Illustrated MEDICAL PHARMACOLOGY

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SECTION 3

Drugs Affecting Central Nervous System

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CHAPTER

3.1

Central Nervous System

The central nervous system (CNS) directs the functions of all tissues of the body. The peripheral nervous system (PNS) receives thousands of sensory inputs and transmits them to the brain via the spinal cord. The brain processes this incoming information and discards 99 percent as unimportant. After sensory information has been evaluated, selected areas of the CNS initiate nerve impulses to organs or tissue to make an appropriate response.

NEUROTRANSMITTERS

The brain produces natural chemical messengers called 'neurotransmitters' (Fig. 3.1.1) that send messages from one nerve cell to another. Serotonin is known as the 'feel good' neurotransmitter because it plays an important role in the regulation of mood. Low levels of serotonin can cause excessive feelings of sadness and anxiety.

Two other important neurotransmitters 'dopamine and norepinephrine (NE)' also affect mood. When the brain does not produce enough dopamine or NE, one can feel tired, unmotivated and foggy-headed.

A fourth neurotransmitter, called gamma aminobutyric acid (GABA), helps to relax. When levels of GABA are low, one will feel anxious and agitated.

Of course, it is normal to feel sad or upset sometimes. But when a chemical imbalance in the brain persists for weeks or months, the result is prolonged depression or anxiety.

Norepinephrine

Norepinephrine is released naturally in both the CNS and in the sympathetic nerves. In the brain, it is responsible for regulating nerve impulses (Fig. 3.1.2). When the body produces the correct amount of NE, a patient's blood pressure (BP) stabilizes. When the amount of this hormone is too low in a patient's system, he/she may experience depression, poor circulation and is at increased risk of heart attack. Norepinephrine, in chemical form, is used to resuscitate patients with cardiac arrest.

Norepinephrine balances epinephrine in the nervous system. The adrenal medulla produces both. When a stressful situation calls for action, the adrenal gland secretes epinephrine, causing the nervous system to enter a state of high alert. At the same time, NE shoots into the bloodstream and allows the brain to make a snap decision. The two chemicals balance and complement each other.

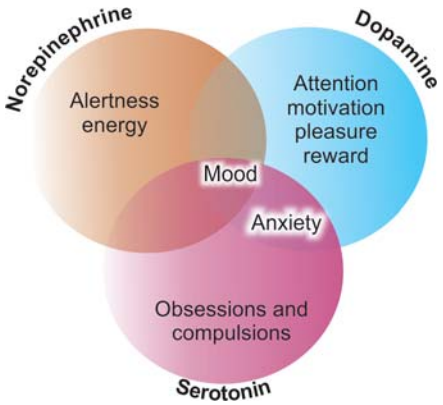

Fig. 3.1.1: Neurotransmitters of brain and their effects

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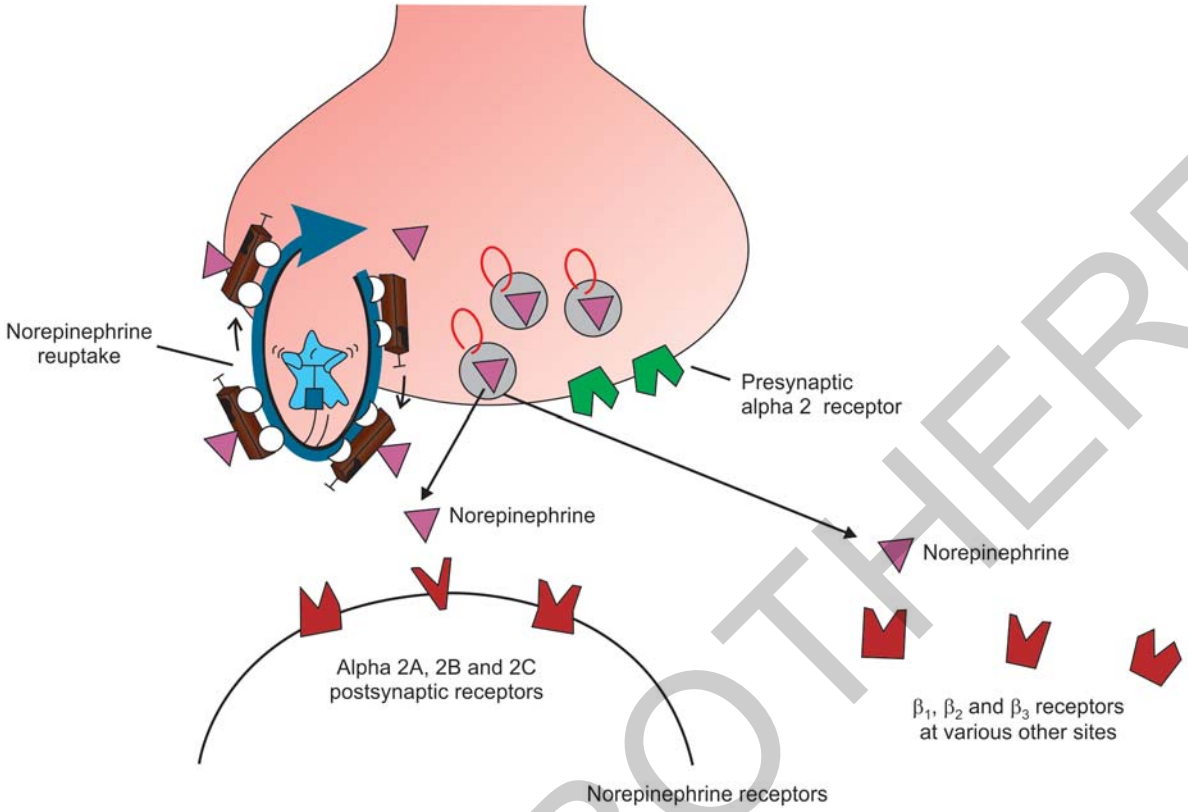

Fig. 3.1.2: Sites of synthesis and action of norepinephrine

Norepinephrine, when administered by intravenous injections to patients suffering from dangerously low BP. It stimulates the heart muscle and dilates constricted arteries. It may also be given to a patient suffering from acute myocardial infarction in an attempt to stabilize the heart rhythm and allow more oxygen to reach the brain.

The locus coeruleus is intimately involved in rapid eye movement (REM) sleep and in addition is involved in clinical depression, panic disorder and anxiety. Some antidepressant medications including reboxetine, venlafaxine, and bupropion, as well as attention deficit hyperactivity disorder (ADHD) medication atomoxetine, are believed to act on neurons in this area.

The locus coeruleus is responsible for mediating many of the sympathetic effects during stress. The locus coeruleus (Fig. 3.1.3) is activated by stress and will respond by increasing NE secretion, which in turn will increase cognitive function (through the prefrontal cortex), increase motivation (through nucleus accumbens), activate the hypothalamic-pituitary-adrenal axis and increase the sympathetic discharge/inhibit parasympathetic tone (through the brainstem). Specific to the activation of the hypothalamopituitary adrenal axis, NE will stimulate the secretion of corticotropin-releasing factor from the hypothalamus, which induces adrenocorticotropic hormone release from the anterior pituitary and subsequent cortisol synthesis in the adrenal glands. Norepinephrine released from locus coeruleus will inhibit its production by feedback mechanism. Corticotropin-releasing hormone will inhibit its production by feedback mechanism, while positively feeding to the locus coeruleus to increase NE production.

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Serotonin

Serotonin is passed by one neuron to another neuron in the brain. Projections from raphe nuclei (Fig. 3.1.4) are mediated by serotonin. Serotonin is commonly known as a 'mood neurotransmitter' and is responsible, when not in sufficient quantity causes depression. However, serotonin has been linked to several other moods, such as mania and aggression.

Serotonin, like any other neurotransmitter, is passed down the vesicle to the presynaptic terminal where a chemical process occurs, allowing that synapse to release the neurotransmitter. On the other end, receptors sit on the next synapse to receive those neurotransmitters, where the process will repeat until it is passed on to the rest of the body. When a neurotransmitter is not received by the next synapse, it will go through the reuptake process, meaning it is carried back to the synapse of origin. It is when too much or too little serotonin is received by the next synapse that problem occurs.

Low levels of serotonin have been linked to depression, aggression and poor impulse control. While scientists are still trying to figure out all the roles serotonin plays, it is clear that it does not affect all people the same way.

Serotonin is believed to carry messages of positive effect, which when too few reach the opposite synapse, will be inhibited. Many symptoms of depression are linked to low serotonin levels such as sleeplessness, hopelessness and psychomotor agitation (involuntary movements in the body).

Commonly used anti-depressants (Fig. 3.1.5) are monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs). Unlike MAOIs, SSRIs block the reuptake process, allowing more serotonin to enter the

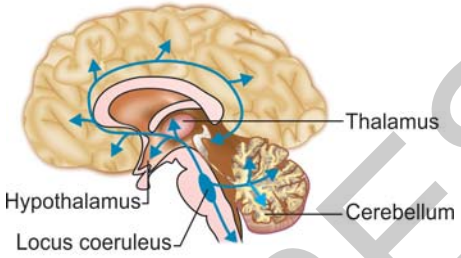

Fig. 3.1.3: Locus coeruleus circuit mediated by norepinephrine

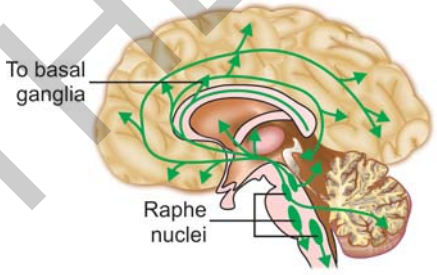

Fig. 3.1.4: Projections from raphe nuclei is mediated by serotonin

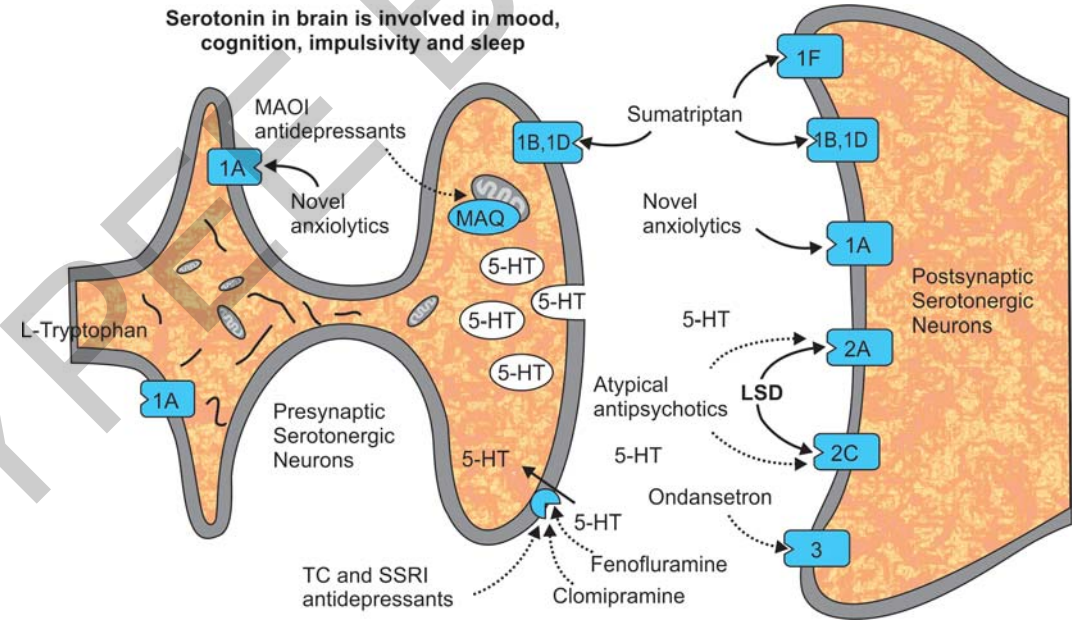

Fig. 3.1.5: Sites of serotonin synthesis and action of commonly used antidepressants
(TC = Tricyclic antidepressants; SSRI = Selective scrotonin reuptake inhibitors; 5-HT = 5-hydroxytryptamine; MAOI = Monoamine oxidase inhibitor; LSD = Lysergic acid diethylamide)

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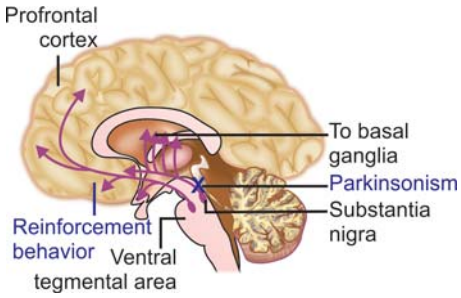

Fig. 3.1.6: Projections of substantia nigra and ventral tegmental area is mediated by dopamine

receptor sites of the opposite synapse. Common SSRIs include Celexa (citalopram), Lexapro (escitalopram), Zoloft (sertraline) and Paxil (paroxetine).

Low levels of serotonin are also linked to aggression and poor impulse control. Several street (illegal) drugs can either impede or enhance the level of serotonin in a person's brain.

1. Amphetamines can increase the concentration of serotonin in certain parts of the brain, generating heightened mood.
2. Cocaine may prevent the reuptake of serotonin, producing a temporary feeling of happiness and increased energy.
3. Lysergic acid diethylamide (LSD) actually shares the chemical structure of serotonin, stimulating receptors and increasing the quantity in certain areas of the brain.

Dopamine

The brain of man contains dopamine-producing neurons, located in the ventral tegmental area and substantia nigra in the midbrain. These neurons extend axons, via the medial forebrain bundle, into the frontal cortex, striatum, hippocampus and amygdala (Fig. 3.1.6), where they release dopamine that activates D_1- and, D_2-receptors at high concentrations (Fig. 3.1.7).

Ambient dopamine concentrations in the brain determine our level of attention. Too much dopamine leads to rigid, inflexible thinking, whereas too little leads to distractibility. Stimulants such as ritalin and coffee increase dopamine tone in the brain. Dopamine reinforces learning and repetition of behaviors that precede them.

Acetylcholine

Increased synaptic release of both acetylcholine (ACh) and serotonin are associated with increased brain activity (Fig. 3.1.8). A new 'neurotransmitter binding theory' is hypothesized, which is then used to associate increased brain activity with elevations in mood and an increased ability to concentrate, think and make rational decisions. The ACh binding to nicotinic receptors in brain is involved in learning and memory.

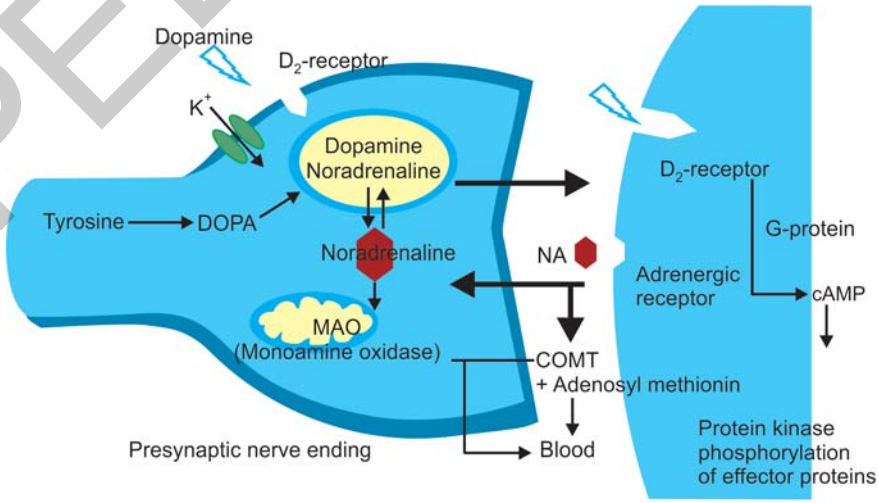

Fig. 3.1.7: Sites of dopamine synthesis in brain and its action (COMT = Catechol-o-methyl transferase; NA = Noradrenaline; DOPA = Dihydroxy phenyl acetic acid; cAMP = Cyclic adenosine monophosphate)

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Alzheimer disease decreases the levels of ACh, a chemical that is responsible for memory, judgment and thought process. Over time, the brain of the Alzheimer's patient shrinks as the cells and tissues are destroyed. The common drugs prescribed for the treatment of this disease work by protecting the cholinergic system, which is the system responsible for memory and learning. They also prevent the levels of ACh from decreasing, which prolongs the deterioration of brain cells.

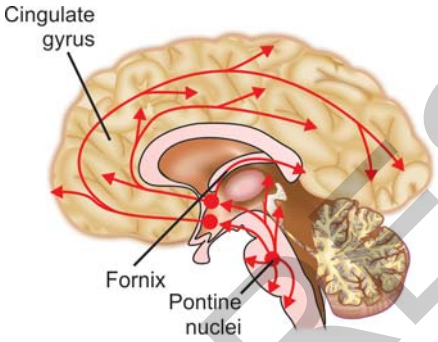

Fig. 3.1.8: Projection from pontine nuclei mediated by acetylcholine

CENTRAL NERVOUS SYSTEM STIMULANTS

Stimulants are drugs that exert their action through excitation of the CNS. Psychic stimulants include caffeine, cocaine and various amphetamines. These drugs are used to enhance mental alertness and reduce drowsiness and fatigue.

Caffeine

Caffeine (Fig. 3.1.9) and the chemically related xanthines [theophylline (Fig. 3.1.10) and theobromine], have stimulatory action in the decreasing order. They are included in over the counter drugs.

However, increasing the dosage of caffeine above 200 mg (about 2 cups of coffee) does not increase mental performance, but may increase nervousness, irritability, tremors and headache. Heavy coffee drinkers become psychically dependent upon caffeine. If caffeine is withheld, a person may experience mild withdrawal symptoms characterized by irritability, nervousness and headache.

The action of caffeine is to block purinergic (adenosine) receptors (P2Y and A2b) as an antagonist (Fig. 3.1.11). The G-protein (Gp) and phospholipase-C coupled P2Y6 receptors are present in the airway are selectively activated by uridine diphosphate (UDP). As caffeine has a similar structure to the adenosine group, it will fit adenosine receptors and block adenosine binding. It inhibits the release of neurotransmitters from presynaptic sites, but works in concert with NE or angiotensin to augment their actions. Antagonism of adenosine receptors by caffeine would appear to promote neurotransmitter release, thus explaining the stimulatory effects of caffeine.

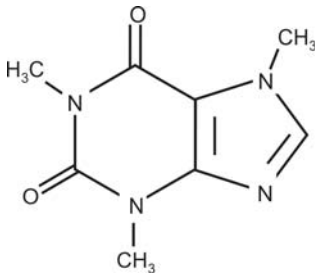

Fig. 3.1.9: Caffeine

Amphetamines

The stimulation caused by amphetamines is due to excessive release of NE from storage sites in the PNS. It is not known whether the same action occurs in the CNS. Two other theories for their action are that they are degraded slower than norepinephrine or that they could act on serotonin receptor sites.

Therapeutic doses of amphetamine elevate mood, reduce feelings of fatigue and hunger, facilitate powers of concentration, and increase the desire and capacity to carry out work. They induce exhilarating feelings of power, strength, energy, self-assertion, focus and enhanced motivation. The need to sleep or eat is diminished.

Levoamphetamine (Benzedrine), dextroamphetamine (Dexedrine) and methamphetamine (Methedrine) (Fig. 3.1.12) are collectively referred to as amphetamines (Fig. 3.1.13).

Benzedrine is a mixture of both the dextro and levoamphetamine isomers. The dextro isomer is several times more potent than the levo isomer.

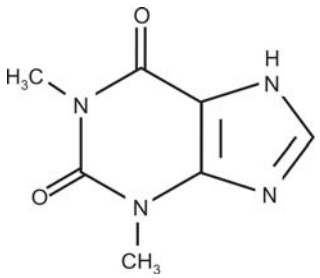

Fig. 3.1.10: Theophylline

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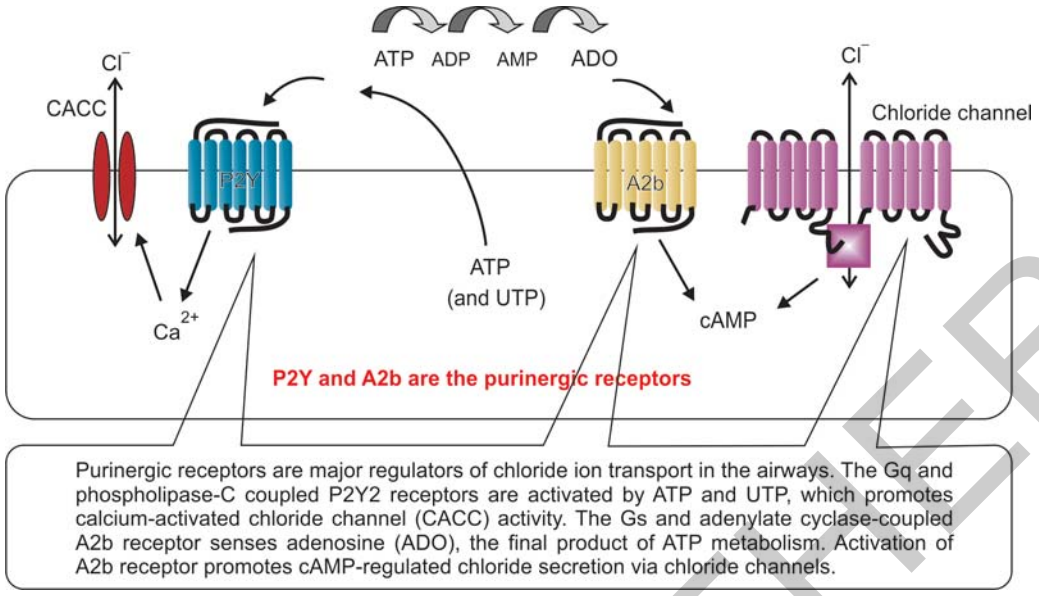

Fig. 3.1.11: Mechanism of action at purinergic receptors (ATP = Adenosine triphosphate; ADP = Adenosine diphosphate; AMP = Adenosine monophosphate; UTP = Uridine triphosphate; CAMP = Cyclic adenosine monophosphate)

The misuse and abuse of amphetamines is a significant problem, which may include the housewife taking diet pills, athletes desiring an improved performance, the truck driver driving non-stop coast to coast or a student cramming all night for an examination.

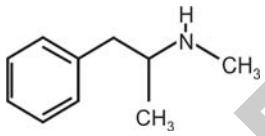

Fig. 3.1.12: Methamphetamine

ANTIDEPRESSANT

Antidepressant drugs are used to restore mentally depressed patient's to an improved mental status. Depression results from a deficiency of NE at receptors in the brain. Mechanisms that increase their effective concentration at the receptor sites should alleviate depression. Antidepressant drugs act by one or more of the following stimulation type mechanisms:

i. *Increase release of norepinephrine:* Amphetamines and electroconvulsive therapy act by this mechanism. Amphetamines mimic NE.
ii. *Prevent inactivation of norepinephrine:* Monoamine oxidase (MAO) inhibitors are thought to act as antidepressant agents in part by preventing the breakdown and inactivation of NE.
iii. *Prevent the reuptake of norepinephrine:* The action of NE at the receptor site is terminated by the reuptake of NE by the neuron from, which it was originally released.

Tricyclic Antidepressants

The tricyclic antidepressants are the most effective drugs presently available for the treatment of depression. These act by increasing the release of NE. Amphetamine and cocaine can also act in this manner.

Imipramine, amitriptyline and other closely related drugs are among the drugs currently most widely used for the treatment of major depression (Fig. 3.1.14).

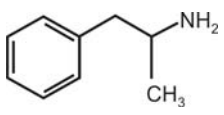

Fig. 3.1.13: Amphetamine

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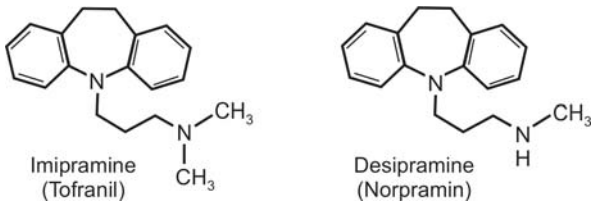

Fig. 3.1.14: Tricyclic antidepressants

Imipramine (Tofranil) and Desipramine (Norpramin)

The activity of the tricyclic drugs depends on the central ring of seven or eight atoms, which confers an angled or twisted conformation. The side chain must have at least two carbons although three appear to be better. The amine group may be either tertiary or secondary.

All tricyclic antidepressants block the reuptake of NE at nerve terminals. However, the potency and selectivity for the inhibition of the uptake of NE, serotonin and dopamine vary greatly among the agents. The tertiary amine tricyclics seem to inhibit the serotonin uptake pump, whereas the secondary amine ones seem better in switching off the NE pump. For instance, imipramine is a potent and selective blocker of serotonin transport, while desipramine inhibits the uptake of NE.

Inhibitory Action of Antidepressants on Serotonin Uptake

Serotonin [5-hydroxytryptamine (5-HT)] is a monoamine neurotransmitter found in cardiovascular tissue in endothelial cells in blood cells and in the CNS (Fig. 3.1.15). The role of serotonin in neurological function is diverse and there is a little doubt that serotonin is an important CNS neurotransmitter.

Although some of the serotonin is metabolized by MAO, most of the serotonin released into the postsynaptic space is removed by the neuron through a reuptake mechanism inhibited by the tricyclic antidepressants and the newer, more selective antidepressant reuptake inhibitors such as fluoxetine and sertraline.

Selective Serotonin Reuptake Inhibitors

In recent years, selective serotonin reuptake inhibitors have been introduced for the treatment of depression. Prozac is the most famous drug in this class. Clomipramine, fluoxetine (Prozac), sertraline and paroxetine (Fig. 3.1.16) selectively block the reuptake of serotonin, thereby increasing the levels of serotonin in the CNS. Note the similarities and differences between the tricyclic antidepressants and the selective serotonin reuptake inhibitors. Clomipramine has been useful in the treatment of obsessive-compulsive disorders.

Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) causes the oxidative deamination of NE, serotonin and other amines. This oxidation is the method of reducing the concentration of the neurotransmitter after it has sent the signal at the receptor site. A drug

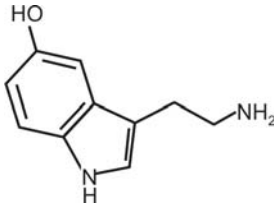

Fig. 3.1.15: Serotonin

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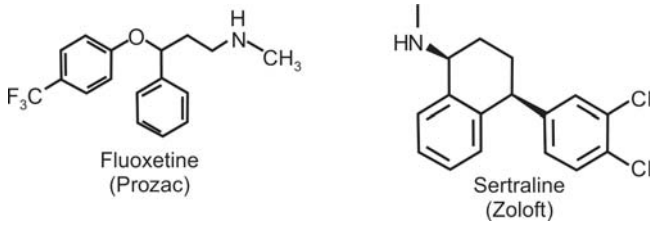

Fig. 3.1.16: Serotonin reuptake inhibitors

that inhibits this enzyme has the effect of increasing the concentration of the NE, which in turn causes a stimulation effect.

Most MAOIs are hydrazine derivatives. Hydrazine is highly reactive and may form a strong covalent bond with MAO with consequent inhibition for up to 5 days.

These drugs are less effective and produce more side effects than the tricyclic antidepressants. For example, they lower BP and were at one time used to treat hypertension. Their use in psychiatry has also become very limited, as the tricyclic antidepressants have come to dominate the treatment of depression and allied conditions. Thus, MAOIs are used most often when tricyclic antidepressants give unsatisfactory results.

Phenelzine: It is the hydrazine analog of phenyl ethylamine, a substrate of MAO. This and several other MAOIs, such as isocarboxazide, are structurally related to amphetamine (Fig. 3.1.17) and were synthesized in an attempt to enhance central stimulant properties.

Phenelzine (Nardil) and isocarboxazid (Marplan):

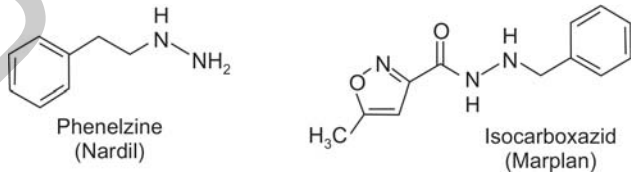

Fig. 3.1.17: Monoamine oxidase (MAO) inhibitors

HALLUCINOGENIC DRUGS

Hallucinogenic agents, also called 'psychotomimetic agents', are capable of producing hallucinations, sensory illusions and bizarre thoughts. The primary effect of these compounds is to consistently alter thought and sensory perceptions. Some of these drugs are used in medicine to produce model psychoses as aids in psychotherapy. Another purpose is to investigate the relationship of mind, brain and biochemistry with the purpose of elucidating mental diseases such as schizophrenia.

A large body of evidence links the action of hallucinogenic agents to effects at serotonin receptor sites (Fig. 3.1.18) in the CNS. Whether the receptor site is stimulated or blocked is not exactly known. The serotonin receptor site may consist of three polar or ionic areas to complement the structure of serotonin as shown in the graphic on the left.

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Mescaline and Psilocybin

The drugs shown in the graphic can be isolated from natural sources: lysergic acid amide from morning glory seeds, psilocybin (Fig. 3.1.19) from the 'magic mushroom', psilocybe mexicana.

The hallucinogenic molecules fit into the same receptors as the neurotransmitter, and over-stimulate them, leading to false signals being created.

Mescaline (Fig. 3.1.20) is isolated from a peyote cactus. The natives of Central America first made use of these drugs in religious ceremonies, believing the vivid, colorful hallucinations had religious significance. The Aztecs even had professional mystics and prophets who achieved their inspiration by eating the mescaline-containing peyote cactus (Lophophora williamsii). This plant is said to have been distributed to the guests at the coronation of Montezuma to make the ceremony seem even more spectacular.

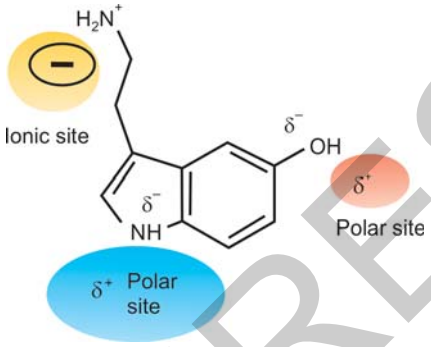

Fig. 3.1.18: Serotonin receptor

Lysergic Acid Diethylamide

Lysergic acid diethylamide (LSD) (Fig. 3.1.21) is one of the most powerful hallucinogenic drugs known. LSD stimulates centers of the sympathetic nervous system in the midbrain, which leads to pupillary dilation, increase in body temperature and rise in the blood-sugar level. LSD also has a serotonin-blocking effect.

The hallucinogenic effects of LSD are also the result of the complex interactions of the drug with both the serotoninergic and dopaminergic systems.

During the first hour after ingestion, the user may experience visual changes with extreme changes in mood. The user may also suffer impaired depth and time perception, with distorted perception of the size and shape of objects, movements, color, sound, touch and the user's own body image.

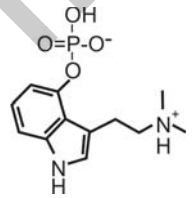

Fig. 3.1.19: Psilocybin

CENTRAL NERVOUS SYSTEM DEPRESSANTS—SEDATIVE AND HYPNOTIC AGENTS

Hypnotic and sedative drugs are non-selective, general depressants of the CNS. If the dose is relatively low, a sedative action results in a reduction in restlessness and emotional tension. A larger dose of the same drug produces a hypnotic sleep inducing effect. As the doses are increased further, the result is anesthesia or death if the dose is sufficiently high.

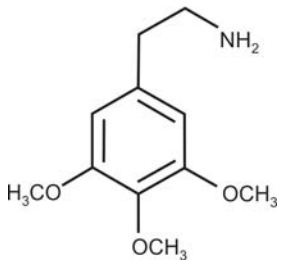

Fig. 3.1.20: Mescaline

Barbiturates

The barbiturates once enjoyed a long period of extensive use as sedative-hypnotic drugs; however, except for a few specialized uses, they have been largely replaced by the much safer benzodiazepines.

Barbiturates are CNS depressants and are similar, in many ways, to the depressant effects of alcohol. To date, there are about 2,500 derivatives of barbituric acid of which only 15 are used medically. The first barbiturate was synthesized from barbituric acid in 1864. The original use of barbiturates was to replace drugs such as opiates, bromides and alcohol to induce sleep.

The hypnotic and sedative effects produced by barbiturates are usually ascribed to their interference of nerve transmission to the cortex. Various theories for the action of barbiturates include: changes in ion movements across the cell membrane; interactions with cholinergic and non-cholinergic receptor

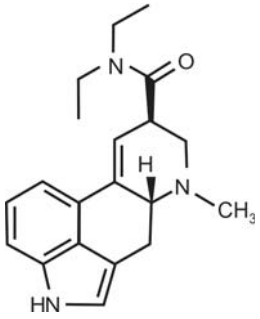

Fig. 3.1.21: Lysergic acid diethylamide (LSD)

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sites; impairment of biochemical reactions which provide energy; and depression of selected areas of the brain.

The structures of the barbiturates (Fig. 3.1.22) can be related to the duration of effective action. Although over 2,000 derivatives of barbituric acid have been synthesized only about a dozen are currently used. All of the barbiturates are related to the structure of barbituric acid shown in Figure 3.1.22.

The duration of effect depends mainly on the alkyl groups attached to carbon-5, which confer lipid solubility to the drug. The duration of effective action decreases as the total number of carbons at C-5 increases. To be more specific, a short chain and/or phenyl group achieves a long effect. A short duration effect occurs when there are the most carbons and branches in the alkyl chains.

Benzodiazepines

The term benzodiazepine refers to the portion of the structure composed of a benzene ring fused to a seven-membered diazepine ring (Fig. 3.1.23). However, since all of the important benzodiazepines contain an aryl substituent ring C and a 1,4-diazepine ring, the term has come to mean the aryl-1,4-benzodiazepines. There are several useful benzodiazepines available: chlordiazepoxide (Librium) and diazepam (Valium).

The actions of benzodiazepines are a result of increased activation of receptors by GABA. Benzodiazepine receptors are located on the alpha subunit of the GABA receptor located almost exclusively on postsynaptic nerve endings in the CNS (especially cerebral cortex). Benzodiazepines enhance the GABA transmitter in the opening of postsynaptic chloride channels that leads to

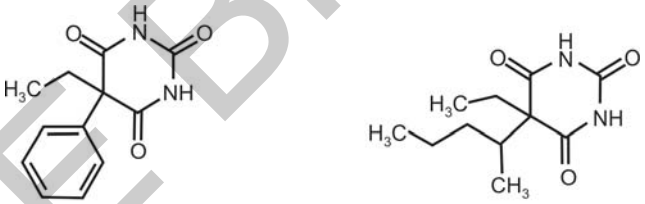

Fig. 3.1.22: Barbiturates

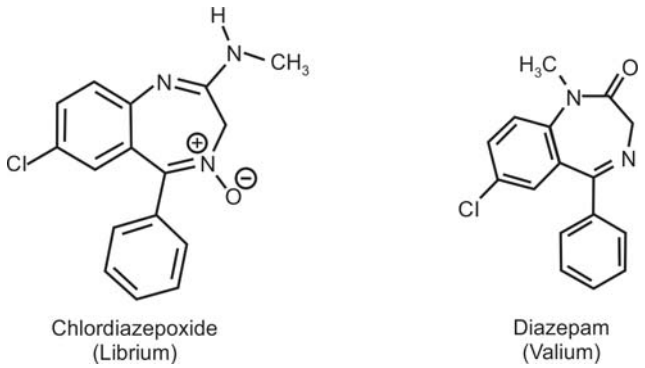

Fig. 3.1.23: Benzodiazepines

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hyperpolarization of cell membranes. That is, they 'bend' the receptor slightly so that GABA molecules attach to and activate their receptors more effectively and more often.

NARCOTIC ANALGESIC DRUGS

Narcotic agents are potent analgesics which are effective for the relief of severe pain. They are selective CNS depressants used to relieve pain. The term analgesic means 'without pain'. Even at therapeutic doses, they can cause respiratory depression, nausea and drowsiness. Long-term administration produces tolerance, psychic and physical dependence called addiction.

Narcotic agents may be classified into four categories:

1. Morphine and codeine—natural alkaloids of opium.
2. Synthetic derivatives of morphine such as heroin.
3. Synthetic agents that resemble the morphine structure.
4. Narcotic antagonists that are used as antidotes for overdoses of narcotic analgesics.

The main pharmacological action of analgesia is on the cerebrum and medulla of the CNS. The other effect is on the smooth muscle and glandular secretions of the respiratory and gastrointestinal tract. The precise mechanism of action is unknown although the narcotics appear to interact with specific receptor sites to interfere with pain impulses.

Receptor Site

The analgesic receptor for morphine need three areas (Fig. 3.1.24); a flat area to accommodate a flat nonpolar aromatic ring, a cavity to accept another series of rings in perpendicular and an anionic site for polar interaction of the amine group.

Natural Peptide Analgesics

Enkephalins

There are two compounds in the brain called 'enkephalins' that resemble the structure of morphine. Each one is a peptide composed of five amino acids and differs only in the last amino acid. The peptide sequences are: tyr-gly-gly-phe-leu and tyr-gly-gly-phe-met. Molecular models show that the structure of the

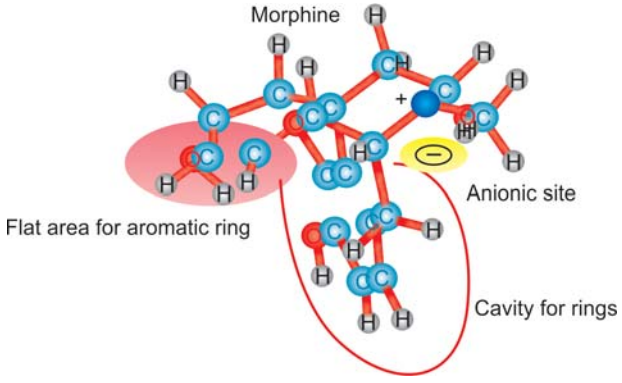

Fig. 3.1.24: Analgesic receptor for morphine

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