Alkaloids – Natural nitrogenous secondary metabolites from plants and microbes
### Some important classes of alkaloids

<table>
<thead>
<tr>
<th>Class</th>
<th>Precursors</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperidine alkaloids</td>
<td>L-lysine (C₅N)</td>
<td>Piperine</td>
</tr>
<tr>
<td>Pyrrolidine/tropane alkaloids</td>
<td>L-ornithine (C₄N)</td>
<td>Cocaine, scopolamine</td>
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<tr>
<td>Pyridine alkaloids</td>
<td>L-Trp or L-Asp</td>
<td>Niacin (Vit. B₃), nicotine</td>
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<tr>
<td>Catecholamines</td>
<td>L-Tyr (C₆C₂N)</td>
<td>Dopamine, adrenaline</td>
</tr>
<tr>
<td>Opiates</td>
<td>2 L-Tyr units</td>
<td>Morphine, tubocurarine</td>
</tr>
<tr>
<td>Phenylalanine-derived</td>
<td>L-Phe (C₆C₃N)</td>
<td>Capsaicin</td>
</tr>
<tr>
<td>Indole alkaloids</td>
<td>L-Trp</td>
<td>Serotonin, ergotamine, LSD</td>
</tr>
<tr>
<td>Purine alkaloids</td>
<td>L-Gly, L-Gln, L-Asp</td>
<td>Caffeine, theobromine</td>
</tr>
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</table>

Building blocks from the acetate, shikimate, or deoxyxylulose phosphate phosphate pathways are also frequently incorporated into the alkaloid structures.
Many alkaloids acquire their N via **transamination** reactions (catalyzed by Vitamin B6).
Most alkaloids are quite toxic and produced by the plant as a defense against herbivores.
Key biological activity of alkaloids: interaction with CNS

- Most of the biological effects of alkaloids are due to their similarity to neurotransmitters in the human body.
- They can either mimic or block the effects of neurotransmitters, or cause fluctuations in the normal levels of neurotransmitters.
- This leads to numerous physiological and psychological effects.

Role of neurotransmitters: to transmit nerve impulses across the synapse (space) between neurons in brain, nervous system

Structures: mostly small molecules containing amino or ammonium functionalities

Action: They are released from nerve endings and bind to receptors on the surface of another neuron in the network

Agonists bind to and stimulate receptors

Antagonists block receptors

Not all alkaloids affect CNS, but many do!
Neurotransmitters that have effects on mood, thought processes

**Dopamine** (a catecholamine)
- Found mainly in the midbrain region (substantia nigra)
- Affects brain processes controlling movement, emotional response, pleasure and pain
- Departure from normal production plays a role in substance addiction, Parkinson’s disease, some mental disorders

**Serotonin** (an indole, aka 5-hydroxytryptamine or 5-HT)
- Found in the brain, the GI tract and blood platelets
- Modulates the excitatory systems in the CNS and is involved in stimulating heartbeat & clotting processes
- Controls memory, mood, sleep patterns, appetite, sex drive
- Depression thought to arise from decreased serotonin levels
Neurotransmitters that control physiological effects throughout the body

Norepinephrine (noradrenaline)  
- Found throughout the body
- As a neurotransmitter, regulates arousal, dreaming, and moods
- Doubles as a hormone which increases blood pressure & heart rate, vasoconstriction

Epinephrine (adrenaline)  
- Released from the adrenal glands in response to emergency
- Stimulates glycogen breakdown (energy), increases respiration

Acetylcholine  
- Found where nerves meet muscles
- Binds to muscarinic and nicotinic receptors in the parasympathetic nervous system
- Causes muscle contraction
Alkaloids derived from lysine (piperidine alkaloids – $C_5N$)

Formation of the 6-membered ring
Formation of piperine: $\text{C}_6\text{C}_3$ unit is lengthened and linked with $2^\circ$ amine to form amide linkage.

Piperine: from black pepper (*Piper nigrum*)

Spicy flavor and CYP3A4 inhibitor
Tropane alkaloids (Solanaceae family)

Formation of first ring (pyrrolidine ring)

- Tropanes are bicyclic non-aromatic alkaloids. They are not common in edible plants, but are found in some botanicals and medicinal herbs.
- The most common natural tropane alkaloids are (-)-hyoscyamine and (-)-scopolamine (also known as hyoscine). High concentrations of these alkaloids have been found particularly in *Datura* species.
- Hyoscyamine is the major alkaloid in most parts of *Datura stramonium* (thorn apple or Jimson weed); scopolamine is the major alkaloid in other *Datura* spp.
Chain building by acetyl Co-A units leads to second ring in bicyclic tropanes

Structural similarity to acetylcholine allows tropanes to block muscarinic ACh receptors, providing anaesthetic effect.

From leaves of *Erythoxylum coca*. Well-known CNS stimulant, also anaesthetic. Extracts of *coca* leaves used in original Coca-cola recipe (cola provided the caffeine) but in 1906 the Coca was eliminated.

Found in belladonna (*Atropa belladonna*), henbane and *Datura* species. Can be used as sedative or external pain relief, but they are toxic and have psychotropic effects (hallucinations, etc.)
Effects of tropane alkaloid contamination in animal feed

From European Food Safety Authority website

- “Tropane alkaloids” are a group of > 200 compounds best known for their occurrence in the family Solanaceae, comprising over 100 genera including Datura.

- Datura plants are toxic for animals if ingested in large amounts. Their seeds contain significant amounts of hyoscyamine and scopolamine, and can be found as botanical impurities in feed materials, particularly in soybean and linseed products.

- Reports on adverse health effects in animals refer mostly to accidental intoxications following the consumption of Datura plants rather than to the contamination of feed.

- Overall, pigs have been shown to be among the most sensitive species to Datura poisoning.

- As competitive antagonists for muscarinic acetylcholine receptors, tropanes prevent binding of acetylcholine, thus affecting the function of smooth muscles and exocrine gland cells, heart rate, respiration and functions in the CNS.

- Most common symptoms reported: dryness of the mucosa in the upper GI and respiratory tract, constipation and colic (in horses), pupil dilation, alterations in heart rate, and CNS effects such as restlessness, irritability, ataxia, seizures and respiratory depression.

- Tropane alkaloids are readily absorbed following oral ingestion, but have a short biological half-life and are rapidly biotransformed or excreted.

- Exposed animals are likely to exhibit symptoms and be removed from the food supply, therefore, it is unlikely that residues of tropane alkaloids in edible tissues, milk and eggs constitute a risk for consumers.
Cocaine and addiction

- Addiction from cocaine and similar drugs arises from its effects on dopamine transmission.
- Normally, dopamine is released from the transmitting neuron, crosses the synapse and binds to receptors on the receiver.
- Excess dopamine is transported back to the transmitting neuron.
- Cocaine blocks the dopamine transporters, inhibiting the re-uptake of dopamine by the transmitter.
- This results in increased dopamine levels in the synapse → euphoria
- Reward system results in addiction
- Users get used to higher levels of dopamine and “crash” when stimulus is removed.

Figure 7.4 The neurotransmitter dopamine transmits brain signals by flowing from one neuron into the spaces between neurons and attaching to a receptor on another neuron. Normally, dopamine is then recycled back into the transmitting neuron by a transporter molecule on the surface of the neuron. But if cocaine is present, it attaches to the transporter and blocks the normal recycling of dopamine, causing an increase of dopamine levels in the spaces between neurons, which leads to euphoria. (Source: NIDA NOTES, National Institute on Drug Abuse, NIH, Volume 13, No. 2, June 1998.)
It’s the real thing...

- Cola (kola) is the dried cotyledon from seeds of *Cola* spp. (Sterculiaceae), e.g. *C. nitida* & *C. acuminata*, trees cultivated mainly in West Africa and the West Indies.
- Fresh cola seeds are chewed in tropical countries as a stimulant.
- Cola seeds (nuts) contain up to 3% caffeine & 0.1% theobromine, partly bound to tannins. On drying, some polyphenol oxidation occurs, forming a red pigment, and free caffeine is liberated.
- Vast quantities of dried seeds are processed for the preparation of cola drinks, e.g. Coca-Cola and Pepsi-Cola.
- Coca-Cola was invented by Atlanta pharmacist John Pemberton in 1886. It originally contained cocaine (from coca leaf) and caffeine from the kola nut (5 oz. coca leaf/gallon of syrup). It once contained ~ 9 mg cocaine per glass, but in 1903 it was removed.
- After 1904, Coca-Cola started using "spent" leaves left over from the cocaine-extraction process. A cocaine-free coca leaf extract is still used for flavoring.
Alkaloids from shikimate precursors via transamination

Figure 6.121
Capsaicin

• Produced by red hot chili peppers (*Capsicum annuum*) of Solanaceae
• Secondary metabolite, probably produced as a deterrent against herbivores & fungi
• Has analgesic properties
• Used medicinally in creams to treat neuralgia or neuropathy caused by diabetes, herpes
• Also in topical pain-relieving preparations for arthritis.
• The initial burning effect of capsaicin affects the pain receptors, depleting substance P, and making them less sensitive
Nicotinic acid/Niacin (Vit. B₃)

- Role: redox cofactor when in form of NAD(P)+/NAD(P)H
- In animals, produced by degradation of L-Trp
- In most plants, L-Asp is the precursor
- Nuc. attack on phosphoglyceraldehyde followed by imine formation
- Reaction with N-methyl pyrrolineinum leads to nicotine
- Nicotinic acid is also produced during the roasting of coffee from the decomposition of N-methyl derivative trigonelline
Structural similarity with acetylcholine leads to stimulant properties

**Tobacco** - the cured and dried leaves of *Nicotiana tabacum* (Solanaceae) an annual herb indigenous to tropical America, cultivated widely for smoking. Tobacco leaves may contain from 0.6–9% of (−)-**nicotine** (an oily, volatile liquid) together with smaller amounts of structurally related alkaloids. Nicotine in small doses can act as a respiratory stimulant, but in larger doses it causes respiratory depression.

**Arecoline** is the major alkaloid in Areca nuts (betel nuts) - the seeds of *Areca catechu* (Palmae/Arecaceae), a tall palm cultivated in India & other parts of Asia. Nuts are mixed with lime, wrapped in leaves of the betel pepper and then chewed for their stimulant effect, and subsequent feeling of well-being and mild intoxication.
Indole alkaloids

Produced from L-tryptophan plus an isoprene unit, the indole alkaloids have polycyclic ring structures.

**Fungi** from *Claviceps* genus are best-known producers because they infect some grain crops, but the indoles are produced by other fungi including *Aspergillus* and *Penicillium*.

Lysergic acid is probably the most well-known, as it is the precursor for hallucinogen LSD (lysergic acid diethylamide) and the ergot alkaloids—mixed agonist/antagonist effects on 5-HT (serotonin) receptors leads to hallucinations.
Ergot – not a fun guy

Ergot is the dried sclerotium of the fungus *Claviceps purpurea* that develops on the ovary of rye and other grasses consumed by humans or animals.

The poisonous properties of ergots are caused by a group of *indole alkaloids*, the *ergot alkaloids* or ergolines. Consumption of ergot-infected rye produces a disease called ergotism. Ergot poisoning affects two types of receptors:

1) The α-adrenergic receptors for norepinephrine which causes
   - GI upsets, e.g. diarrhea, abdominal pains, and vomiting.
   - Circulatory changes, e.g. coldness of hands and feet due to vasoconstriction of the blood vessels to the extremities
2) Ergot also acts on the serotonin (5-HT) receptors and the $\alpha$-dopaminergic receptors causing neurological symptoms: Headache, vertigo, convulsions, psychotic disturbances, hallucinations

Vasoconstriction can cause restricted blood flow in small terminal arteries, death of the tissue, gangrene, and even the loss of hands, feet, or limbs.

Gangrenous ergotism was known as St Anthony’s Fire because the Order of St. Anthony cared for the sufferers during the Middle Ages in Europe when outbreaks of the disease in humans and animals were relatively frequent.
Indole-isoprenoid is modified by attachment of a small peptide (Phe & Pro usually). Ergotamine’s vasoconstrictive activity has led to its use in treatment of migraines.
From amino acids to purines to caffeine and xanthine alkaloids

Purine heterocyclic ring system is derived from amino acids and various one C donors
The xanthines

*Caffeine, Theobromine, and Theophylline*

- The *purine alkaloids* caffeine, theobromine, and theophylline are all methyl xanthines that commonly co-occur in plants. Major sources are stimulant beverages and foods such as tea, coffee, cocoa, and cola.

- Xanthines competitively inhibit phosphodiesterase, causing an increase in cyclic AMP and adrenaline release. This leads to CNS stimulation, relaxation of bronchial smooth muscle, and induction of diuresis. Inhibition of TNF-α and leukotriene synthesis is thought to occur, reducing inflammation and innate immunity.

- The effects vary among the three compounds. **Caffeine** is the best CNS stimulant. As a vasoconstrictor it can be combined with a therapeutic agent to increase effectiveness (e.g. compound analgesics). It has weaker diuretic action.

- **Theobromine has little stimulant** action, but has more diuretic activity and also muscle relaxant properties. **Theophylline also** has low stimulant action and is an effective diuretic, but it relaxes smooth muscle better than caffeine or theobromine and is frequently used in slow-release formulations.
Figure 7.8  The central nervous system (CNS) consists of the brain and spinal cord. Caffeine excites the CNS at all levels. One theory of its mechanism proposes that caffeine competes with adenosine for receptors in the brain that block mood-raising cells. Caffeine can bind to these receptors but does not block mood raising the way adenosine does.
Caffeine and adenosine

• Caffeine readily crosses the blood-brain barrier, and once in the brain, the principal mode of action is as a **nonselective antagonist of adenosine receptors** (competitive inhibition)

• Adenosine is found in every part of the body, but it has special functions in the brain. Concentrations of brain adenosine are thought to be increased by metabolic stresses such as anoxia or ischemia. It also may have a specific role in **control of the sleep-wake cycle**.

• Brain adenosine may also protect the brain by suppressing neural activity and **increasing blood flow** through A\textsubscript{2A} and A\textsubscript{2B} receptors located on vascular smooth muscle. By counteracting adenosine, caffeine reduces resting cerebral blood flow – it’s a vasoconstrictor.

• Adenosine is released in the brain through a complex mechanism. It is not likely that adenosine is the primary neurotransmitter for any group of neurons, but rather is released together with other transmitters by a number of neuron types.
So you can’t start the day without Joe? You’re not alone!

• **Is caffeine addictive?** Several classes of adenosine receptors are known, and there is evidence that $A_{2A}$ receptors interact with the dopamine system, which is involved in reward and arousal.

• **Tolerance:** because caffeine is primarily an antagonist of adenosine receptors, regular caffeine consumers may adapt to its continuous presence by increasing the number of adenosine receptors.

• This reduces the stimulatory effects (tolerance adaptation) and makes one much more sensitive to adenosine, so that reducing caffeine intake results in withdrawal symptoms.
<table>
<thead>
<tr>
<th>Beverage or Preparation</th>
<th>Caffeine Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espresso, 2 fl. oz.</td>
<td>120–150</td>
</tr>
<tr>
<td>Coffee, 1 cup, 6 fl. oz. drip or percolated</td>
<td>100–150</td>
</tr>
<tr>
<td>Coffee, 1 cup, instant</td>
<td>50–70</td>
</tr>
<tr>
<td>Tea, 1 cup, 6 fl. oz., 5-minute steep</td>
<td>30–60</td>
</tr>
<tr>
<td>Coffee, decaffeinated, 1 cup</td>
<td>1–6(^a)</td>
</tr>
<tr>
<td>Cola beverage, 12 fluid oz.</td>
<td>72 maximum(^b)</td>
</tr>
<tr>
<td>Milk chocolate, 1 oz.</td>
<td>1–15</td>
</tr>
<tr>
<td>Chocolate cake, 1 slice</td>
<td>20–30</td>
</tr>
<tr>
<td>Hot cocoa, 1 cup</td>
<td>5(^c)</td>
</tr>
<tr>
<td>No-Doz, 1 tablet</td>
<td>100</td>
</tr>
<tr>
<td>Excedrin, 1 dosage unit</td>
<td>65</td>
</tr>
<tr>
<td>OTC products including Anacin, Midol, and Vanquish</td>
<td>32</td>
</tr>
<tr>
<td>Vivarin, 1 tablet</td>
<td>200</td>
</tr>
</tbody>
</table>

\(^a\)Some years ago, a process was developed to remove up to 97% of the caffeine from unprocessed coffee beans. FDA tests on decaffeinated coffee, both ground and instant, have confirmed the claims for the low caffeine content of such products (about 0.6 mg of caffeine per fluid ounce).

\(^b\)Federal regulations permit a 0.02% maximum caffeine content in any soda water drink with the words “cola” or “pepper” in the name, when such beverage is obtained from kola nut extracts or other natural extracts. Manufacturers routinely add enough caffeine to bring the concentration up to a range of 33–52 mg/12 fluid ounces; they use some of the 200 tons of caffeine obtained in the process of decaffeinating coffee.

\(^c\)One cup of cocoa may contain up to 200 mg of theobromine, a chemical relative of caffeine.
Chocolate and pet poisoning

- Dogs are most often affected, due to their ability to find chocolate and the common 'sweet tooth' they develop, but cats and other mammals are susceptible to the toxic effects of chocolate, too.

- Theobromine is the major stimulant in chocolate. Its effects:
  - CNS and cardiovascular stimulant
  - Increases blood pressure (mild)
  - Nausea and vomiting

- Are some chocolates more toxic than others?
  Yes. Unsweetened chocolate contains 8-10 times the amount of Theobromine as milk chocolate. Semi-sweet or dark chocolate falls roughly in between the two.

- The toxic dose of Theobromine (or caffeine) for pets is 100-200mg/kg body weight. However, reports by the ASPCA have noted problems at doses much lower than this - i.e. 20mg/kg.

- Using the 20mg/kg as a measure of "problems can be seen" a 50 lb (23 kg) dog would have to consume 9 oz of milk chocolate. Some dogs won't see problems at this rate but others may.

http://vetmedicine.about.com/cs/nutritiondogs/a/chocolatetoxici.htm