The Pharmacology of Psychedelics

What are Psychedelics?

- Psychedelic drugs are drugs that cause powerful mind-altering effects, commonly causing altered sensory perception, for example:
    - Visual hallucinations
    - Synaesthesia (interconnected senses, eg hearing colours, seeing sounds)
- All psychedelics cause altered perception of time, place and self and produce **ego dissolution** (feeling a loss of sense of self, and greater interconnectedness with the universe)

Mechanism of Action

- There are many different types of psychedelics, but they can be broadly classified as **typical** vs **atypical psychedelics**
- **Typical psychedelics**:
    - Act as 5-HT2A (serotonin 2A receptor) *biased* agonists
        - **Biased agonism** = where binding to the same receptor as an endogenous ligand (ie serotonin) activates a *different* signalling pathway
        - The **beta-arrestin** signalling pathway is activated by psychedelics, but NOT by serotonin, and is thought to be responsible for their effects
- **Atypical psychedelics**
    - Produce hallucinations, altered sensory perception and other psychedelic symptoms, but do NOT act via 5-HT2A
    - Examples (discussed below) include
        - MDMA (ecstasy)
        - Ketamine
        - Salvia

Types of Psychedelic Drugs

- **Tryptamines:**
    - Tryptamines are structural analogues of serotonin (they have similar structure)
    - **Psilocybin**
        - The active component in magic mushrooms

        - Most studied psychedelic
        - In the brain, psilocybin is dephosphorylated into **psilocin** – the active compound
    - **DMT**
        - The active ingredient in ayahuasca (a South American plant-derived drink) which has been used by native tribes in traditional ceremonies for hundreds of years
        - Unlike psilocybin, DMT has an extremely short half-life
- **Ergolines:**
    - **LSD** (Lysergic acid diethylamide) is the most famous ergoline
    - While LSD is a relatively non-selective serotonin agonist, its psychedelic effects are mediated via 5-HT2A receptor effects
    - Compared to other psychedelics, LSD is more likely to produce long-lasting sensory distortions
        - For example, some people continue to see vivid colours for weeks or months after use
- **Phenylethylamines:**
    - These drugs are often termed **entactogens** or **empathogens**
    - Compared to other psychedelics, they produce less dissociation and sensory disturbance, and promote social bonding and emotion
    - Examples include:
        - **Mescaline**
            - Found in San Pedro cactus
        - **MDMA (ecstasy)**
            - Produces powerful feelings of social interconnectedness, stimulant-like effects but relatively weak sensory disturbances
            - Currently being investigated for PTSD, as it is believed to 'switch off' fear circuits in the brain, allowing traumatic memories to be *reprocessed*
- **Other Psychedelics:**
    - **Ketamine** is a dissociative that causes severe sensory distortion and a dissociated experience
        - It is a weak NMDA receptor antagonist
            - This is important because NMDA receptors are also important in autonomic functions such as respiration, cardiovascular control
            - Strong NMDA receptor antagonists can therefore cause respiratory depression, cardiac arrest