

NEUROTRANSMITTERS, PSYCHOACTIVE DRUGS AND CONTROLLED SUBSTANCES

1. NEUROTRANSMITTERS

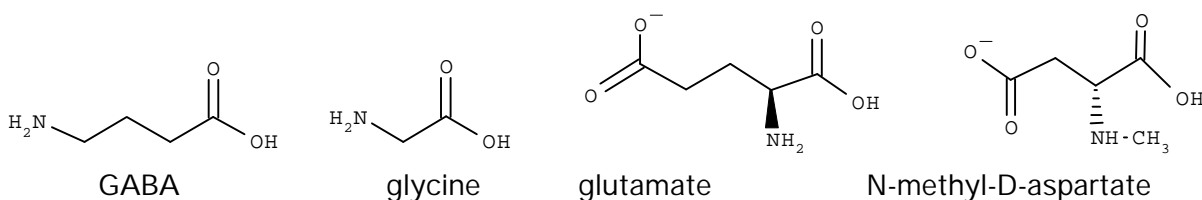
Communication between nerve cells and between nerve, muscle and gland cells makes all activity and thought possible. The nerve cell membrane has receptors which normally bind the neurotransmitter released by an adjacent cell from its axon membrane. The binding of the neurotransmitter to the receptor acts as a switch to transmit an electrical pulse through that cell, triggering neurotransmitter release to the next cell; other reactions to the pulse initiate release and destruction or reuptake of the original neurotransmitter to stop the conduction. The receptors themselves are complex assemblages of proteins but the neurotransmitters that trigger them, the internal messengers they release, and the various modulators, drugs, and nerve poisons that affect the process, are often small molecules.

The delicate control of these molecules determines cognition, mood, blood pressure, appetite (for food and reproduction), muscle coordination, etc. In recent years, studies of the mechanism of action of drugs using radioactive or fluorescent labels and spectroscopic identification of tiny amounts of material, have begun to unravel the normal processes that the drugs augment or hinder. For example, a search for the morphine receptor in the brain uncovered the enkephalins and endorphins, simple peptides which block the pain response.

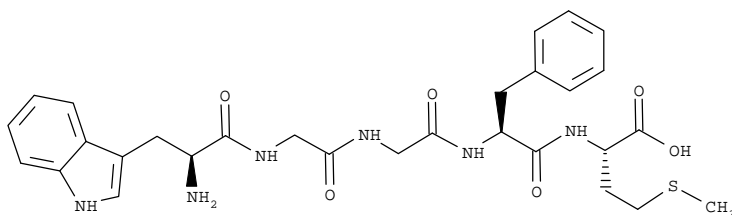
In the peripheral nervous system, the sorting of nerve signals is mostly spatial and most neurotransmitters travel only short distances (20 - 50 nm) to the next cell. The severe crowding of nerve cells in the brain necessitates more selectivity and thus specialized neurotransmitters and receptors. Perhaps the most famous neurotransmitters are adrenaline (epinephrine) and acetylcholine, but amino acids are probably the major transmitters in the mammalian central nervous system (CNS). Neurotransmitters may be: amino acids, peptides, quaternary ammonium salts, 2-arylethyl amines. Transmission of signals from nerves to other nerves and muscles is often facilitated in a remarkable way - using NO, nitric oxide, a reactive and toxic oxidizing agent that survives for only a short time and a short distance from the cell which synthesizes it.

a. AMINO ACIDS AND PEPTIDES

Gamma-aminobutanoic acid (GABA) is found in high concentrations in the brain and spinal cord but not in peripheral nerve tissue; like glycine, alanine and serine it serves as an inhibitor (depressant). On the other hand, glutamate, aspartate and N-methylaspartate (NMDA) are powerful CNS stimulants.



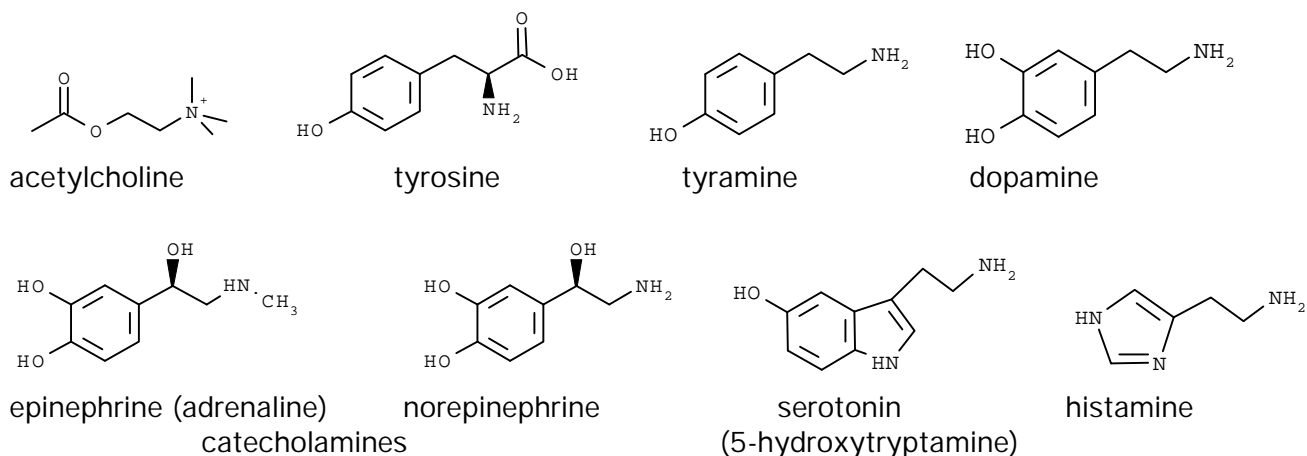
Short amide polymers of amino acids (called peptides) are also effective stimulants and inhibitors of the nervous system. Vasopressin affects blood pressure and memory, substance P increases sensitivity to pain and enkephalins and endorphins suppress the pain response. The simplest of these are the enkephalins, e.g. Met-enkephalin:



b. 2-ARYLETHANAMINES AND AMMONIUM SALTS

Acetylcholine is the major messenger from nerves to muscles. Classic studies showed that the organophosphorus nerve agents (and insecticides) block its destruction, causing muscle spasms which can result in death. Acetylcholine shortages are associated with *myasthenia gravis* and Alzheimer's disease.

A small fraction of neurotransmitters seem to be responsible for most of the nervous system disorders that are currently understood, namely the 2-arylethylamines. They are synthesized by decarboxylation (reduction) of amino acids, e.g. tyrosine to tyramine and tryptophan to tryptamine, and subsequent modification (e.g. tyramine to dopamine). Most are stored in membrane vesicles for rapid release and have a variety of receptors (serotonin has at least 14!). They are destroyed after use by monoamine oxidase (MAO).



Many disabling psychiatric, addictive and motor conditions are now understood to result from imbalances in the brain's neurotransmitters. Migraines may be caused by insufficient MAO to remove tyramine. Parkinson's disease is caused by destruction of dopamine-producing neurons and can be partially reversed by dopamine sources such as the amino acid L-DOPA. Serotonin, which coordinates muscle movement, is normally shut off during REM sleep (during which we are temporarily paralyzed) and a chronic shortage results in depression. Alzheimer's disease is characterized by shortages of acetylcholine, adrenalin and serotonin. The powerful tricyclic antidepressants like reserpine block dopamine receptors and serotonin reuptake, producing an overall calming effect, whereas lithium ions improve mood by increasing synthesis of serotonin. (*S*)-Nicotine mimics acetylcholine and stimulates dopamine release. Our ability to understand and treat many faults in neurochemistry has begun to transform public perception of "mental illness".

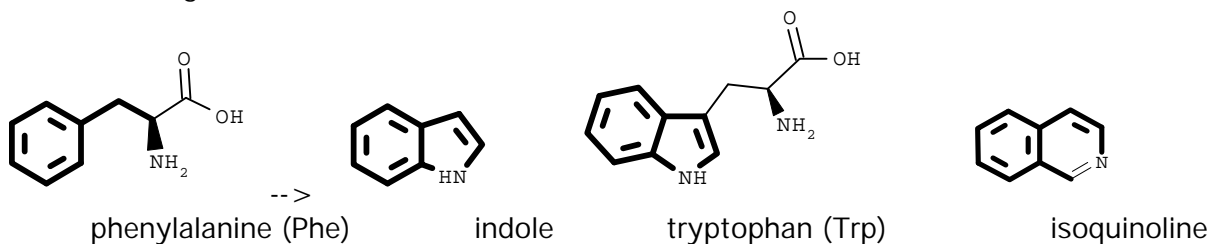
2. PSYCHOACTIVE DRUGS

Most psychoactive drugs are also amines and either mimic the natural neurotransmitters (agonists) or modify the receptors. Since these amines are responsible for both good moods and bad, it is not surprising that their use and abuse have affected the course of history (e.g. opium and China, cocaine and Columbia or Peru). The addictive nature of many of these drugs results from their disruption of the complex feedback mechanism that keeps the natural neurotransmitters in balance - they may block the receptor, overwhelm the recycling system, or depress the production of the natural neurotransmitters. Normal neural activity may be suppressed and recover only slowly; during the recovery (withdrawal) time, depression, hallucinations, convulsions can occur. Cocaine, for example, exerts its stimulant effect by blocking the transport of dopamine away from the receptors after use and suppress dopamine production. Stereochemistry can be important: (*R*)-(-)-epinephrine is much more active than its enantiomer, ephedrine's diastereomers act as either stimulants or decongestants, but (*R*)- and (*S*)-

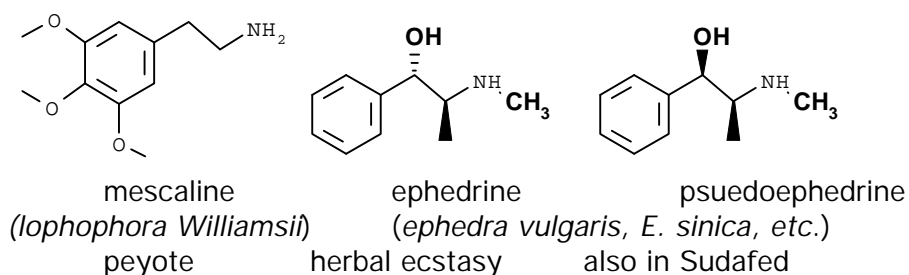
amphetamine are equally potent.

a. NATURAL PRODUCTS

The traditional drugs of abuse are natural plant materials, called ALKALOIDS because of their basicity; they were among the early natural products studied because of the ease with which they can be extracted from plants (with acid, of course). Alkaloids are classified structurally, with names often derived from that of the plant. Alkaloid biosynthesis involves the construction of complex rings and chains, beginning with the decarboxylation of an amino acid; some of the amino acid origins are shown below.

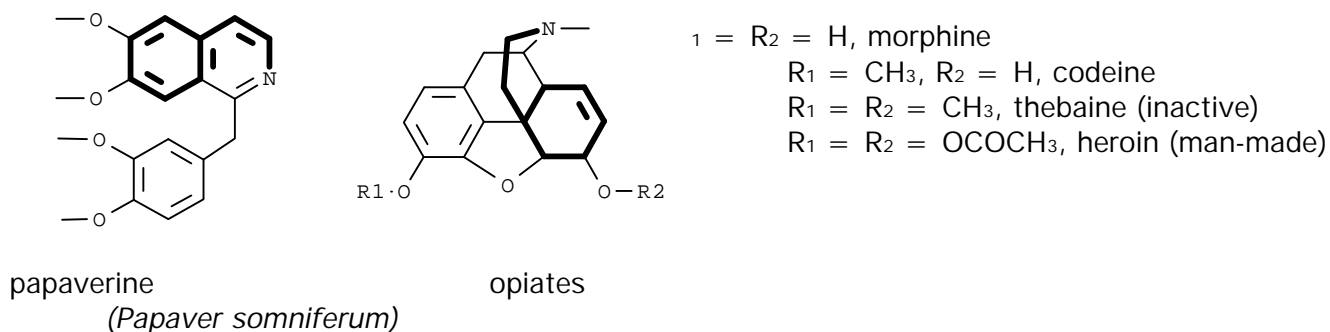


Simple Phenylalanine (2-Phenylethanamine) Alkaloids (dopamine agonists, stimulants)



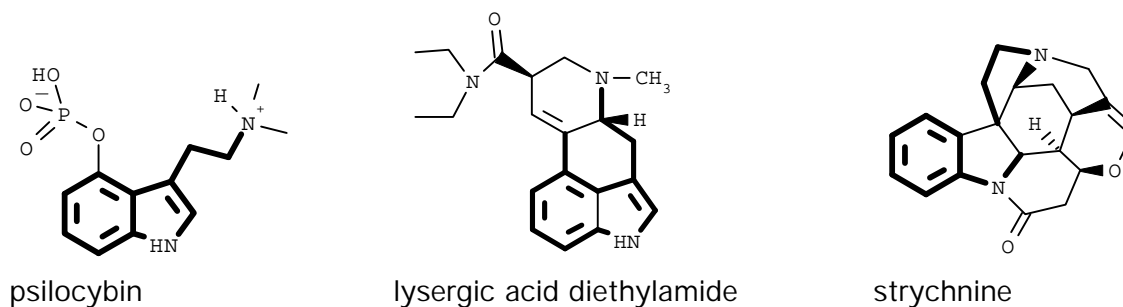
Isoquinoline alkaloids (enkephalin agonists, analgesics)

Note that this family still contains a 2-phenylethanamine.

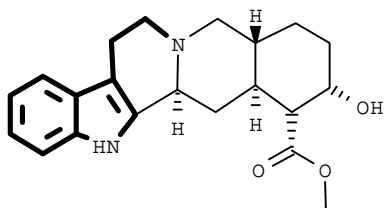


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Indole alkaloids (serotonin agonists and antagonists, often hallucinogens)

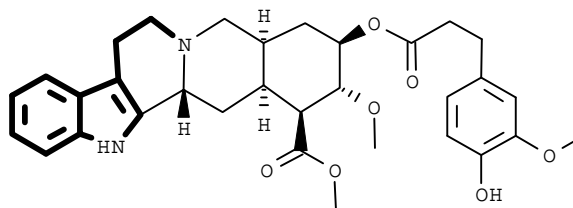


(*Psilocybe mexicana*) (man-made from ergotamine
from *Claviceps purpurea*)



yohimbine
(aphrodisiac? from *Coryanthe johimbe*)

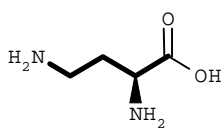
(*Strychnos nux-vomica*)



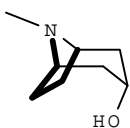
reserpine
(tranquilizer from *Rauwolfia serpentina*)

A wide variety of other drugs also contain the indole group, such as the anti-cancer drugs vincristine and vinblastine.

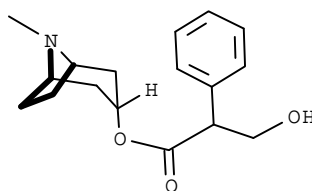
Tropane alkaloids (dopamine agonists, stimulants)



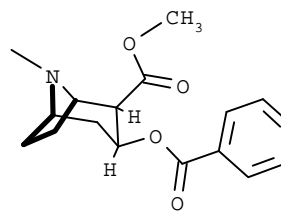
ornithine
amino acid



tropine

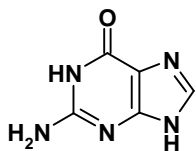


atropine
(*Atropa belladonna*)

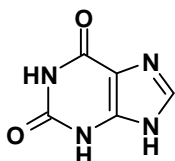


cocaine
(*Erythroxylon coca*)

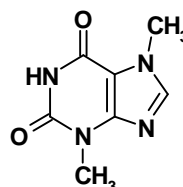
Xanthine alkaloids (stimulants of heart and CNS)



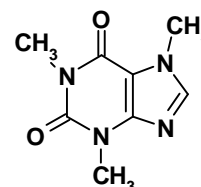
c.f. guanine
DNA base



xanthine
yeast, liver, coffee, tea

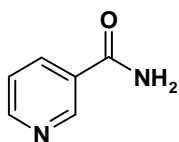


theobromine
chocolate, teacoffee, tea, cola nuts

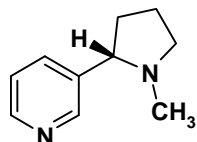


caffeine
euphoria, hallucinations
testosterone reduction

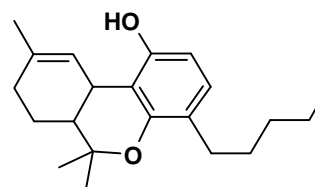
Pyridine alkaloids and miscellanea



c.f. nicotinamide
Vitamin B3, anti-pellagra
a redox enzyme cofactor
LD₅₀ 5 g/kg s.c. rat



(S)-(-)-nicotine
lowers MAO, raises dopamine
LD₅₀ 50 mg/kg oral rat
44 mg oral human

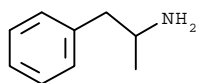


Δ-9-tetrahydrocannabinol
(*Cannabis sativa*)
euphoria, hallucinations
testosterone reduction

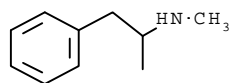
b. SYNTHETIC PSYCHOACTIVE DRUGS

Simple 2-phenylethanamine (phenethylamine) derivatives stimulate the CNS like dopamine

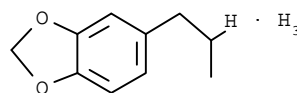
and adrenaline and are relatively easy to make (the starting materials are *also* controlled substances). The effect may not be direct replacement of a neurotransmitter; it often involves interference with reuptake or release of the natural neurotransmitter. The dangerous combination of anorexigenics phen-fen was recently popular for weight reduction (other amphetamines also work) and has been known to result in heart attacks and primary pulmonary hypertension.



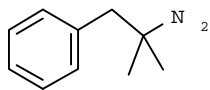
amphetamine
"speed"



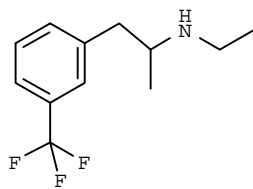
methamphetamine
"ice", "meth"



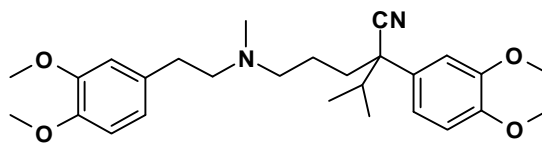
methylenedioxyamphetamine
"ecstasy" MDMA



phentermine

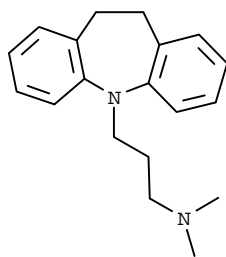


fenfluramine

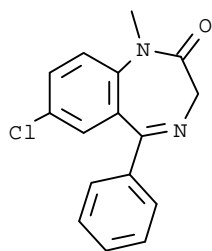


verapamil, reduces hypertension, angina
side effects can include psychosis and confusion

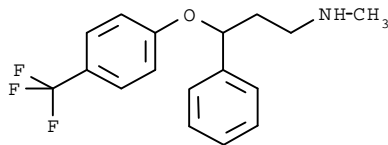
Tranquilizers and sedatives exhibit a great deal of structural variety and may depress the CNS by inhibiting serotonin reuptake (if selective, an SSRI), enhancing GABA binding, blocking catecholamine receptors, etc.; some of the major classes are illustrated by the compounds below:



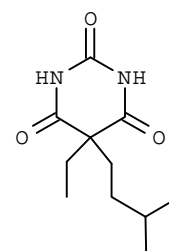
imipramine, a tricyclic
antidepressant



valium,
a benzodiazepine



prozac
an SSRI



amobarbital
a sedative

3. CONTROLLED SUBSTANCES

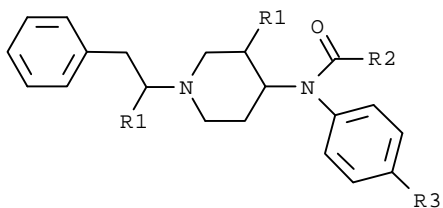
Every country (and the UN) has official sanctions to prevent drug abuse. In the USA, a list of Controlled Dangerous Substances was created by the Bureau of Narcotics and Dangerous Drugs (BNDD); it is a violation of State and Federal law to possess, buy or sell compounds on this list or their precursors without permission. The CDS list includes heroin, cocaine, cocaine hydrochloride, marijuana, amphetamines, etc., and calls all of them *narcotics*, even though most are medically stimulants, rather than *narcotics* (sleep inducers). Originally, only CDS-listed chemicals were illegal, leaving a big loophole, filled by the so-called "designer drugs", in which small change in substituent left the activity intact but created a substance that was completely legal. A good example of a series of designer drugs is the fentanyl family, drugs so potent that only 1 µg is needed per dose, and it takes an expert to synthesize it without accidentally ingesting a lethal dose. The law has since been changed to make possession of structural *classes* like the fentanyls illegal.

fentanyl

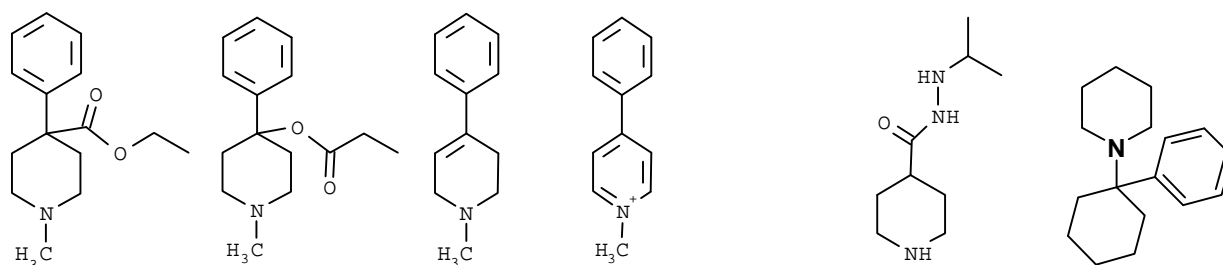
R1 = H or CH₃

R2 = CH₃ or CH₂CH₃

R3 = H or F



Many of the drugs sold illegally on the street are even worse than the LD₅₀ would lead you to believe - they may have been made or extracted under poorly controlled conditions and their purity is often poor. Street samples of steroids often contain *none* of the compound claimed. One of the most frightening street drug stories is that of MPPP, a demerol analog 3 times as potent as heroin. Four drug users in San Francisco were hospitalized with symptoms of advanced Parkinson's disease: paralysis, dopamine deficiency and destruction of the brain (*substantia nigra*). An team of toxicologists, MD's and clinical chemists unravelled the mystery. A similar case was uncovered in Virginia; the affected teenager made MPPP in his basement and kept careful laboratory notes (donated by his parents). Excess heat during his synthesis had produced traces of MPTP in the MPPP. The MPTP is able to cross the blood-brain barrier and is oxidized to MPP⁺, which destroyed dopamine-producing neurons and caused the symptoms. MAO inhibitors (MAOI's), used to treat Parkinson's disease in Europe, slowed the progression of the symptoms in several of the users (none recovered). Recent studies indicate that MPP⁺ may in fact be the natural cause of Parkinson's disease. Shown next to this family are two other drugs with piperidine (from pyridine) rings, the MAO inhibitor iproniazid and the animal tranquilizer PCP (phencyclidine) which causes dissociative anesthesia, hallucinations and insomnia.



demerol

MPPP

MPTP

MPP⁺

iproniazid

PCP

4. FURTHER READING AND VIEWING

The Case of the Frozen Addict, NOVA, WGBH, Boston, available in the TSU library.

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J. R. Lancaster, Jr., "Nitric Oxide in Cells", *American Scientist*, **1992**, 80, 248 - 259.

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P. S. Zurer, "Scientists Struggling To Understand And Treat Cocaine Dependency", *Chem. Eng. News*, **1988**, Nov. 21, 7 - 13.

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ORGANIC ENRICHMENT, L. M. SWEETING 1995, 1997

SUMMARY OF NEUROTRANSMITTERS

| <u>Molecule</u> | <u>Normal Effect</u> | <u>Shortage Symptom</u> | <u>Excess symptom</u> | <u>Drugs anti</u> | <u>Drugs that replace, assist, stimulate</u> |
|---|--|---|---|--|---|
| Acetylcholine | neuromuscular autonomic cognition (brain) | myasthenia gravis Alzheimer's | convulsions | botulinum blocks release scopolamine | organophosphorus agents block hydrol -> spasms, death (rev. with atropine). black widow spider venom |
| tyramine octopamine | more common in invertebrates | | dilation of blood vessels -> migraine? | | |
| dopamine | motor coordination | Parkinson's disease (loss of neurons) | schizophrenia | reserpine and other antipsychotics block receptor but stim. natural production e.g. chlorpromazine | amphetamine, cocaine See Note. MAO inhibitors. |
| adrenaline epinephrine norepinephrine | orientation to external world, alertness | depression vegetative state Alzheimer s | agitation | reserpine, and other tricyclic antidep. block reuptake and storage -> depletion and depression. yohimbine. | amphetamine, cocaine block reuptake and increase release, but not antidepres. MAO inhibitors. |
| serotonin | muscle movement; coord of sensory and motor patterns, sleep-inducing | depression paralysis (e.g. during REM sleep) | | reserpine, which then causes depression LSD? | antidepressants, e.g. imipramine, prozac, block reuptake. Li+ increases synthesis LSD? |
| histamines | regulate water, heat, food, hormones, smooth muscle contraction | Alzheimer s | vasodilation, itchiness | antihistamines block receptors, e.g. diphenhydramine. tripeleennamine chlorpheniramine | |

Note: amphetamines may cause chronic depletion of catecholamines, tolerance and rebound depression on withdrawal (thus dependence). Amphetamines also cause paranoia and psychosis like schizophrenia. Cocaine blocks reuptake of dopamine but depresses natural production; the overall effect is an increase in dopamine levels, plus the direct effect of the cocaine.