

## Lecture 3

### Psychedelic Drugs

This class of drugs is well known and has been called by a variety of different names. Those more commonly taken for euphoria are more usually discussed under drugs of abuse. The word psychedelic was created specifically to describe the behavioural reactions produced by these drugs, the concept is meant to convey an altering of sensory perception and unique mind expanding properties.

#### Chemistry and Classification

Most of the psychedelic chemicals resemble neurotransmitters and/or are thought to derive their properties from an ability to bind specific receptors of important neurotransmitters involved in normal cognition. This forms the basis for a convenient classification:

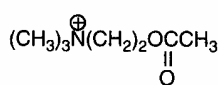
1. Anticholinergic psychedics
2. Catecholamine analogs
3. Serotonin-like psychedelics
4. Psychedelic anaesthetics

#### Anticholinergic psychedelics

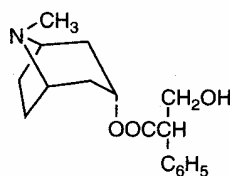
- Compounds block acetylcholine receptors on postsynaptic membrane
- Occupy but do not activate receptors (i.e. anticholinergic rather than cholinergic)
- Effects are intoxication, amnesia and delirium
- Effects not limited to mental changes
- Atropine and Scopolamine also depress salivation and sweating, increase body temperature and heart rate, dilate pupils and blur vision. These are well known anticholinergic properties.
- On occasion they have been used as anti-ulcer medications as they also block secretion of stomach acid.

Main interest is in CNS effects of these drugs. Low doses of scopolamine produce mild euphoria, sleepiness, amnesia, mental confusion and delirium. Larger amounts of atropine are required to achieve the same effects since it is less capable of crossing the blood-brain barrier. Actually these drugs do not expand the mind, they can produce sensory misperception, a hallucination-like state, but the mental experience associated with their use is more likely to be described as confused and mind-scrambling. Larger doses cause a psychotic like experience with delirium and confusion the dominant symptoms.

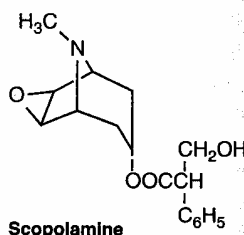
- Not used as psychedelics on a repetitive basis.
- Sometimes taken by young people misinformed as to the nature of the experience.
- Once tried, they are not generally tried a second time.



Acetylcholine



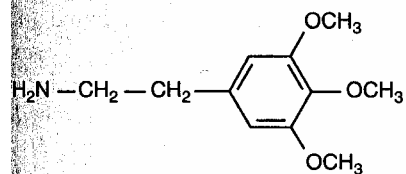
Atropine



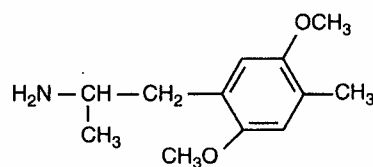
Scopolamine

## Catecholamine analogs

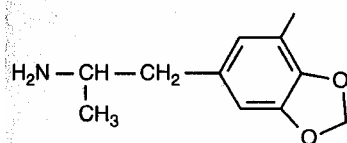
Ecstasy, Mescaline etc are all included in this class as are the amphetamines and cocaine. However, the former have more prominent psychedelic reactions with lower euphoria properties, whereas the latter are more commonly thought of as euphoriant and are usually discussed with other drugs of abuse. The structures of some members of this group are given below.



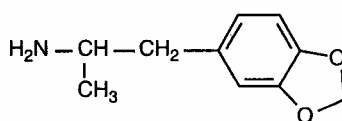
**Mescaline**



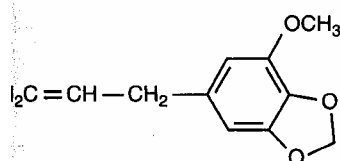
**DOM**



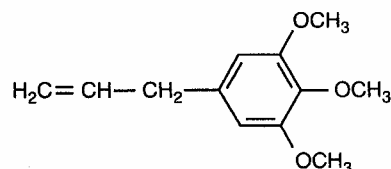
**MDA**



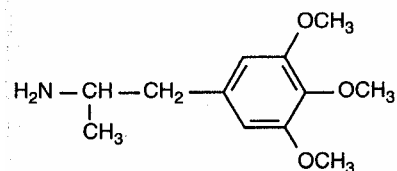
**MDMA**



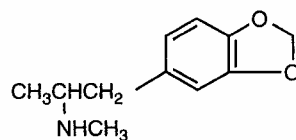
**Myristin**



**Eleminin**



**TMA**



**MDMA**

Note the structural similarities to amphetamine and norepinephrine.

- Methoxy substitution at the benzene ring is a strong feature
- This structural feature appears to heighten the psychedelic nature of the compound (the reason for this is as yet unknown)
- These compounds are believed to bind at adrenergic receptors (i.e. those that employ norepinephrine as a neurotransmitter)
- They also appear to affect serotonin neurotransmission
- Their psychedelic properties may relate to interaction at the physiological locus connecting adrenergic neurons and serotonergic neurons

## Mescaline

The peyote cactus, found in South-Western USA and Mexico consists of a crown plus a long root. If the crown is cut away and dried it becomes a brown-coloured disk called the mescal button, which contains about 50mg of the psychedelic agent

mescaline. The peyote cactus is a component in the religious practices of Native Americans and its use is permitted in many states in the context of religious expression. The structure of mescaline was obtained in 1918 and led to the synthesis of many derivatives which were also psychedelic.

Mescaline is rapidly absorbed and produces a psychedelic state lasting for 9-10 hours. It is not especially potent and hallucinogenic doses are about 5mg/kg orally. More than half the mescaline dose is excreted as the parent drug with acidic compounds accounting for the majority of its metabolites.

Pharmacological manifestations of use include classical symptoms of adrenergic stimulation:

Hypertension, tachycardia, hyperthermia, mydriasis and other stimulatory signs.

Psychedelic symptoms include:

Hallucinations (involving bright lights, geometric designs and strange animals and people), anxiety, tremors and impairment of colour and space perception.

Overdose of mescaline is characterised by:

Hypertension, chest pain, bradycardia, vomiting, mydriasis and tachypnea. CNS symptoms include ataxia, tremor and possible coma. Hallucinations may proceed to psychotic manifestations.

### **Other derivatives**

The related catecholamines DOM, MDA, TMA, MDMA and DMA have the adrenergic effects and hallucinatory effects of mescaline, however, they are more potent. DOM (STP = serenity, tranquillity, peace) is a synthetic analog of mescaline and belongs to a group known as designer drugs. DOM is 100 times more potent than mescaline. Doses of just 3mg will produce euphoria followed by hallucinations. In common with many substances arising from primarily illicit laboratories, DOM is marketed with a very wide range of quality and purity. Its potency has led to many overdoses which are associated with tremors which may progress to seizures, some deaths have been reported. DOM use is not widespread due to fear of the repercussions of its use.

MDA, MDMA and TMA are all similar to mescaline, and like DOM, are products designed to circumvent existing drug laws by marketing agents not specifically banned because they came into existence after the laws were written (designer drugs). In general their effects and toxicities are very similar to mescaline.

MDMA (Ecstasy) is allegedly able to cause both euphoria and self-awareness.

- First synthesised in Germany in 1912 as an appetite suppressant.
- Hallucinogenic properties prevented its use as an anorectic.
- Used as an aid in psychotherapy in 1950s.
- Placed on schedule I by the FDA in 1985 and has since disappeared from use in psychotherapy.
- In wide use illicitly since 1985, 24% of students at one university admitted to using it at least once in 1991.
- Users take about 2mg/kg and boost this with an additional 1mg/kg after about three hours.
- Drug taken in many ways – ingested, injected, snorted or smoked.
- Onset of activity is about 30-45 minutes after oral ingestion.
- MDMA affects serotonergic and dopaminergic neurons in the CNS.

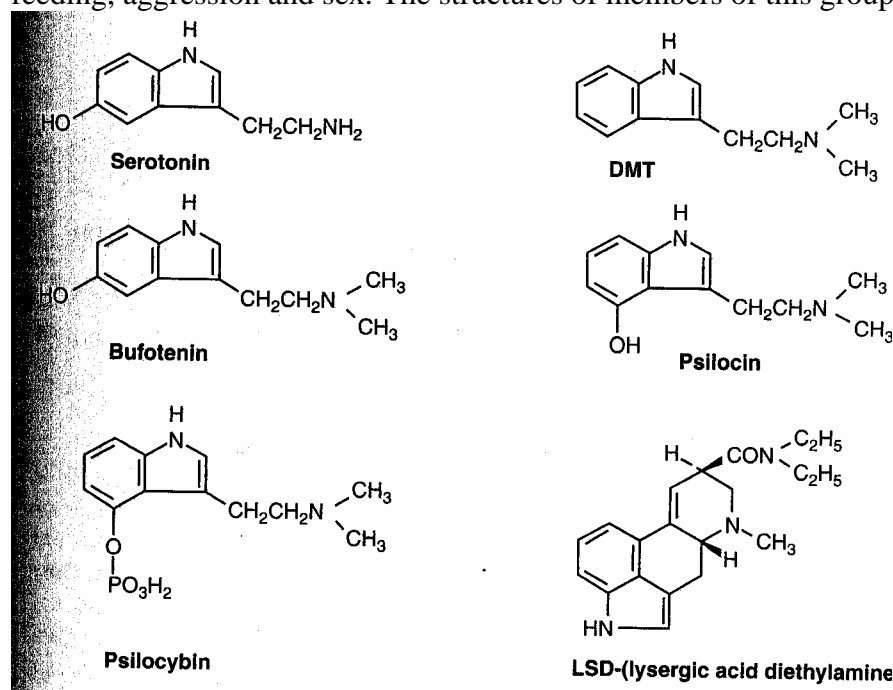
The enhancement of serotonin release on the presynaptic side and the inhibition of serotonin reuptake appear to cause a stimulating effect, a euphoria and a seeming

ability to experience reduced inhibitions and congeniality with others. Remarkable psychological effects are claimed for MDMA including: Enactogenesis (a feeling that all is well with the world), empathogenesis (a feeling of emotional closeness to others) and enhancement of the senses of touch, taste, vision, smell and proprioception. In some studies including human, MDMA has been implicated in damage to serotonergic neurons and adverse reactions such as altered mental status, tachycardia and tachypnea, acute renal failure, cardiovascular collapse, hepatic failure, disseminated intravascular coagulation and malignant hyperthermia have been observed. Profound psychosis has occurred in acute exposure. Although it is possible that impurities in the drug mixture taken may be responsible for some or all of these adverse reactions, the FDA has not been convinced and MDMA remains under severe restriction in the USA.

Myristin and elemicin are found in the spices nutmeg and mace. They are derived from the seeds and seed coats of *Myristica fragans*, the nutmeg tree which grows mainly in India and parts of the Caribbean. Nutmeg is a popular home remedy for gastrointestinal upset, arthritic disorders and sometimes for psychiatric conditions. A large quantity is required to achieve a euphoric or hallucinatory effect, with as much as 15g of nutmeg taken in some cases. Ingesting this amount leads to many unpleasant side-effects such as vomiting, nausea and tremors. The hallucinations are also of impending doom or other frightening scenarios and the toxic side effects are usually sufficient to convince a user not to repeat the experience.

### Serotonin-like psychedelics

This group of drugs includes LSD, psilocybin, psilocin, dimethyltryptamine and bufotenin. Their effects derive from interference in normal serotonin activity. This neurotransmitter is involved with increasing a person's sleep time and reduces feeding, aggression and sex. The structures of members of this group are given below:



### Lysergic acid diethylamide (LSD)

- Prototypical member of this category (note some structural similarity to serotonin)

- Proven that LSD antagonizes some of the actions of serotonin
- LSD decreases the rate of discharge of serotonin neurons
- LSD has been shown to bind to serotonin-2 receptor and this binding is associated with an agonist action (i.e. LSD stimulates serotonin activity)
- The stronger the binding to the serotonin-2 receptor the greater the psychedelic reaction.
- After bonding to the serotonin-2 receptor a cascade of neural reactions including reaction with other (especially adrenergic –catecholamine like) neurons occurs.
- The final psychedelic response may start with serotonergic neurons but appears to involve other types in its complete expression.
- One theory involves the pontin raphe, a major central area of serotonin activity, which is thought to function as a filtering station for the evaluation and classification of incoming sensory stimuli, by screening perceptions prior to their deeper evaluation by higher brain centres.
- LSD and other serotonin related psychedelics prevent this early stage of filtering, which may result in an overload of sensory input which would overwhelm customary abilities of discrimination.

Theories relating LSD action to serotonin are also supported by the observation that LSD-psychoses can be treated with neuroleptics (drugs which are known to block serotonin receptors).

LSD has an interesting history and has been known for at least 2000 years, with the ancient Eleusinians and the native people of Mexico using derivatives of LSD in religious ceremonies. In Mexico the seeds of the morning glory plant were used and this plant is known to contain LSD. In the Middle Ages the fungus *Claviceps purpurea* infested rye and other grains and caused poisonings due to the ergot it excreted. Ergot is a mixture of alkaloids containing many pharmacologically active components which can easily be converted into psychedelic compounds.

- Albert Hofmann (Sandoz Laboratories) worked on ergot and discovered the psychoactive properties of LSD in 1943
- In 1965 the FDA reviewed LSD and decided that the few if any pharmaceutical benefits were outweighed by its potential for abuse and it was placed on schedule I.
- Currently moderately popular with street doses of 20 - 200µg selling for \$3 to \$10.

LSD has primarily psychological effects but some physiological reactions are known, including, raised body temperature, tachycardia, hypertension, dizziness (even ataxia) and drowsiness.

- Hallucinatory experience depends on dose and also personal expectation and experience.
- Major reported findings are perceptual changes, visual hallucinations and sensory distortions.
- LSD provides up to 12 hours of reaction from a single ingestion. Its half-life is 3hours and it is extensively metabolised with only 1% of a dose being excreted.
- LSD analysis is a huge challenge because of the extensive metabolism and the low dosage.

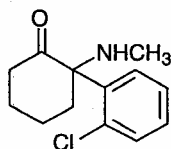
Dimethyltryptamine (DMT) is very similar to serotonin in structure and produces effects similar to those of LSD. DMT is found in snuff used in various parts of the world, including cohoba from South American beans and yopo from the West Indies. Bufotenin is also found in snuff. DMT resembles LSD to a large degree but differs in that it is not absorbed via the oral route and must be inhaled or snorted, it only provides a 1-hour drug experience.

### DMT derivatives

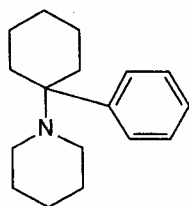
Psilocybin is 4-phosphoryl DMT psilocin is 4-hydroxy-DMT. They are found in more than a dozen species of mushrooms. *Psilocybe mexicana* is known as 'magic mushroom' and has been used for centuries by the natives of Mexico. The pure compounds have only 0.5% of the psychedelic potency of LSD and are ingested directly by eating the mushrooms without any specific preparation.

### Psychedelic anaesthetics

- 2 compounds in this category, phencyclidine and ketamine.
- Referred to as dissociative anaesthetics due to patients feeling dissociated from others and their environment.
- Users often become agitated but euphoric and lose inhibitions.
- May become rigid and speechless.
- Overdose results in coma which if survived produces a long period of confusion or even psychosis lasting several months.
- Ketamine is less potent as a psychedelic agent.



**Ketamine**



**PCP (phencyclidine)**