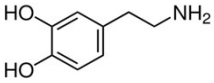
PSYC1022: The Psychology of Addiction

Topic 6: Neuropharmacology (II)

Dr. Helena Pacitti

Outline:

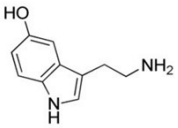
- Neurotransmitters
- Agonist & Antagonist drugs
- Dose Response curve
- Dopamine
- Serotonin
- Endorphins



Dopamine

Methamphetamine: Dopamine agonist

MDMA: Serotonin agonist



Serotonin

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Neurotransmitters

Neurotransmitters: chemical messengers that are released by one neuron (pre-synaptic) and that alters the electrical activity on another neuron (post-synaptic)

- excite or inhibit post-synaptic neurons
- Important in addiction:
    1. Dopamine
    2. Serotonin
    3. Endorphin
    4. Acetylcholine
    5. GABA
    6. Glutamate
    7. Endocannabinoid
- primary site of action of addictive drugs
- form a crucial part of the downstream cascade that drives the formation of addictive behaviour.

System	Compound
Amino acidergic	γ-Aminobutyrate (GABA) Aspartate Glutamate Glycine Taurine
Cholinergic	Acetylcholine
Histaminergic	Histamine
Monoaminergic	Adrenaline Dopamine Noradrenaline Serotonin Tryptamine
Peptidergic	Angiotensin Bombesin family (2 members) Bradykinin Calcitonin gene related peptide (CGRP) Carnosine *Caerulein Cholecystokinin family (5 members) Corticotropin Corticotropin releasing hormone (CRF) Dynorphin family (5 members) *Eledoisin Endorphin family (2) Encephalin family (2) Gastrin family (2 members) Luteinizing-hormone-releasing-hormone (LHRH) Melatonin Motilin Neurokinins (2 peptides) Neuromedin family (4 members) Neuropeptide K Neuropeptide Y Neurotensin Oxytocin Peptide Histidine Isoleucine (PHI) *Physalaemin Sleep-inducing peptides (4 peptides) Somatostatin Substance K Substance P Thyroid hormone releasing hormone (TRH) Vasoactive intestinal peptide (VIP) Vasopressin
Purinergic	Adenosine ADP AMP ATP
Gaseous neurotransmitters	Carbon monoxide Nitric oxide

*found mainly in lower vertebrates.

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Neurotransmitters

Drugs act on primary "target" neurotransmitter receptors which sets in motion a cascade of "downstream" neural communication.

- The ability of drugs to release dopamine, either directly or indirectly, is crucial for addiction.
  - Cocaine & amphetamines act primarily on the dopamine system.
  - Unique properties of other drugs, arising from their target receptor specificity, makes them attractive for different reasons

Drug	Primary receptor
Cocaine/Amphetamine	Dopamine
MDMA	Serotonin
Opium/Morphine/Heroin	Endorphin (Opioid)
Nicotine	Acetylcholine
Alcohol	GABA/glutamate
Cannabis	Endocannabinoid

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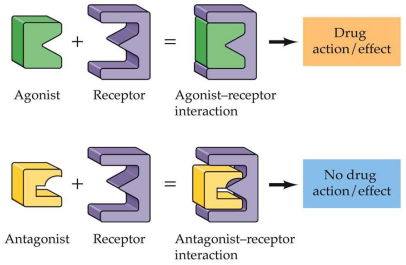
Agonists & Antagonists



Video: Agonist & Antagonists

Ion channels are opened or closed by neurotransmitters. Depending upon what ions these channels allow to flow in which direction, the neurotransmitters either excite or inhibit the cell.

- Drugs modify cell activity by having a similar molecular shape to the shape of a neurotransmitter molecule.
  - Drugs are classified as agonistic if they fit a receptor perfectly & thus cause the linked channel to open or close.
  - Drugs are classified as antagonistic if they fit a receptor imperfectly & thus block the action of the neurotransmitter.
- Drugs may be both agonists and antagonists at different receptors, creating complex effects in different parts of the brain.

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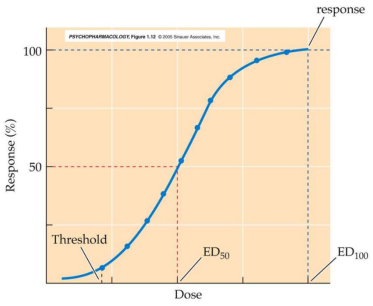
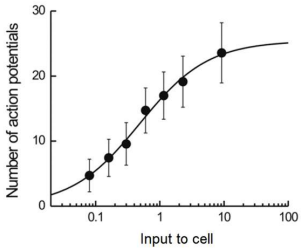
Dose-response curve

Dose-response curves: plot the response to drugs, indexed by a measure of behaviour or experience (e.g. pain relief) against the dose of the drug administered.

- at low doses there is little response
- as the dose increases so does the response, until an upper limit is reached where further increases in dose produce no additional response.
- Effective Dose (ED) 50: is the dose at which 50% of the maximum response is achieved.

- The S shape dose-response curve may reflect the underlying physiological limits of cell firing rates, which are also S shaped.





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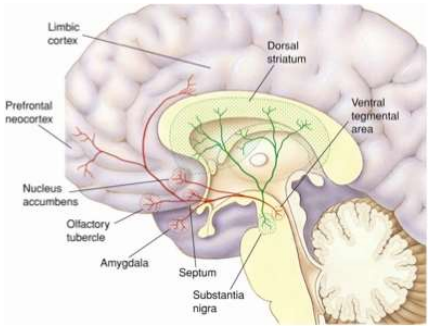
Dopamine

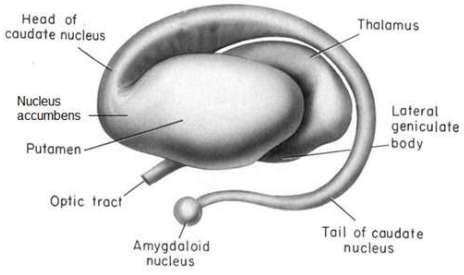
Mesolimbic pathway: Ventral tegmental area (VTA) to the nucleus accumbens

- key for drug reward learning
- common path for drugs to produce their rewarding effects (Pierce et al. 2006)

Video: Reward System



Striatum



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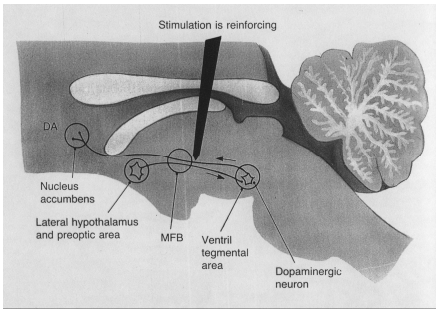
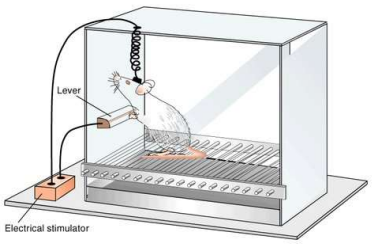
Dopamine: reward

Olds & Milner (1954): early evidence for the role of dopamine in reward

- rats favoured the location of the box in which they had received electrical stimulation of the medial forebrain bundle (midpoint of the mesolimbic pathway).
- found that rats would learn to press a lever to obtain this electrical stimulation, indicating that this stimulation was rewarding.
- conceivably this may underpin drug addiction.





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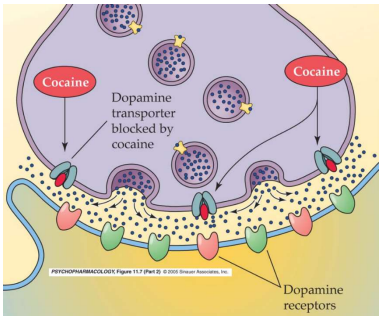
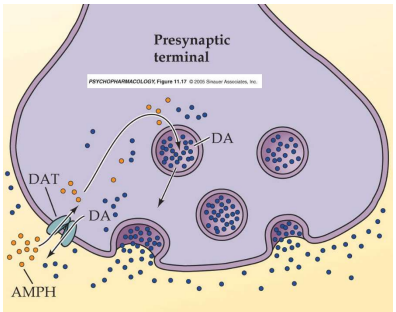
Dopamine agonists

Cocaine & amphetamine are dopamine (DA) agonists- increase the amount of DA presence in the synaptic cleft (via different mechanisms).

- Cocaine blocks DA reuptake
- Amphetamine causes DA to be released from synaptic vesicles into the terminal button
  - And, reverses the direction of the DA reuptake transporter

- Supernormal increase in DA availability within the synaptic cleft





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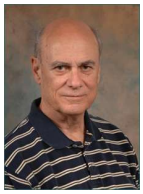
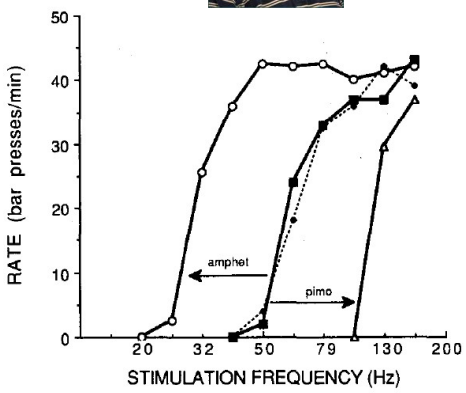
Dopamine: reward

Wise (1996): found that electrical self-stimulation reward was mediated by the mesolimbic DA pathway

- measured change in rats' rate of lever pressing to obtain electrical stimulation across different frequencies of stimulation
- higher frequencies were more rewarding & supported higher rates of lever pressing to obtain the stimulation.
- Admin. of amphetamine (DA agonist) shifted the curve to the left, making a lower frequency of stimulation more rewarding
- Admin. of Pimozide (DA antagonist) shifted the curve to the right, requiring higher levels of stimulation to achieve the same level of reward.

- Indicates that behaviours which cause an increase in DA activity will increase to the extent that DA is released.
- Addiction appears to form by virtue of drugs releasing dopamine





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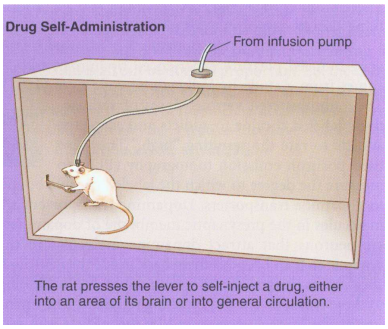
Dopamine: drug reward

Drug self-administration procedure: used to model human addiction. Rats are given access to a lever which if pressed causes the infusion of a drug into the blood stream. The fact that rats acquire the self-administration response to obtain drugs indicate that drugs are rewarding.

- The mesolimbic DA pathway has been implicated in drug reward by the finding that lesions of the nucleus accumbens abolishes cocaine (Roberts et al. 1980) & amphetamine self-administration (Lyness et al. 1979)

- Thus, drugs must activate DA in the nucleus accumbens in order to stamp-in self-administration behaviour.



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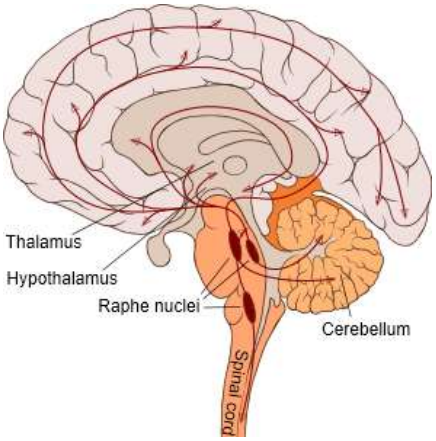
Serotonin

Neurons that express serotonin (5-HT) are located in the raphe nuclei of the brain stem

- axons project extensively across the brain
  - consistent with 5-HT having a modulatory role on total brain function
- 5-HT neurons in the raphe nuclei play an important role in maintaining conscious arousal level (wakefulness)
  - these cells are inhibited during sleep.



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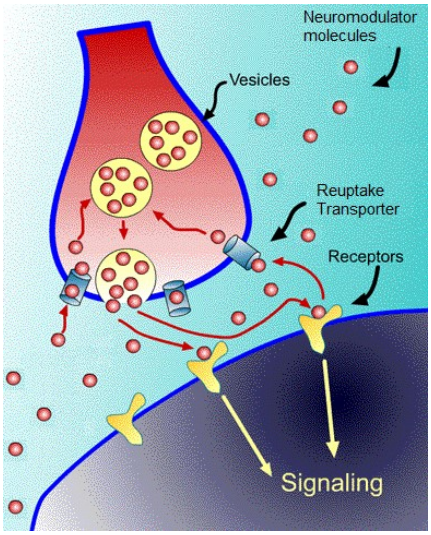
Serotonin: multiple roles

Multiple roles in synaptic communication:

- acts on different ion channels to produce excitatory & inhibitory transmission of action potentials
- diffuses into the extracellular fluid to excite neighbouring neurons
- interacts with other neurotransmitter systems including glutamate and GABA to influence learning & memory.
  - important for cognition

(Ögren et al 2008; Kehagia et al. 2010).



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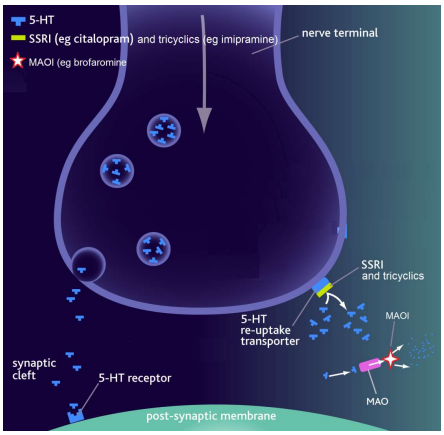
Serotonin: mood

5-HT is best known for its role in positive mood

- the main antidepressant medications all influence 5-HT neurotransmission to increase the availability of 5-HT in the synaptic cleft (i.e. they are agonists)
  - Increases positive mood



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Serotonin: MDMA

Video: MDMA therapy

MDMA has high affinity for blocking 5-HT reuptake from the synaptic cleft

- Serotonin agonist
- Hallucinogens (psilocybin, mescaline, peyote, LSD) & Stimulants (cocaine, amphetamine) also block 5-HT reuptake
- Suggests that positive mood may be a common element amongst these drugs which helps maintain their recreational use.

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MDMA: addictive potential

MDMA (& hallucinogens) also release dopamine in the nucleus accumbens (Gudelsky et al, 2008)

- it is the dopamine enhancing effect of the drug which determines their addictive potential (Ritz & Kuhar, 1989)
- MDMA'S relatively lower affinity for releasing dopamine compared to amphetamine & cocaine may explain why these compounds are ranked as having a lower addiction potential than other drugs with higher dopamine affinity (Nutt et al. 2007)

Drug	Dependence score
Heroin	3
Cocaine	2.39
Tobacco	2.21
Street methadone	2.08
Barbiturates	2.01
Alcohol	1.93
Benzodiazepines	1.83
Amphetamine	1.67
Ketamine	1.54
Cannabis	1.51
Methylphenidate	1.25
LSD	1.23
GHB	1.19
Ecstasy	1.13
Khat	1.04
Solvents	1.01
Anabolic steroids	0.88

(Nutt et al. 2007).

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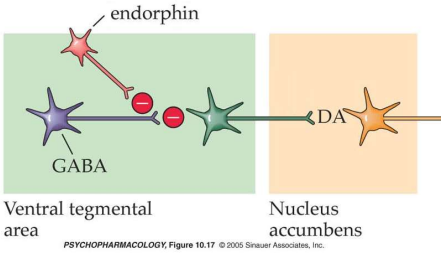
Endorphins (Opioids): Pain & Pleasure

Endorphins: (neuropeptide) play a key role in pain reduction (analgesia) & subjective pleasure (euphoria).

- receptors are called opioid receptors because they respond to opioids/opiates
  - receptors are located throughout the spine & sensory-motor pathways of the brain
- either open K+ channels or close Na+ channels reducing the likelihood of action potentials carrying pain signals.
- Endorphins are released by the pituitary gland during a fight or flight response
- Endorphins are also located within the VTA of the mesolimbic dopamine pathway
  - they inhibit inhibitory GABA neurons causing an increase in dopamine release in the nucleus accumbens (Spanagel et al. 1990)



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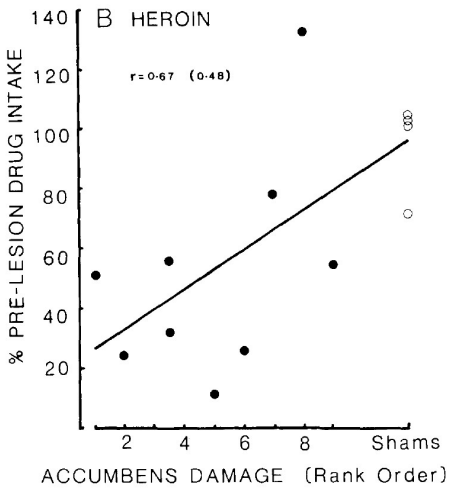
Heroin & Dopamine

Zito et al. (1985): rats self-administered heroin until their behaviour had stabilized

- lesioned the accumbens & measured the percent decline in self-administration relative to the pre-lesion baseline.
- Animals ranked as having the greatest accumbens damage (2-4) showed the smallest percent of self-administration relative to pre-lesion (20-60%), whereas animals ranked as having little accumbens damage & sham animals who had no damage, showed self-administration rates which were closer or matched their pre-lesion baseline

- Nucleus accumbens & DA are essential for heroin self-administration.



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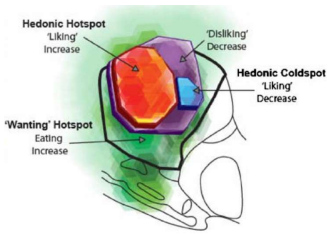
Endorphins: Pain & Pleasure

Hedonic reactions procedure: an animal model of subjective emotional experience

- a sweet (pleasant) or bitter (unpleasant) solution is squirted into a rat's mouth
  - facial reaction is recorded with a close up camera.

Berridge & Kringelbach (2008): explored the neural mechanisms underpinning subjective reactions to opiates

- whether injections of opiates into subregions of the nucleus accumbens increased sweet liking ('liking increase'), decreased bitter disliking ('disliking decrease'), or decreased sweet liking.
- In response to opiates, a large region (purple) decreased disliking, a smaller region (red) increased liking, and a very small region (blue) decreased liking.
  - Subregion specificity within the accumbens



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