PSYC1022: The Psychology of Addiction

Topic 6: Neuropharmacology (III)

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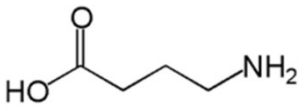
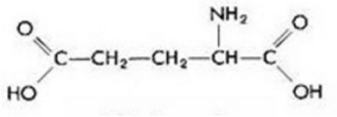
Outline:

- Acetylcholine
  - Nicotine
- GABA
- Glutamate
  - Alcohol
- Cannabinoid
  - THC



GABA



Glutamate

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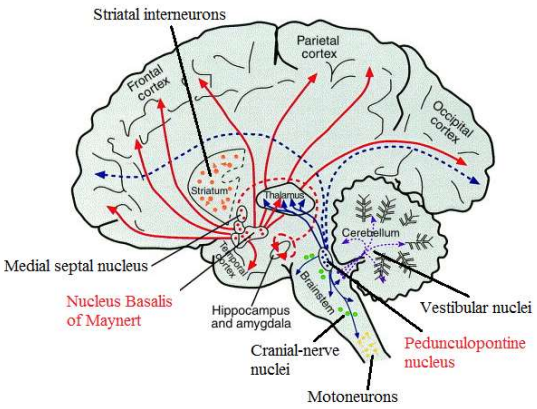
Acetylcholine

Has a role in cognitive capacity: sensitivity to sensory events, memory, speed of responding etc.

- Alzheimer's disease is marked by broad impairments in cognitive capacity & characterised by destruction of acetylcholine cell bodies (Auld et al. 2002)
- These cells project broadly across the cortex, they are believed to modulate higher cortical functions as a whole.



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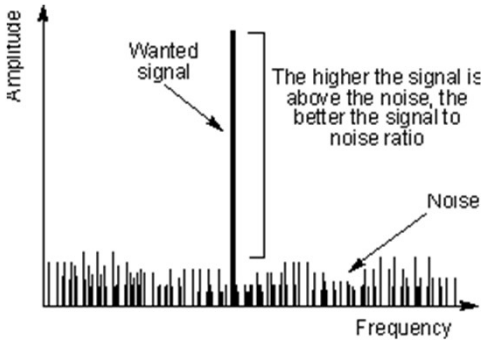
Acetylcholine: cognitive function

Functions as a cognitive enhancer, improving attention & reactivity to environmental events.

At the cellular level, acetylcholine (ACH) increases the signal to noise ratio in the firing rate response to stimulation

- cells have a background firing rate & increase this rate in response to appropriate stimulation (AKA 'tuning').
- The difference between the signal & the noise (background) is crucial for detection & responding to environmental events.



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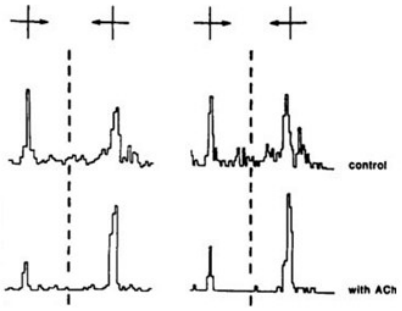
Acetylcholine: cognitive function

Sillito & Kemp (1983): Cells in the visual cortex of anesthetised cats are tuned to respond preferentially to bars of light moving across the visual field in a particular direction (left or right).

- Selectivity of this tuning is weak in the control (anesthetised) animals. However, when ACH is applied the tuning of the cells become much more selective to the preferred stimulation.



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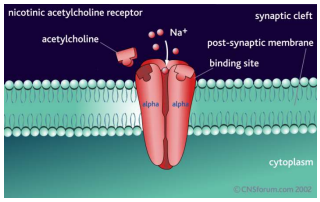
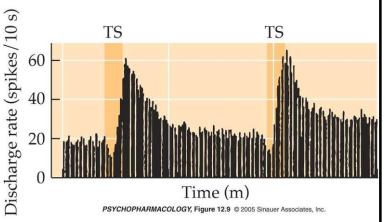
Acetylcholine: Nicotine

Nicotine, an ACH agonist, binds to ACH receptors on the post-synaptic cell. These receptors are coupled to Na+ channels, which open in response to binding, exciting the cell & thus increasing the probability of an action potential.

- Nicotine also binds to pre-synaptic ACH receptors located on the terminal button of cells which express endorphins (Berrendero, 2010) & DA (Sidhpura et al., 2007; Nisell et al., 1994).
- Cells in the VTA increase firing rate in response to tobacco smoke (TS, bottom right figure).
  - activation is essential for nicotine to maintain self-administration behaviour (David et al., 2006).



Post-synaptic nicotine acetylcholine receptor



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Nicotine: Addictive potential

Addictive potential of nicotine stems from its three main actions:

1. Increasing cognitive function by activating the ACH system (Levin et al. 2006; Miwa et al. 2011).
2. Increasing pleasure, well-being or pain/stress relief by activating the endorphin system (Gilbert 1979; Pomerleau et al. 1984; Berrendero 2010)
3. Increasing reward of self-administration behaviour by activating the DA system (Wise, 2004).

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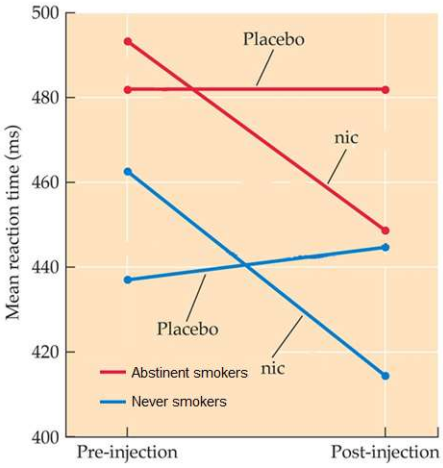
Acetylcholine: Nicotine

Foulds et al. (1996): abstinent smokers & never smokers completed a RVIP task before & after nicotine or placebo.

- RVIP: participants presented with a series of digits, 100 digits p/m for 10 mins. Press a button when see target.
- Placebo: neither abstinent smokers or never smokers showed an improvement
- Nicotine: both groups showed an improvement of target detection

- Overall slower target detection of smokers compared to never smokers is consistent with a withdrawal or tolerance effect or neurocognitive damage from smoking.



From Meyer & Quenzer (2005). After Foulds et al. (1996)

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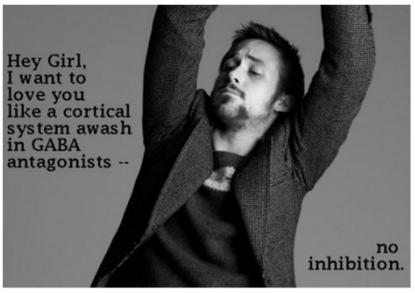
GABA: Inhibition

GABA (gamma-amino butyric acid): the chief inhibitory neurotransmitter regulating neural activity throughout the nervous system.

- Release of GABA onto receptors causes a shift in ion channels which causes the cell to hyperpolarize (negative charge)
  - decreases the probability of an action potential.

GABA cells often play the role of inhibitory "interneurons" by holding other cell groups inhibited (unless they themselves are inhibited by another cell)

- provide "negative feedback" in the sense that excitatory cell firing rates cannot exceed an upper limit
  - capping of firing rate is important for cells to avoid excitotoxic death, produced by overstimulation.



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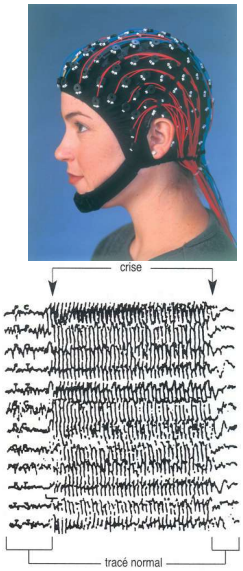
GABA: Inhibition

Support GABAs role in limiting the excitatory output of cells throughout the brain comes from Epilepsy.

- Hallmark of seizures is a transition to a supernormal level of action potentials within the brain as a whole as shown in the EEG trace (electrical activity recorded from the scalp).
- Anticonvulsant drugs act to increase inhibition of brain cells by targeting three main neural mechanisms:

1. Increase GABA availability (agonists)
2. Block voltage-gated sodium channels to reduce action potentials
3. Antagonise the actions of the main excitatory neurotransmitter glutamate.



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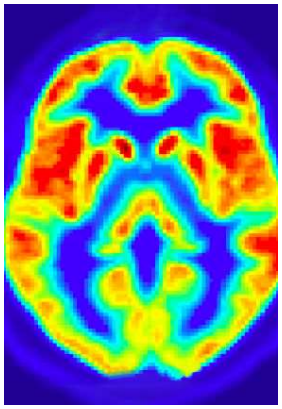
Glutamate: Learning

Glutamate (Glu) is the most abundant neurotransmitter in the brain

- present in over 50% of CNS tissue.
- plays a crucial role in learning & memory

Neuroplasticity: the process by which pathways & synapses in the brain are changed as a result of experience

- Environment, behavior, learning, drugs



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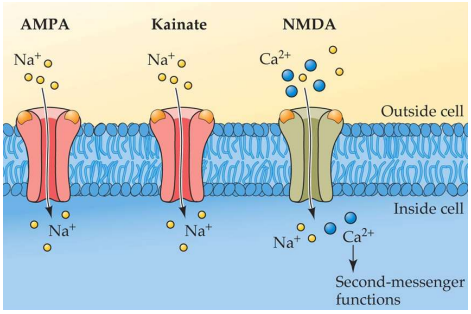
Glutamate: Learning

Two functions performed by Glu receptors:

- AMPA & Kainate receptors: respond to Glu release by opening Na+ channels thus initiating an action potential within the receiving cell.
- NMDA receptors: respond to Glu by opening calcium (Ca2+) channels which activates an intracellular process "second messenger system"
  - this increases the number of AMPA receptors & thus increases the strength of the synaptic connection (long-term potentiation)



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Alcohol

Antagonises post-synaptic Glu receptors & reduces the release of Glu

- reduces the overall level of excitation within the brain
- impairs learning and memory (black-outs)

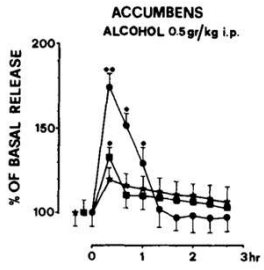
GABA agonist: further reduces excitation levels, responsible for sedative effects, anxiety reduction & motor incoordination.

Releases endorphins producing the euphoric & analgesic effect

- Opiate release partially responsible for alcohol reward because alcohol self-administration can be reduced by opiate antagonists (e.g. naltrexone).

Dopamine agonist: increases in Nucleus Accumbens

- responsible for rewarding self-administration behaviour.



Di Chiara (1986)

Neurotransmitter	Acute cellular effects	Behavioral effects
Glutamate	Receptor antagonism and reduces release	Memory loss
GABA	Acutely enhances GABA-induced Cl^- influx to hyperpolarize	Sedative effects: anxiety reduction, sedation, incoordination, memory impairment
Dopamine	Acute increase in transmission in mesolimbic tract	Reinforcement
Opioids	Acute increase in endogenous opioid synthesis and release	Euphoria analgesia

PSYCHOPHARMACOLOGY, Table 9.3 © 2005 Sinauer Associates, Inc.

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Cannabinoid receptors- Retrograde inhibition

Anandamide: the neurotransmitter (endocannabinoid) which binds to CB1 receptors

- only recently discovered (Devane et al. 1992)
- one type of endocannabinoid now known to act on CB1.
- CB1 receptors tend to be located on the pre-synaptic terminal button of neurons
  - exert an inhibitory effect on the release of neurotransmitters including Ach, DA, GABA & Glu
  - produces increases or decreases in overall neural activity in different brain regions depending upon the neurotransmitter effected (Iversen, 2003).
- Endocannabinoids are manufactured on demand by post-synaptic cells in response to neurotransmitters binding from the pre-synaptic cell
  - Retrograde messenger: information is carried back across the synapse to CB1 receptor (as opposed to pre-post)
  - feedback inhibits neurotransmitter release in pre-synaptic cell

Video: Endocannabinoid System

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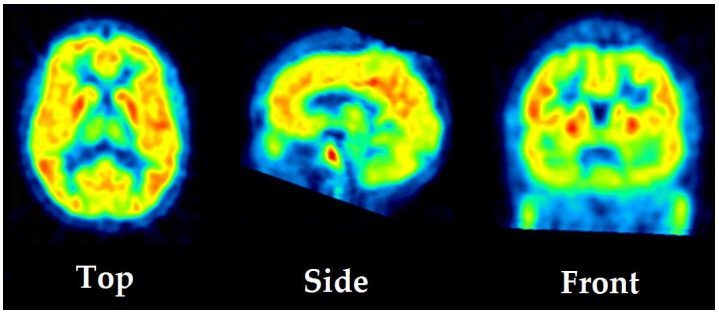
Cannabinoid & THC

THC binds to CB1 receptor (agonist)

- CB1 receptor has a broad distribution in the brain (Terry et al. 2010)
  - the various psychological effects of cannabis can to some extent be attributed to binding within particular regions (Glass et al. 1997).



Some areas with high concentrations of cannabinoid receptors:	Corresponding effects of marijuana:
Cerebral cortex	
Plays a role in memory, thinking, perceptual awareness and consciousness	Altered consciousness; perceptual distortions; memory impairment; occasional delusions and hallucinations
Hypothalamus	
Governs metabolic processes such as appetite	Increased appetite
Brain stem	
Controls many basic functions including arousal, the vomiting reflex, blood pressure and heart rate	Nausea relief; rapid heart rate; reduced blood pressure; drowsiness
Also plays a role in pain sensation, muscle tone and movement	Pain reduction; reduced spasticity; reduced tremor
Hippocampus	
Is key to memory storage and recall	Impairment in memory
Cerebellum	
Governs coordination and muscle control	Reduced spasticity; impaired coordination
Amygdala	
Plays a role in emotions	Anxiety and panic in some cases; reduced anxiety and blocking of traumatic memories in other cases; reduced hostility

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THC & Dopamine

THC administered to rats increases firing rate of dopamine cells in the VTA
- projects to the nucleus accumbens
- The same activation in response to THC can be seen in humans

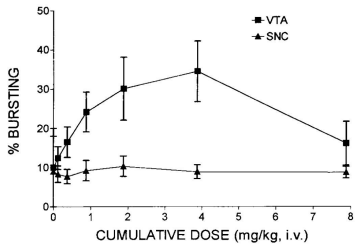
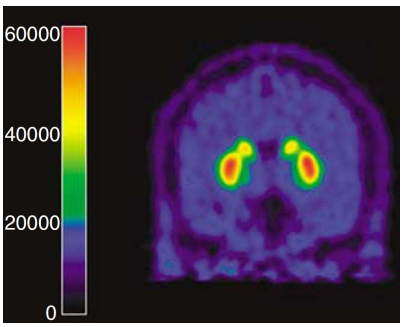


FIG. 1. Dose-dependent effects of the psychoactive cannabinoid Δ9-THC on firing rate (top graph) and burst firing (bottom graph) in VTA and SNC dopamine neurons.

French et al. 1997



Bossong, 2008

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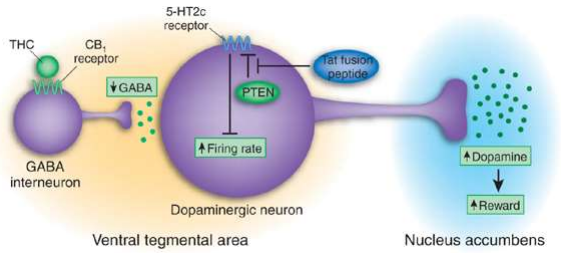
Cannabinoid: retrograde inhibition

Increased DA activity in the mesolimbic pathway is thought to be mediated by THC binding to CB1 receptor on GABA interneuron
- As a result, the GABA interneuron is inhibited
  - GABA interneurons hold DA cells in the VTA inhibited
    - DA cell firing is thus disinhibited (increased), resulting in the experience of reward that drives the formation of addictive behaviour.

Thomas (2006)



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Summary

Knowledge and understanding of:

- Key historical findings and ideas about the CNS
- structure of neurons, the processes involved in neuron potentials & how neurotransmission occurs.
- neurotransmitters, the concept of agonists and antagonists & their influence on neural communication.
- Dose response curves, what they are & how they relate to cell firing rates.
- DA and the role it plays in the rewarding effect of drugs
- mesolimbic pathway, particularly the Nucleus Accumbens & VTA.
- 5-HT, role in the CNS and in addiction.
- Opioid receptors, their role in the CNS & addiction.
- Ach, role in the CNS & how nicotine agonises the Ach system.
- GABA & Glutamate, their roles in the CNS & relevance to alcohol.
- CB1 receptor, mechanism in the CNS & how THC influences them and subsequently DA.

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