Psychoactive drugs

• Drugs which affect mental processes
  • mood, perception, memory, state of consciousness

• May be illegal:
  • Heroin
  • Cocaine

• Legal:
  • Alcohol
  • nicotine

• Legal but restricted (by prescription only)
  • Abused: e.g., Demerol (synthetic heroin)
  • Not generally abused: e.g., Prozac (anti-depressant)

• Transitional status? – Marijuana
Mechanisms

• Psychoactive drugs have their effects by influencing neurotransmitter systems

• Several possible mechanisms

  1) Stimulate neurons to release natural neurotransmitters

    E.g. MDMA – stimulates the release of Serotonin

    involved in modulation of mood, emotions, appetite, sexual arousal
• Produced by neurons in Raphe nuclei

• project to wide regions of brain

• particularly important in limbic structures, high density of serotonin receptors

• Reduced serotonin levels associated with depression

[one of treatments for depression: medications…indirectly raise level of serotonin]
• Psychoactive drug which elevates serotonin is
  • MDMA ("ecstasy")
  • stimulates the Raphe nuclei to release high levels of serotonin
  • Among reported effects: feeling of well-being, comfort, self-acceptance, closeness to others

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2) Another mechanism: Psychoactive drug may have chemical structure so similar to that of a natural neurotransmitters that
- it can lock into the receptor binding site for that neurotransmitter

>> the drug stimulates the neuron (or inhibit it) as neurotransmitter would do
- the drug is said to “mimic” the neurotransmitter)
- Example: nicotine
- Has effect, largely, by mimicking the effect of acetylcholine (ACh) at ACh receptor sites
  - Many neurons in brain’s reward system have such receptors

- Effects of nicotine:
  - some evidence of enhanced attention, memory, reported “calming” effect
  - no “high”
  - so, why so powerfully addictive?
• Nicotine mimics ACH [thus excites these neurons, increases dopamine levels]...
Release of dopamine (esp. into nucleus accumbens region) has strong reinforcing/rewarding effect.

- Most addictive drugs known to directly or indirectly raise dopamine levels in nucleus accumbens (NAc)
2nd example (of psychoactive drug having effect by mimicking effect of neurotransmitter) is marijuana (cannabis)

- THC identified as active ingredient ..... → discovery of CB-1 receptors
- discovery of anandamide by Raphael Mechoulam; later, 2-AG)
• Marijuana has effects on short-term memory, thought processes, mood, attention
• What could account for these diverse effects?
• Regions of high density of CB-1 receptors
• 3rd mechanism whereby psychoactive drugs have effects:
  Attaching to auxiliary binding sites on certain NT receptors
• Example: Auxiliary binding sites on GABA_A receptor

[Drug binding to auxiliary receptor site can’t open channel by itself, but can sensitize the receptor to GABA (GABA binds more readily) or make GABA bind for longer period of time (>> channel open longer)]
Valium (diazepam, a benzodiazepine) has a tranquilizing effect because it enhances effectiveness of GABA

- acts to inhibit activity in brain regions activated during stress and fear responses (primarily amygdala and hypothalamus)

Valium has “side effects” (incl. drowsiness, clumsiness, unsteadiness) because GABA receptors are located on neurons in widespread regions of brain
• A 4th way in which psychoactive drugs can affect brain functioning:
  involves disruption of the mechanisms by which neurotransmitters are deactivated
  • Neurotransmitters normally have only limited period of time to bind to receptors
  • Shortly after being released
    • will either be broken down by enzymes (e.g. MAO)

OR
• Will be actively removed from synapse and carried back into presynaptic neurons (neurons that released them) by reuptake transporters
Some psychoactive drugs block transporters, thus, keep the NT available in the synapse longer than normal. Is how some antidepressants work; e.g., Prozac. Is an SSRI = selective Serotonin Reuptake Inhibitor.
• Some drugs of abuse also operate this way
  • Cocaine:
    • Blocks the reuptake of dopamine from synapses in nucleus accumbens....
Psychoactive drug-related phenomena: terminology

• Tolerance:
  • After using drug repeatedly, original dose no longer produces desired effect
    • thus user must take increasingly larger doses
  • occurs due to changes in the nervous system, usually at the neuronal level
• Habitual cocaine users develop tolerance quite quickly
• One of the mechanisms underlying cocaine tolerance, discovered by Moore et al (1998)

Density of dopamine (D1) receptors in nucleus accumbens and surrounding regions of striatum of: Right, control (normal) monkeys and; Left, monkeys after long-term (18-22 months) use of cocaine. Green coloring represents receptor density about half that represented by yellow. Effectively, the brains of cocaine-using monkeys have become less responsive to dopamine (after Moore et al., 1998)
• This tolerance mechanism helps to explain one of the long-term effects of cocaine use
  • Decreased motivation, decreased pleasure, depressed mood
  • Brain is becoming less responsive to dopamine as a signaling agent within the reward/pleasure system
• This mechanism provides basis for understanding related phenomenon:

• Physical (physiological) dependency:
  Repeated use of drug leads to adaptations in nervous system and other physiological systems to accommodate to new norm
  Sudden withdrawal of the drug leads to unpleasant withdrawal symptoms
  Body is struggling to restore equilibrium (the altered norms)
Example - Alcohol withdrawal symptoms:
• Anxiety, feelings of jumpiness or nervousness
• Headache
• Sweating
• Excessive thirst
• Nausea, vomiting
• Tremor of the hands
• **Addiction** (= substance dependence):
  - Used to be thought addiction always involved physical dependency
  - Now clear that what’s most important is pattern of behavior surrounding drug usage—
  - pattern of behavior characteristic of addiction can occur in absence of physical dependency or withdrawal symptoms
  - Addiction now defined in terms of the behavioral pattern (preferred term becoming **substance dependence**):
    = a behavioral pattern repeated drug use marked by an overwhelming desire to obtain and use the drug.
    Use continues even in face of adverse consequences
    Even after stopping, P has a strong tendency to relapse (has been linked to changed in brain functioning).