Psychedelics

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Introduction

○ We decided to research the topic of psychedelic drugs because of the interesting effects this specific group of drugs/toxins have on the human mind
○ The ability of psychedelics to produce effects such as the intense hallucinations that are experienced by schizophrenics is fascinating
○ Psychedelics also have a rich history of use throughout the years for many different aspects of human culture across societies
○ We will provide general information on all psychedelics as well as specific information on the different classes including: History, Mechanism of Action, Effects, and Use
What are Psychedelics?

- Defined as "any agent that causes alterations in perception, cognition, and mood as its primary psychobiological actions in the presence of an otherwise clear sensorium." (Julien, R. 2008)
- Produced by nature or synthetically
- Have been used throughout history and are used today for recreational, spiritual, and therapeutic purposes
- Target neurotransmitter systems
Neurotransmitters

- Generally, neurotransmitters are released into the synapse when a signal arrives at the presynaptic neuron (signal sending neuron).
- Once they are in the synapse, the neurotransmitters bind to appropriate receptors on the postsynaptic neuron (signal receiving neuron).
- After receptor binding, neurotransmitters can have different effects.
Neurotransmitters (cont.)

Two types of receptors:
1) **Ligand gated ion channels** - the neurotransmitter binds to the receptor, the channel opens, and ions flow across their pre-established gradient either relaying a signal or producing an effect.

2) **G-Protein Coupled Receptors** - the neurotransmitter binds, which activates the G-protein, the G-protein subunits or intracellular messengers bind and modulate an ion channel that then opens to allow ions to flow through and the signal or effect to occur.
Mechanism of Action of Psychedelics

- Enters bloodstream via various exposure pathways
- Distributed to target synapse by cardiovascular system
- In synapse, binds to various neurotransmitter receptors and either stimulate (agonistic) or inhibit (antagonistic) the effects of that specific neurotransmitter
- Through stimulation or inhibition of normal physiological pathways, effects of psychedelics are observed
- Alteration in different neurotransmitter systems will produce different physiological effects
Psychedelic Classes

- Typically classified based on affected neurotransmitter systems in the CNS
  - Anticholinergic (Scopolamine)
  - Serotoninlike (LSD, DMT, Psilocybin)
  - Catecholeaminelike (Mescaline, Ecstasy)
  - Glutaminergic (PCP, Ketamine)
  - Opioid kappa receptor agonist (Salvinorin A)
Anticholinergic Psychedelics

- Include Scopolamine and Hyoscyamine
- Induce delirium, hallucinations, and deep sleep
- Used in magic, sorcery, witchcraft, and religion
- Can be used to treat asthma or Parkinson's disease due to anticholinergic effects
Anticholinergic (Scopolamine): History

- Occurs naturally in high concentrations in some plants:
  - *Atropa Belladonna* (deadly nightshade)
  - *Datura Stramonium* (Jamestown weed, devil's apple)
- Ingestion of datura berries was reason behind crippling of whole armies
  - Marc Anthony's army in 36 B.C.
  - Bacon's Revolution against British soldiers
- Consumption lead to people's belief in being witches and ability to fly: the origin of some halloween costumes
Scopolamine: Mechanism of Action

- **Antagonist to muscarinic acetlycholine receptors**

![Structural formulas of Scopolamine and Ach]  
Scopolamine | Acetylcholine

- Most commonly is ingested, but can be inhaled (smoking of D. stramonium leaves) or administered transdermally for medicinal purposes
- Effective dose around 0.3 mg/kg
- Can cross Blood Brain Barrier
Scopolamine: Effects

○ **Psychiatric Effects**: restlessness, excitement, hallucinations, euphoria, and disorientation
○ **Peripheral Nervous System Effects**: dry mouth, reduced sweating, dry skin, increased body temperature, dilated pupils, blurred vision, tachycardia, and hypertension
○ **Central Nervous System Effects**: sedation, amnesia, mild euphoria, fatigue, mental confusion, loss of attention, and delirium

* high doses can lead to toxic psychosis, respiratory depression, and coma
Medical Relevance of Scopolamine

Research has shown it can be used medically for:

- Motion Sickness
- Asthma
- To treat addiction to drugs such as heroin and cocaine
- Has been shown to be effective against major depressive disorder when administered intravenously and to treat bipolar disorder when administered transdermally
Scopolamine: Miscellaneous

- Fictional belief that scopolamine can be used as a truth serum
  - Used by Czech secret police in 2009

- Recreational use is rare compared to other hallucinogens due to mental and physical unpleasantness

- There have been rare occurrences of scopolamine poisoning for criminal purposes
Serotoninlike Psychedelic Drugs

- Includes DMT, LSD, psilocybin/psilocin ("shrooms"), and bufotenine.
- Similar structure to serotonin
- Activate serotonin or 5-hydroxytryptamine (5HT) receptors, especially the 5HT$_2$ receptor
- Distort thinking processes, create illusions and visual hallucinations, and impair ego functioning
For centuries Amazon Indians in tropical regions of South America would drink a beverage containing DMT called Ayahuasca.

Drank in religious, spiritual, and medicinal contexts.

Found in various South American plants
- *Virola calophylla*
- *Mimosa hostilis*
**DMT: Mechanism of Action**

- Partial agonist at serotonin 5-HT$_2$ receptors of the medial prefrontal cortex and anterior cingulated cortex.

- Can be injected, snorted, smoked, or snuffed

- Threshold dose of 0.2 mg/kg for psychedelic effects
DMT: Effects

○ Elevates blood pressure, heart rate, and temperature, dilates pupils, and increases body endorphin and hormone levels
○ Produces visual hallucinations, intoxication, and hinders awareness of surroundings
○ Results in loss of control with rushes of euphoria and anxiety
○ Separation of mind and body
○ Disconnect with time and humanity
○ Effects last around 30 minutes
"Movie excerpt: DMT research volunteers describe their experience" - YouTube

We found this YouTube clip interesting to say the least:

"... the essence of the soul"

"A thousand years of experience in fifteen minutes"
Catecholaminelike Psychedelics

- Common types include
  - Mescaline (Peyote)
  - Synthetic mescaline/amphetamine derivatives: Designer drugs: DOM/STP, MDA, TMA, MMDA (Ecstasy)
  - Myristicin and Elemicin (found in nutmeg and mace)
- Structurally similar to the catecholamines norepinephrine and dopamine
- Many effects including euphoria, vivid mental images, and synesthesia (the perception of seeing music and hearing colors)
Catecholaminelike (Mescaline/Peyote): History

- Peyote is a spineless cactus with small "buttons" containing mescaline.
- Peyote's use as one of the oldest psychedelics known to man extends back 5000 years or more in North America.
- Used by Aztecs and other Mexican Indians to treat illnesses, communicate with spirits, and for highly religious ceremonies.
- In 1918, in order to preserve the legal right to use peyote, the Native American church was formed.
- Mescaline was first synthesized in 1919.
Mescaline: Mechanism of Action

- Structurally similar to dopamine and norepinephrine

![Structural formulas of Mescaline, Dopamine, and Norepinephrine]

- Psychedelic effects due to high-affinity for 5-HT2A serotonin receptor as a partial agonist, also activates 5-HT2C receptor
- Stimulates dopamine receptors as well
- The binding process is still unknown.
- Avg. dose is b/w 200-400 mg
- Effects begin 1-2 hours after ingestion and may last 12-18 hours
Mescaline: Effects

- Compared to amphetamines/cocaine: more intense psychedelic effects and less intense behavioral stimulant effects.
- Physical effects: numbness, tension, anxiety, rapid reflexes, muscle twitches and weakness, impaired motor coordination, dizziness, trembling, dilation of the pupils.
- Psychological effects: vivid mental images and distorted vision, synesthesia, altered space and time perception, joy, exhilaration, panic, extreme anxiety, terror, distorted sense of body, heightened sensory experiences, loss of sense of reality, melding past experiences with present.
- "Geometricization" - unique to mescaline, is the formation of three-dimensional objects. The object can appear flattened and distorted, similar to the presentation of a Cubist painting.
Dangers of Mescaline

○ Increased blood pressure and heart rate, intense nausea and vomiting, elevated body temperature and sweating

○ Highly adverse reactions can occur ("bad trips"):  
  ○ frightening hallucinations, confusion, disorientation, paranoia, agitation, depression, panic, and/or terror

○ Currently, there is no known physical dependence or psychological dependence although it may be possible
Mescaline: Production

- Like many monoamines, mescaline can be produced through biosynthetic metabolism from tyrosine.
- *Lophophora williamsii*, the primary cactus that produces peyote, synthesizes mescaline from dopamine through biosynthetic pathways in which aromatic hydroxylation and consequent m-O-methylation occur.
- Chemical synthesis in a lab produces mescaline sulfate, a crystalline which is put in a capsule.
Medical Relevance of Peyote

- Can be used for neurasthenia, hysteria, and asthma
- Research has shown positive antimicrobial properties of peyocactin
- Mice were given peyocactin to test for protection against normally lethal *Staphylococcus aureus* infections
- The untreated mice all died within 60 hours of infection, while all treated mice survived

(McCleary et al., 1960)
Glutaminergic Psychedelics

- Includes Phenylcyclidine (PCP/Angel Dust), Ketamine, Dextromethorphan (DXM), and to some degree Nitrous Oxide

- Produce symptoms extremely similar to schizophrenia

- Also known as dissociatives
  - Known for amnesia, analgesia, catalepsy (muscular rigidity and decreased sensitivity to pain)
Glutaminergic (Phencyclidine): History

- Common names include PCP or Angel Dust
- First synthesized in 1926
- Used as an anesthetic in humans in 1950s but was quickly abandoned due to side effects
- Later used as a veterinary anesthetic, mainly as an immobilizing agent
- Emerged as a recreational drug in US in 1967
- 1978 People's Magazine termed PCP the country's number one drug problem
- Use has declined but periodic resurgences in popularity are seen
Phencyclidine Mechanism of Action

- Unlike other psychedelics, do not involve actions on serotonin, acetylcholine, or dopamine neurons
- Non-competitive antagonist to NMDA/glutamate receptors
- Inhibit by two mechanisms
  - 1) blockade of the open channel by occupying a site within the channel in the receptor protein
  - 2) reduction in the frequency of NMDA channel opening by binding to a second attachment site on the outside of the receptor protein
PCP: Effects

- Individuals dissociate from themselves and their environment
- Induces unresponsive state with analgesia, amnesia, mild agitation, euphoria, disinhibition, excitement
- Induces a psychotic state: subjects become withdrawn, autistic, negativistic, unable to maintain a cognitive set
- Produces symptoms almost indistinguishable from schizophrenia
Dangers of PCP

○ Increased blood pressure, seizure activity, respiratory depression, and pulmonary edema
○ Severe anxiety, aggression, panic, paranoia, and rage
○ Violent reactions to sensory input leading to falls, drowning, burns, and driving accidents
○ Self inflicted injuries are frequent
○ Addictive due to stimulatory brain awards
Opioid Kappa Receptor Agonists

- There are a large list of opioid kappa receptor agonists that we will not list as they do not have psychedelic effects.
- The compound in this group with psychedelic effects is Salvinorin A (found in *Salvia divinorum*).
- Some other natural opioid kappa receptor agonist that are well-known include menthol (produced in many species of mint) and ibogaine (used to treat addiction).
  - Menthol is used and applied in a variety of ways, perhaps most commonly known as a food flavor agent in chewing gum (peppermint).
Opioid Kappa Receptor Agonist (Salvinorin A): History

- Salvinorin A is a psychoactive drug that affects k-opioid receptor
  - Salvinorin A is the active ingredient from the species *Salvia divinorum*
- Indigenous to the Sierra Mazateca of Oaxaca, Mexico - traditionally used by folk healers for a spiritual experience
- Common names include *ska Maria Pastora* and *la Maria* to reflect the Mazatec belief that Salvia is the incarnation of the Virgin Mary
- First named in 1982
Opioid Kappa Receptor Agonist

Mechanism of Action

○ Salvinorin A exerts an agonist action on kappa opioid receptors to illicit a response
  ○ Does not bind to 5-HT$_{2A}$ receptor like classical hallucinogens such as LSD
○ Traditionally ingested by chewing or drinking as a tea
  ○ The more effective way is to smoke Salvia in the manner of marijuana
  ○ Smoking 2.86x10$^{-3}$ to 7.14x10$^{-3}$ mg/kg of pure Salvinorin A induces hallucinations (very potent!)
○ Effect lasts a few minutes to an hour
**Salvia divinorum Production**

- *Salvia divinorum* is grown naturally and indigenous to Mexico.
  - Also found to grow in some parts of California
- Biosynthesized via a 1-deoxy-d-xylulose-5-phosphate pathway
- Difficult to chemically synthesize
  - a 24-step pathway has been developed that only yields 0.15% Salvinorin A
- However, synthetic analogs of the natural Salvinorin A molecule show promise in medical practice
Salvinorin A Effects

- "A short-lived inebriant state with intense, bizarre feelings of depersonalization."
- This active ingredient causes a powerful hallucinogenic experience.
- Users have reported relaxation, laughter, colored visions, out of body experience and loss of consciousness.
- Results from Gonzales, et al. state that incapacitation was the highest ever recorded from their research. Even higher than results from the highest DMT dose.
- Survey results convey strong fatigue, weakness and sluggishness. High insight into another reality. Highly decreased ability to react with self or surroundings.
Salvinorin A Effects (Cont'd)

- Research shows similarities between salvia and classical psychoactive drugs in perception, mood and somatic sensations. However, salvia has a higher derealization and a larger decrease in interactions with self and surroundings.
Medical Relevance of Salvinorin A

- **Studies on lab rats show potential for:**
  - Pain reduction
  - Antidiarrheal
  - More importantly is salvinorin A's potential with treating depression. k-Opioid receptor agonists (salvia) have been associated with depression whereas antagonists show antidepressant effects.

- **Research into the mechanism of salvinorin A and its derivatives could provide new techniques for treating the above medical issues.**
Psychedelic Legality in the US

- Most psychedelics are regulated under the Controlled Substance Act
  - Scopolamine is uncontrolled and legal for use in motion sickness treatment
  - DMT is a Schedule I drug and illegal
  - Mescaline is a Schedule 1 illegal drug, but was made legally available for religious practice of Native American Church of North America.
  - PCP is considered a Schedule II drug and illegal
  - Salvinorin A is not regulated under the act, but some states have passed their own laws: New Mexico has very recently made it illegal to sell Salvia
Conclusion

- Psychedelics encompass a wide variety of drugs that vary in mechanism of action, effects, history of use, danger, and legality.
- It is important to know the discussed information as use of psychedelics has been and continues to be a part of human society.
- Medical implications of various psychedelics have been introduced and continued research for beneficial uses is needed.
References

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- http://www.psychelic-library.org/drugsandrights.htm