepressants and psychostimulants.

Presynaptic terminals also express neurotransmitter autoreceptors that function as local circuit negative feedback inhibitor mechanisms to inhibit further exocytotic release of the transmitter when its synaptic concentration is elevated.

Figure 1.5 illustrates the comparison of presynaptic terminals for the biogenic amine neurons: dopamine, norepinephrine, and 5-hydroxytryptamine (serotonin). The biosynthesis of each biogenic amine transmitter is indicated with uptake and storage in synaptic vesicles. The vesicular uptake of all three biogenic amines depicted is mediated by a common transporter, vesicular monoamine transporter 2 (VMAT2). VMAT2 is the vesicular monoamine transporter that transports dopamine, norepinephrine, and 5-hydroxytryptamine into neuronal synaptic vesicles. VMAT2 is an H^+-ATPase antiporter, which uses the vesicular electrochemical gradient to drive the transport of biogenic amines into the vesicle (Lohr et al. 2017). In contrast to VMAT2 being expressed in all three biogenic amine neurons, each neurotransmitter neuron expresses a distinct plasma membrane transporter. These transporters are members of the SLC6 symporter family that actively translocate amino acids or amine neurotransmitters into cells against their concentration gradient using, as a driving force, the energetically favorable coupled movement of ions down their transmembrane electrochemical gradients. The dopamine transporter (DAT), the norepinephrine transporter (NET), and the serotonin transporter (SERT) are all uniquely expressed in their respective neurotransmitter neurons and couple the active transport of biogenic amines with the movement of one Cl^- and two Na^+ ions along their concentration gradient. The ionic concentration gradient is

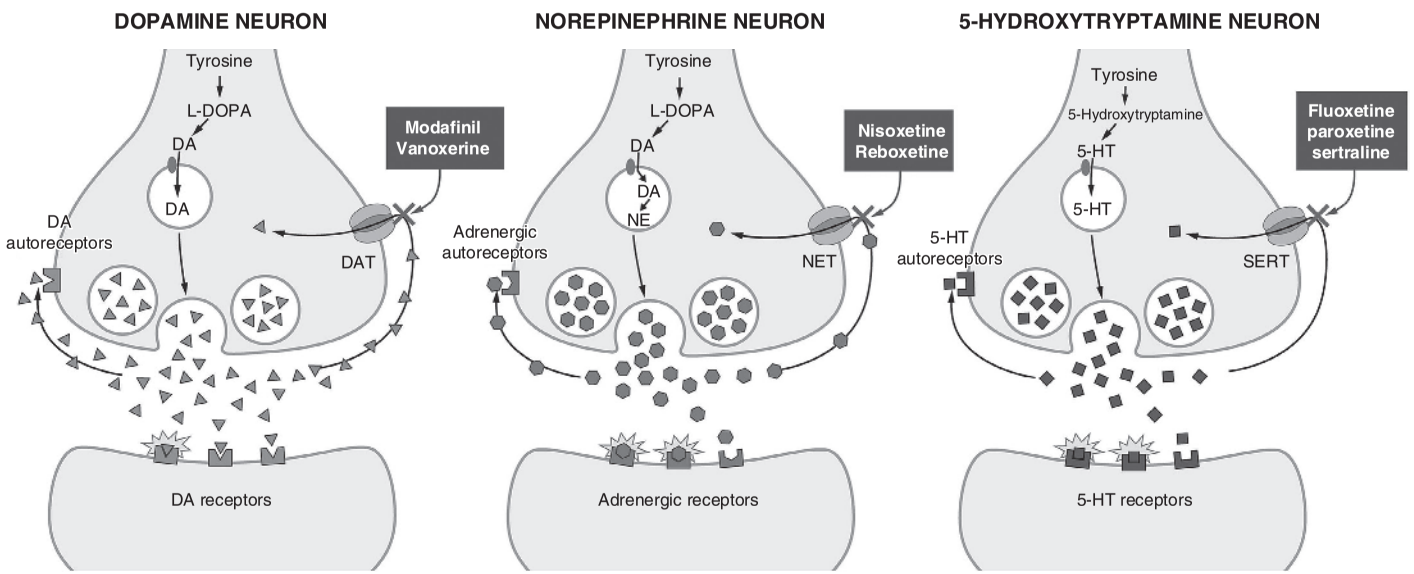

Figure 1.5 Schematic comparison of dopamine, norepinephrine, and 5-hydroxytryptamine (serotonin) synapses. Each neuron expresses a monoamine transporter selective for its neurotransmitter. These transporters function as reuptake pumps that terminate the synaptic actions of the transmitters and promote uptake and eventual storage of the transmitter in vesicles. Selective drug inhibitors of each monoamine transporter are shown. Abbreviations: DA, dopamine; DAT, dopamine transporter; NE, norepinephrine; NET, norepinephrine transporter; 5-HT, 5-hydroxytryptamine; SERT, serotonin transporter.

created by the plasma membrane Na^+/K^+ ATPase and serves as the driving force for transmitter uptake. Examples of drugs that act as selective inhibitors for all three biogenic transporters are listed. The three monoamine transporters, DAT, NET, and SERT, represent important pharmacological targets for many behavioral disorders including depressive, compulsive and appetite-related behavioral problems. The three neurotransmitter terminals also express unique presynaptic autoreceptors that regulate exocytotic release.

Biogenic Amine Neurotransmitters and Affective Disorders

The role of biogenic amines in affective disorders has a long history, beginning in the 1950s. The biogenic amine theory for affective disorders emerged as pharmacologists and psychiatrists began to explore the biologic basis for mental disorders. Initially, insights were gained from better understanding of the cellular actions of drugs and correlation of this knowledge of drug action with the therapeutic and behavioral responses to the same drugs in the clinic. In its original formulation, the biogenic amine theory for affective disorders stated that depression was due to a deficiency of biogenic amines in the brain, while mania was due to an excess of these transmitters. In the 1950s, iproniazid was used in the treatment of tuberculosis, and it was observed that in some patients with depressive symptoms, their mood improved over the course of a chronic regimen with iproniazid. Concurrently, preclinical research showed that iproniazid was an inhibitor of the enzyme monoamine oxidase (MAO). MAO catalyzes the degradation of dopamine (DA), norepinephrine (NE), and serotonin (5-HT), and inhibition of MAO was found to elevate the levels of these transmitters in animal brains. Also, in the 1950s, reserpine was being used as an antihypertensive. Some patients treated with reserpine developed depressive symptoms severe enough in some cases to produce suicide ideation. Animals given reserpine also developed depression-like symptoms consisting of marked sedation. Reserpine was shown to deplete the CNS of DA, NE, and 5-HT by virtue of its ability to block the vesicular uptake of these monoamines. Blocking the vesicular uptake of monoamines leads to a depletion of the transmitters due to degradation by the mitochondrial enzyme MAO. Therefore, vesicular storage of monoamines is not only a prerequisite for exocytosis but also a means of preventing degradation of the transmitters in the cytosolic compartment. One other observation in the 1950s was that imipramine, developed initially as an antipsychotic drug candidate, elevated mood in a subpopulation of schizophrenic patients with comorbid depressive illness. Preclinical research revealed that imipramine, and other tricyclic antidepressants, were able to block monoamine transport into presynaptic terminals. This action would therefore produce an elevation of synaptic levels of biogenic amines. All these observations with iproniazid, reserpine, and imipramine were therefore consistent with the original formulation of the biogenic amine hypothesis for affective disorders.

Although today we continue to recognize the role of biogenic amines in depression, several discrepancies in the original hypothesis are appreciated. As an example, some clinically effective antidepressants do not block the presynaptic transport of monoamines and are not MAO inhibitors. However, importantly for a hypothesis that attempts to correlate synaptic levels of monoamines with mood, while synaptic levels of monoamines are elevated within a time domain of a few hours after antidepressant administration, the symptoms of depression do not resolve until several weeks of chronic therapy with antidepressant drugs. Contemporary hypotheses to explain the mechanism of action of antidepressant drugs

therefore seek an appropriate temporal correlation between neurochemical drug action and the mitigation of the symptoms of depression. Rather than a focus on the synaptic levels of biogenic amines, contemporary views of the mechanism of action of antidepressants are focused on the regulation of receptor signaling.

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