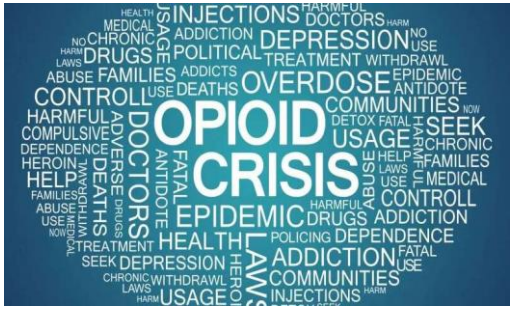
Addiction and the Brain (PSGY1005)

Opioids



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Outline

Part 1

- Opioids, their physiological and psychological effects, use and misuse, harms: overview
- Neuropharmacological targets of opioids: opioid receptors and neural effects mediated by opioid receptors

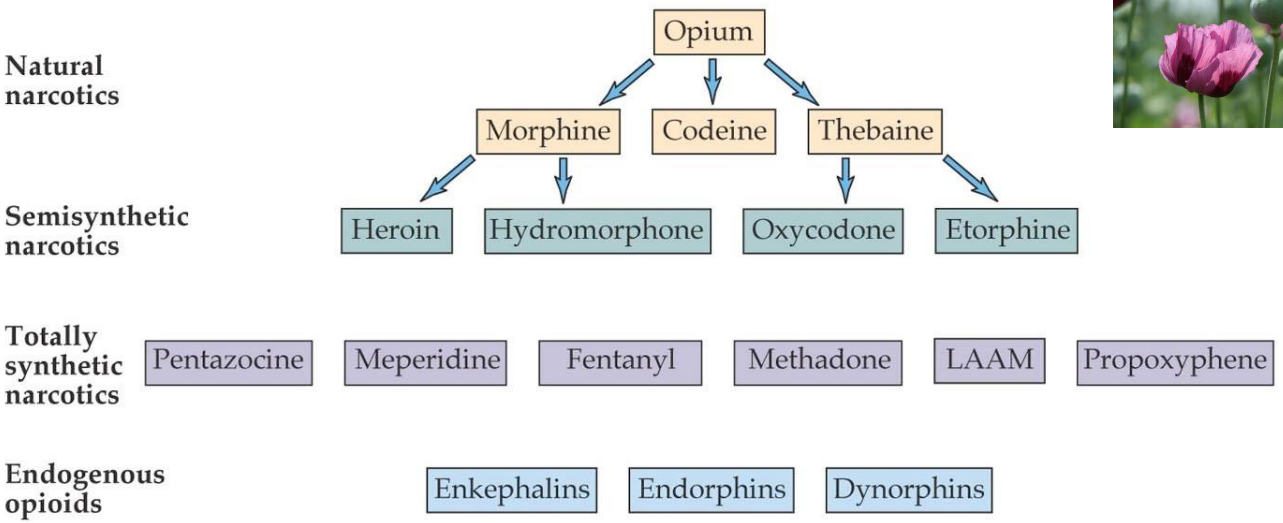
Part 2

- Pain and opioids
- Reinforcing properties of opioids
- Opioids and pleasure
- Opioid abuse and dependence
- Treatment of opioid dependence

Opioids

- Narcotic analgesics, i.e. drugs that produce analgesia (reduction of pain) without anaesthesia (loss of all sensation), but promote a sense of relaxation and sleep and at overdoses lead to coma and death.

- 1) opiates, i.e. opium – an extract of the opium poppy plant – and substances directly derived from opium;
  2) related semisynthetic and synthetic compounds;
  3) endogenous peptides acting on the same receptors, the opioid receptors



Physiological and psychological effects opioids

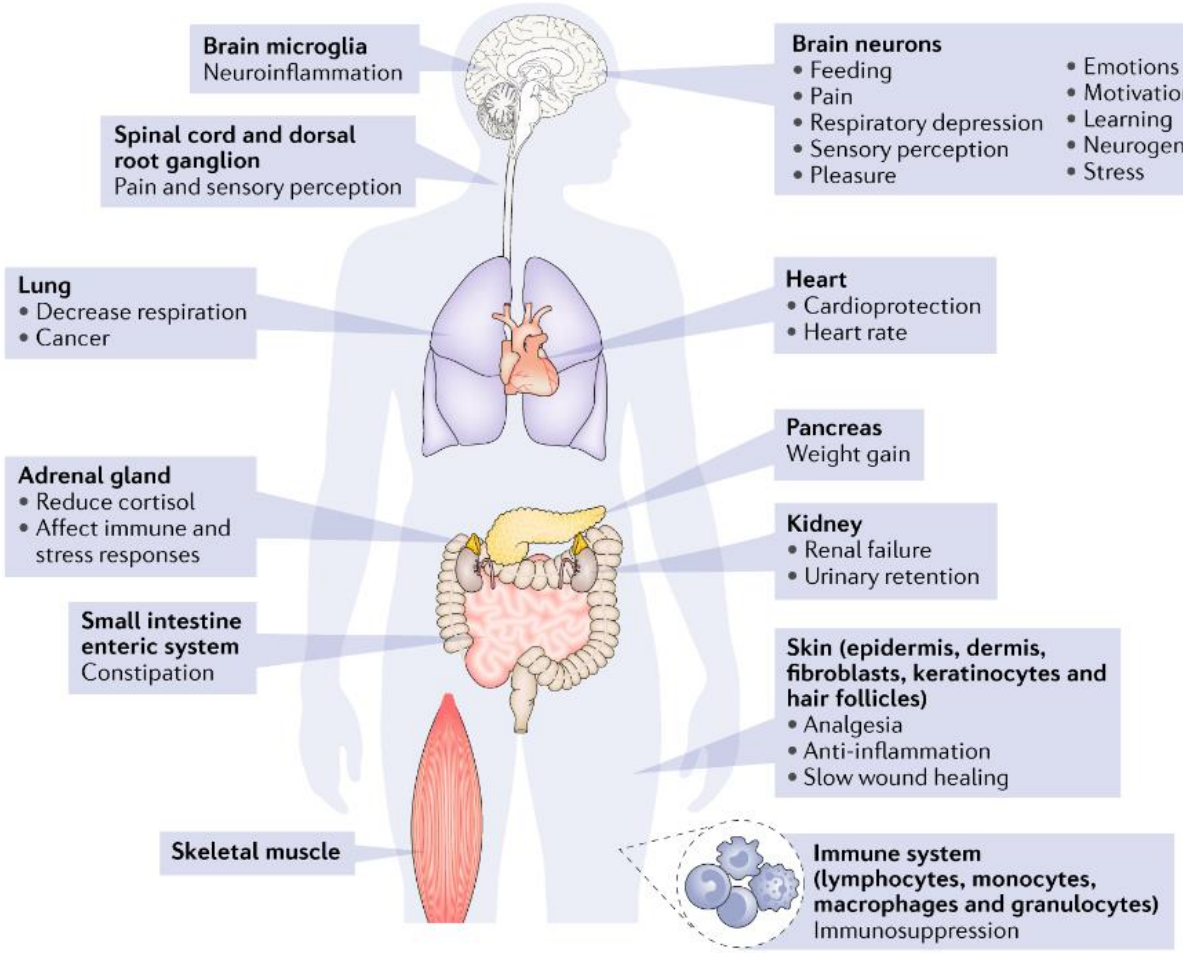


TABLE 11.2 Acute Effects of Opioids and Rebound Withdrawal Symptoms

Acute action	Withdrawal sign
Analgesia	Pain and irritability
Cough suppression Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation
Flushed and warm skin	Chilliness and "gooseflesh"

PSYCHOPHARMACOLOGY 2e, Table 11.2

Fig. 1a, Kibaly et al. (2019) *Nature Rev Neurosci* 20:5-18

Which of the following is a key acute effect of opioids?

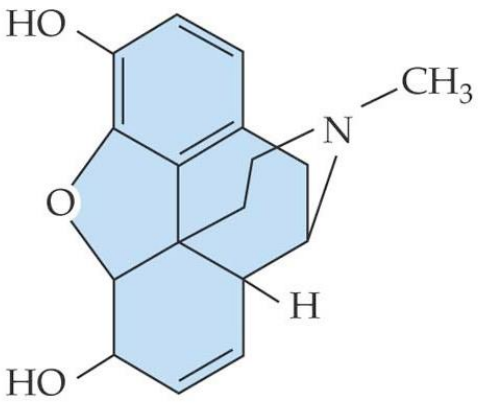
a) analgesia

b) anaesthesia

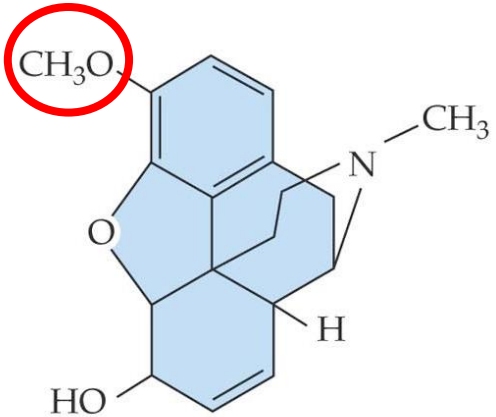
c) diarrhea

d) all of the above.

Molecular structure of opiates and related compounds, and relationship to physiological effects

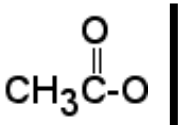


Morphine



Codeine

Less analgesic, but also less side effects, still very potent cough suppression

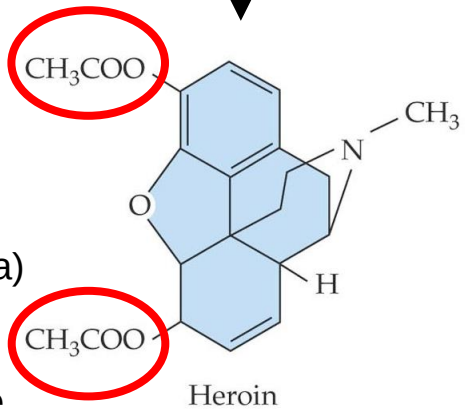


Acetic acid

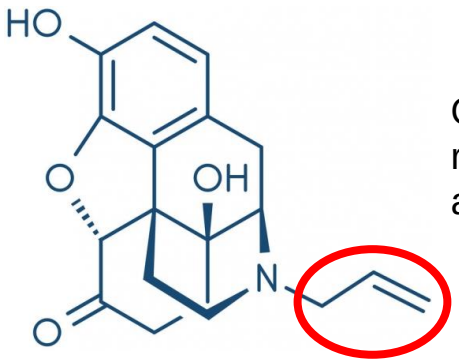
Added acetyl-groups:

- more lipophil
- Crosses blood-brain barrier more quickly
- Strong high (euphoria)

In brain, heroin is converted to morphine.



Heroin



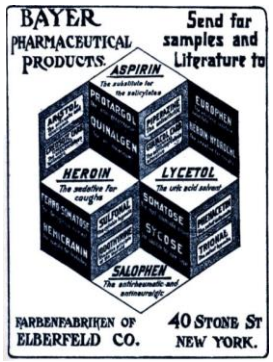
Naloxone

Opioid receptor antagonist!

Opioid use and misuse

Long history of medical use (against pain, coughing, diarrhoea) and recreational use (for euphoria and relaxation); nowadays, medical use is strictly regulated and recreational use illegal.

Victorian times (19th and early 20th c.)



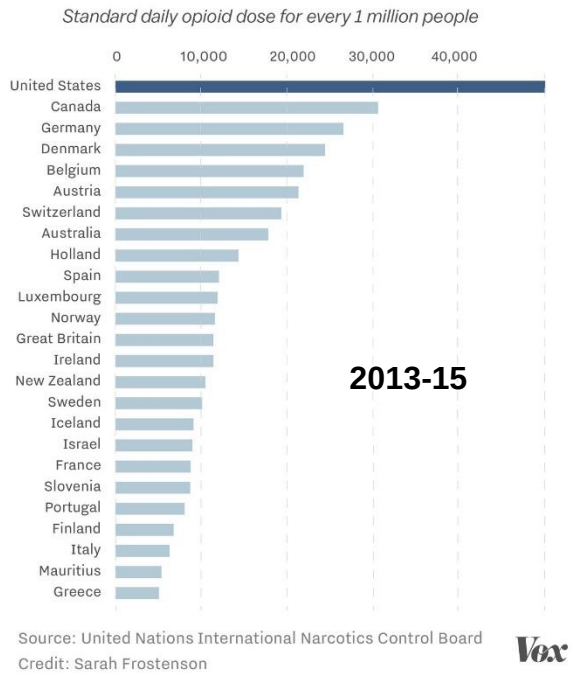
Now (since mid 20th c.)

https://www.forbes.com/sites/carmendrahl/2017/06/12/five-things-heroins-curious-chemistry-history/

Opioid epidemic/crisis

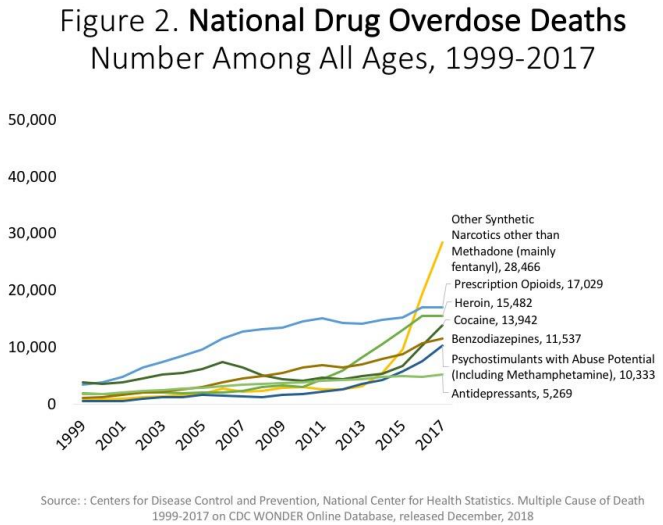
Opioids are the main cause of overdose deaths

High levels of opioid use



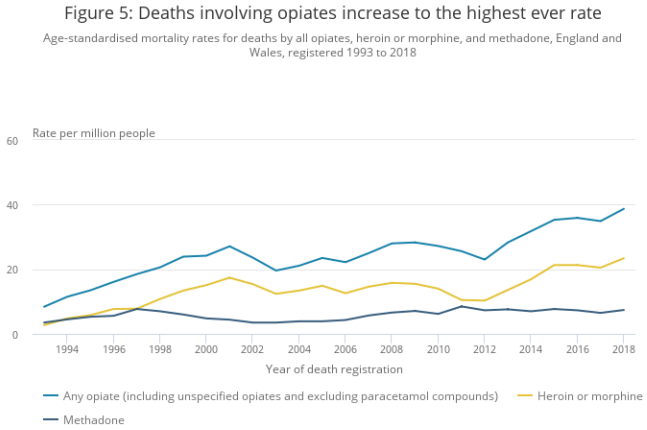
https://www.vox.com/policy-and-politics/2017/6/28/15881246/drug-overdose-deaths-world

US



https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

UK



In 2018, a total of 2,208 drug poisoning deaths had an opiate mentioned on the death certificate (51% of all drug poisoning deaths).

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2018registrationsRelated-Deaths-Report-161212.pdf

▲ People who have lost loved ones to OxyContin and opioid overdoses leave protest messages written on pill bottles outside the headquarters of Purdue Pharma in Stamford, Connecticut on 17 August 2018. Photograph: Jessica Hill/AP

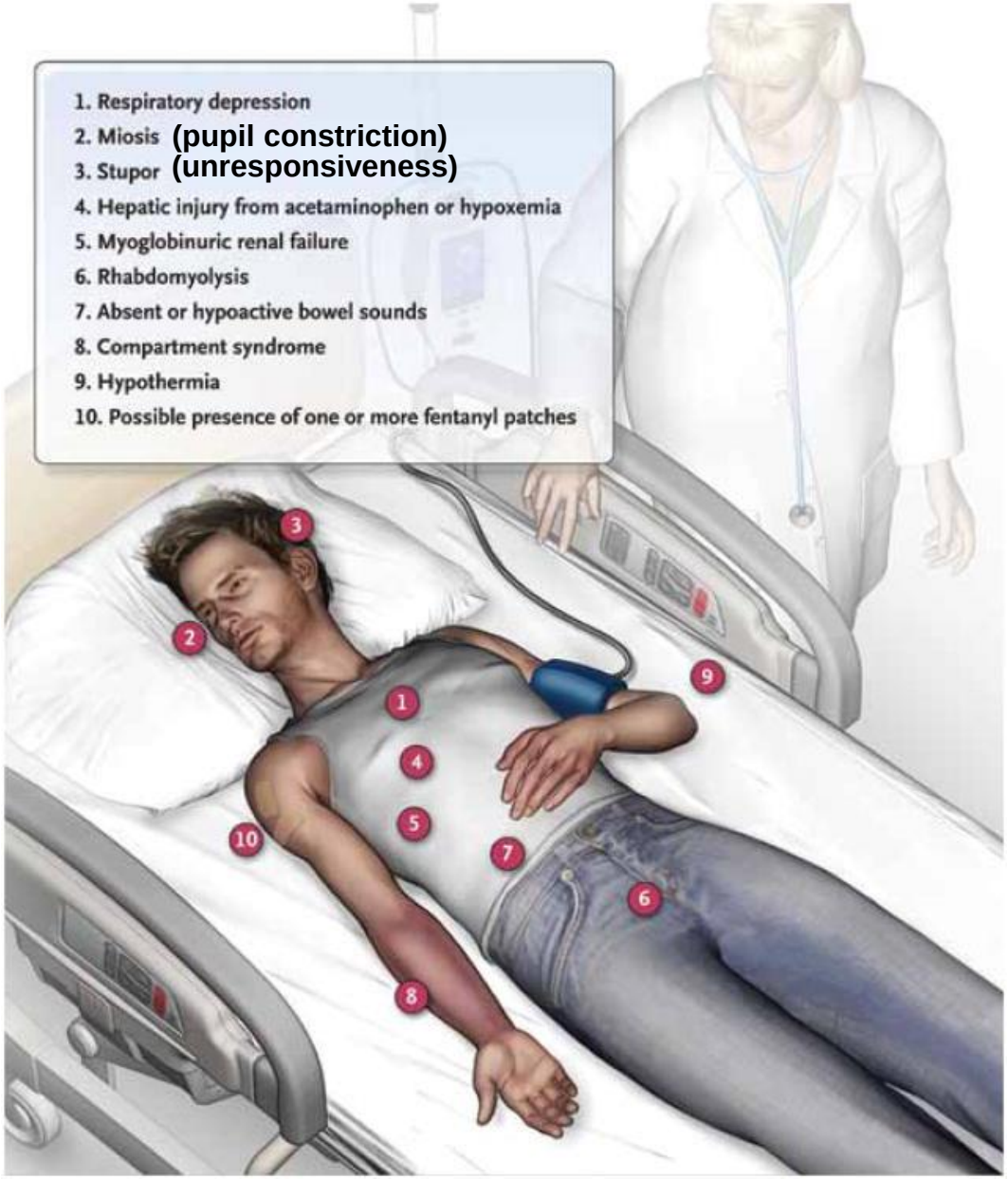
Capitalism gone wrong: how big pharma created America's opioid carnage

A web of firms ramped up narcotic painkiller sales, creating the biggest drug epidemic in American history as profits surged

by Chris McGreal

https://www.theguardian.com/us-news/2019/jul/24/opioids-crisis-big-pharma-drugs-carnage

Opioid overdose



Opioid overdose can be treated by injection with the opioid antagonist naloxone.

Boyer (2012) New England Journal of Medicine, 367(2), 146-155.

The suggestion that alcohol is more harmful than heroin or crack is based on:

a) an expert assessment of drug harms to users.

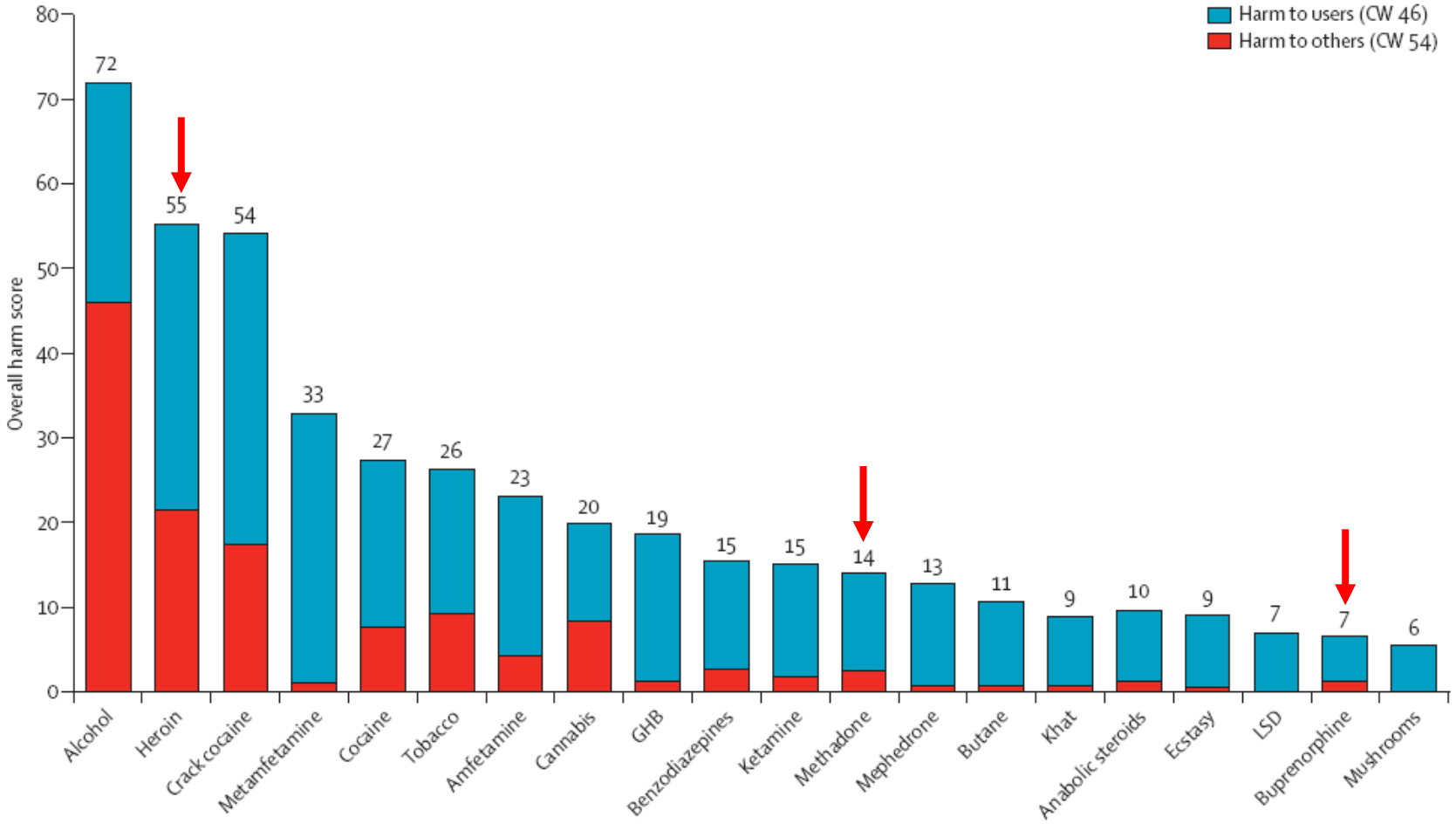
b) an expert assessment of drug harms to others (i.e., society).

c) both a) and b).

d) none of the above.

Harmfulness of different drugs

Only opioids considered were heroin, methadone and buprenorphine



Nutt et al. (2010) *Lancet* 376:1558

Correctly complete the following statement:

In the heroin molecule, two hydroxyl groups of morphine are replaced by acetyl groups. This chemical difference makes heroin more _____ and is responsible for heroin crossing the blood-brain barrier _____ and causing _____ highs than morphine.

a) lipophil; better; stronger

b) hydrophil; better; stronger

c) lipophil; more slowly; weaker

d) hydrophil; better; weaker

Use and misuse of opioids: Which statement is incorrect?

a) Opioid use is illegal in the UK.

b) Opiods are the main cause of drug-related deaths in the UK.

c) Heroin was freely available to buy in the UK to treat coughs at the end of the 19th and the beginning of the 20th century.

d) The opioid codeine can be bought without prescription in UK pharmacies.

Which is true about an opioid overdose?

a) Only heroin overdoses, but not overdoses of other opioids, can be deadly.

b) Opioid overdose can be treated with a dopamine receptor antagonist.

c) Opioid overdose can be treated with naloxone.

d) None of the above.

Which of the following drugs may cause withdrawal symptoms in a person dependent on opioids?

a) Codeine

b) Morphine

c) Naloxone

d) Heroin

Opioid receptors

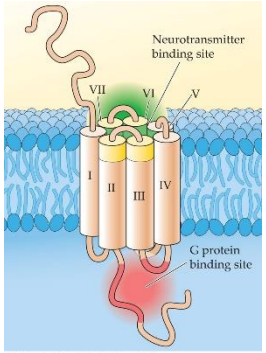
TABLE 11.1 Location, Function, and Endogenous Ligand for Opioid Receptor Subtypes

Receptor subtype	Endogenous ligand (prohormone source)	Location (most dense)	Functions
μ	Endomorphins (unknown), endorphins (POMC)	Thalamus, periaqueductal gray, raphe nuclei, spinal cord, striatum, brain stem, nucleus accumbens, amygdala, hippocampus	Analgesia, reinforcement, feeding, cardiovascular and respiratory depression, antitussive, vomiting, sensorimotor integration
δ	Enkephalin (proenkephalin), endorphins (POMC)	Neocortex, striatum, olfactory areas, substantia nigra, nucleus accumbens, spinal cord	Analgesia, reinforcement, cognitive function, olfaction, motor integration
κ	Dynorphins (prodynorphin)	Pituitary, hypothalamus, amygdala, striatum, nucleus accumbens	Neuroendocrine function, water balance, feeding, temperature control, dysphoria, analgesia
NOP-R	Nociceptin/orphanin FQ (pronociceptin/orphanin FQ)	Cortex, amygdala, hypothalamus, hippocampus, periaqueductal gray, thalamus, substantia nigra, brain stem, spinal cord	Spinal analgesia, supraspinal pronociception, feeding, learning, motor function, neuroendocrine function

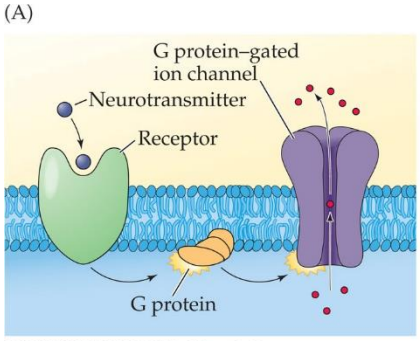
PSYCHOPHARMACOLOGY 2e, Table 11.1

There are also **peripheral opioid receptors**, including on peripheral nerve endings (Stein et al, 2003, Nature medicine 9:1003-1008) and in the gastrointestinal tract (Holzer, 2009, Regulatory peptides 155:11-17).

Opioid receptors are G-protein-coupled receptors



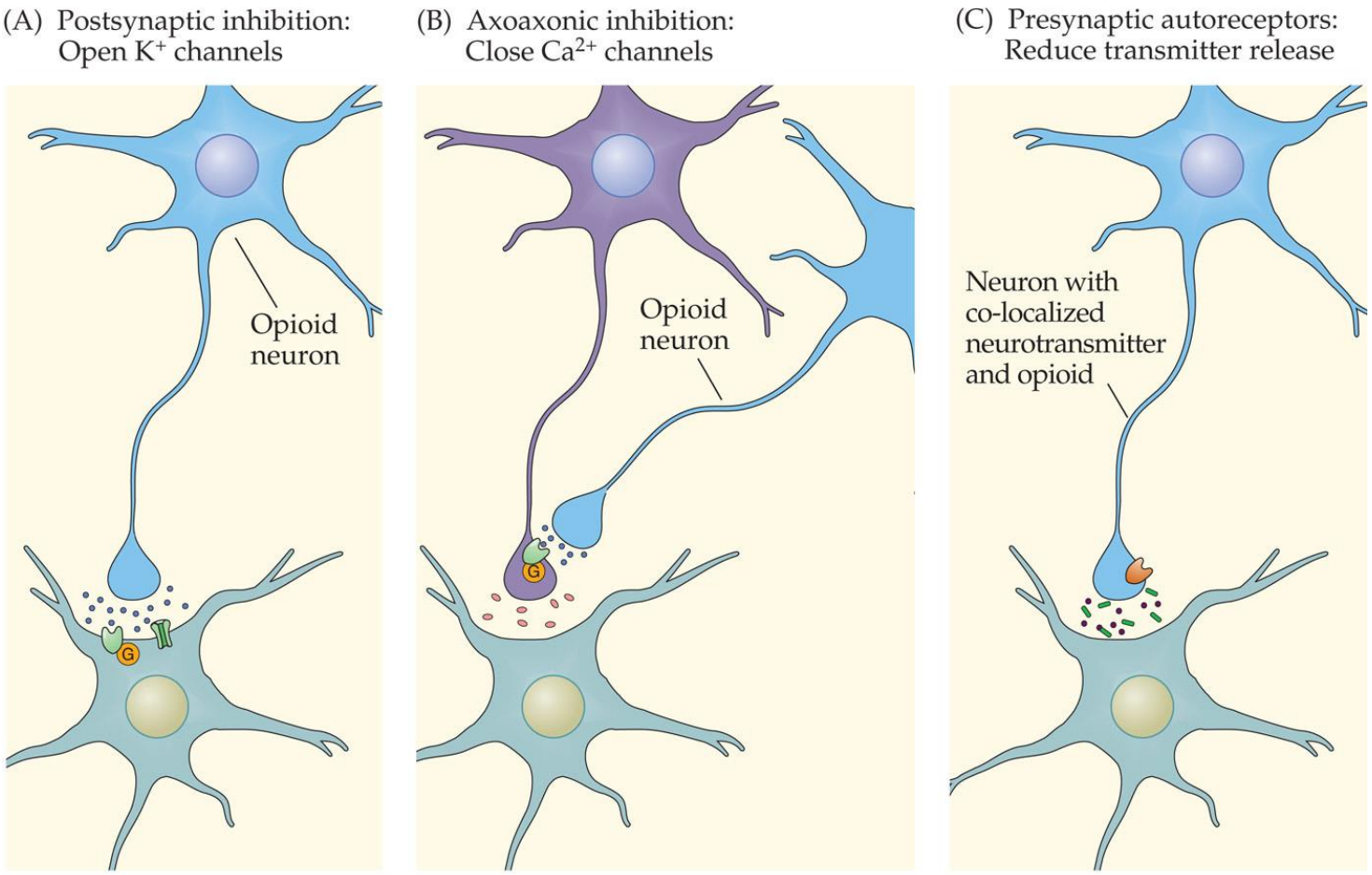
PSYCHOPHARMACOLOGY 2e, Figure 3.10



PSYCHOPHARMACOLOGY 2e, Figure 3.11

Opiod-receptor mediated neural inhibition

Activation of opioid receptors tends to inhibit neural activity or neurotransmitter release of the neurons carrying the opioid receptor.



***PSYCHOPHARMACOLOGY 2e*, Figure 11.11**

Opioid receptors and effects mediated by these receptors

Which statement is correct?

a) Some opioid receptor subtypes are ligand-gated ion channels.

b) Opioid receptors are not expressed in the peripheral nervous system.

c) Opioids activate inhibitory neurons expressing opioid receptors.

d) Opioids inhibit neural activity or neurotransmitter release by neurons expressing opioid receptors.

Some questions for revision

- What are opioids, why are they used and misused, how harmful are they?
- What are the neuropharmacological targets of opioids?
- What are the general effects of opioids on neural transmission?

The MCQs related to opiods will all be based on the material dealt with in my two lectures on opioids. If you understand the material, so that you can answer the lecture MCQs and revision questions well, you should have no difficulties with the exam MCQs.

Selected reading – Opioids 1

***Textbook chapter*:**

Chpt. on Opioids – for general overview

Other sources:

Online article on opioid crisis: https://www.vox.com/policy-and-politics/2017/6/28/15881246/drug-overdose-deaths-world

All references given in lecture are available online via Nottingham University access.

Outline

Part 1

- Opioids, their physiological and psychological effects, use and misuse, harms: overview
- Neuropharmacological targets of opioids: opioid receptors and neural effects mediated by opioid receptors

Part 2

- Pain and opioids
- Reinforcing properties of opioids
- Opioids and pleasure
- Opioid abuse and dependence
- Treatment of opioid dependence

Pain

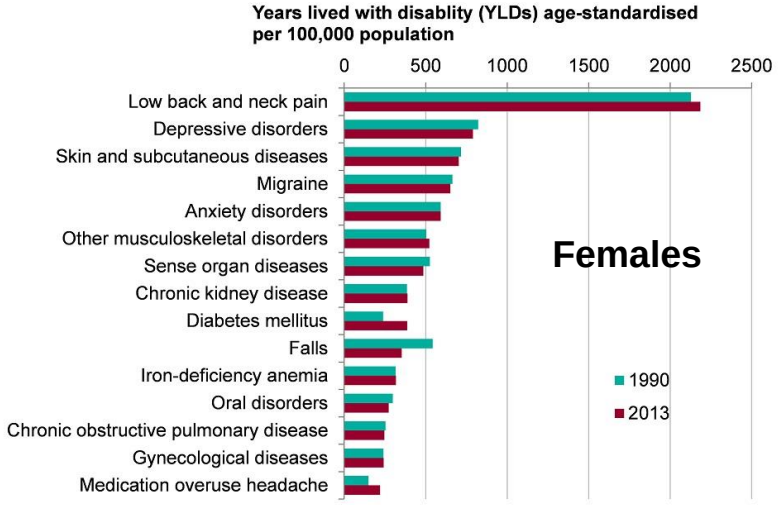
Pain
An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

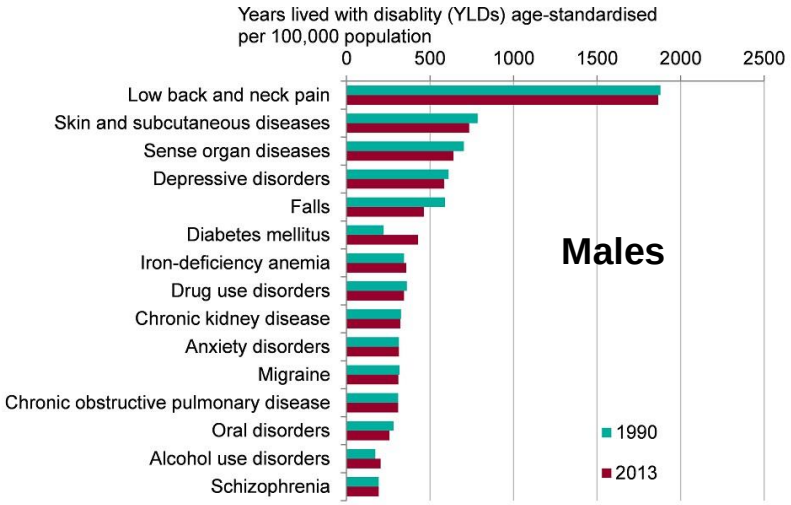
Nociception
The neural process of encoding noxious stimuli, i.e. stimuli causing tissue damage.

https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698

Chronic pain
Pain that lasts or recurs for longer than 3 months; can be symptom or disease in itself, i.e. with no clear relation to tissue damage. Affects about 20% of people worldwide!
Treede et al. (2019) *Pain* 160(1): 19-27.

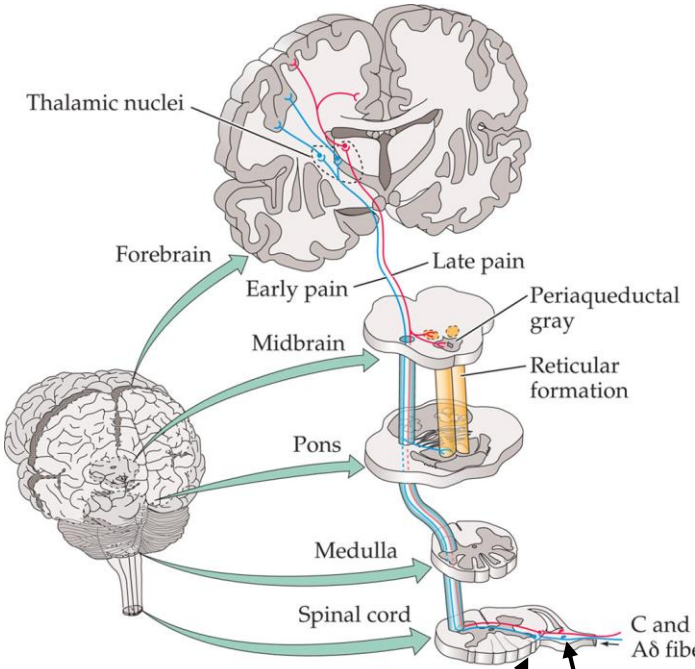
Pain is the leading cause of disability in the UK





Pain pathways

Ascending



PSYCHOPHARMACOLOGY 2e, Figure 11.12
© 2013 Sinauer Associates, Inc.

Dorsal horn of spinal chord

Primary sensory neurons (PSNs) in dorsal root ganglion (DRG)

PSN in DRG → Neuron in dorsal horn of spinal chord → Thalamus → Cortex

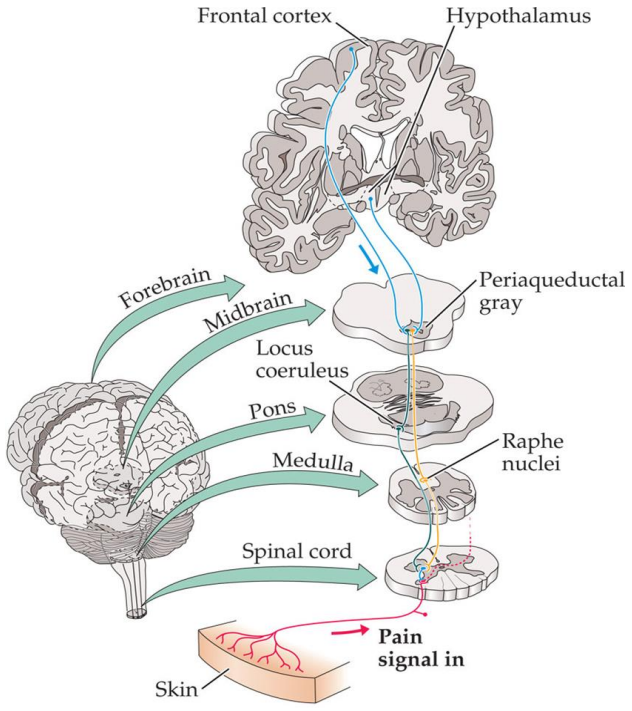
'First/fast' pain

PSNs with Adelta fibres → Somatosensory cortex

'Second/slow/late' pain

PSNs with C fibres → Other cortical and subcortical areas

Descending



PSYCHOPHARMACOLOGY 2e, Figure 11.15
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Descending pathways originate in midbrain regions, including periqueductal gray, and INHIBIT pain processing.

Opioids inhibit pain processing

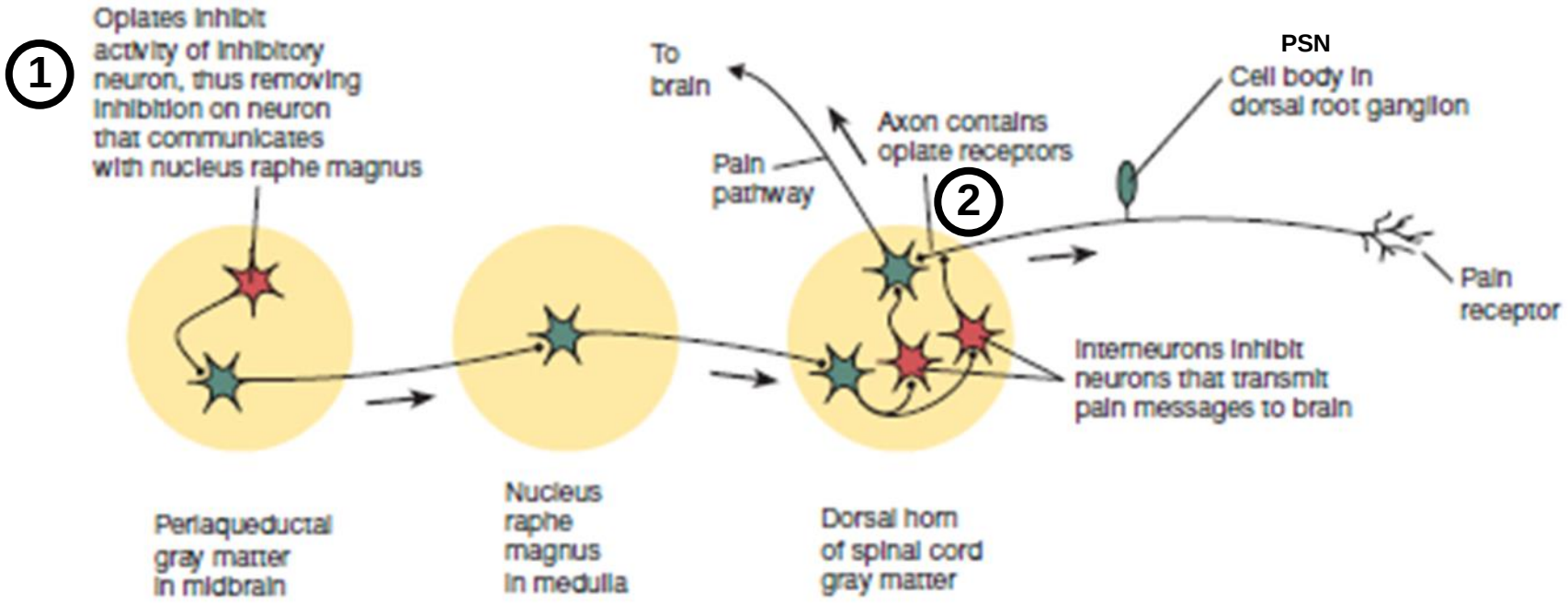

Fig. 7.31 from Carlson & Birkett (2013) Physiology of Behavior (11th ed)

1. Opioids disinhibit a descending pain pathway that inhibits pain.
2. Opioids inhibit the ascending pain pathway.

Opioids inhibit acute pain, but there is limited evidence that they inhibit chronic pain

Cochrane Database of Systematic Reviews

High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews

Cochrane Systematic Review - Overview | Version published: 30 October 2017 see what's new

https://doi.org/10.1002/14651858.CD012299.pub2

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Charl Els | Tanya D Jackson | Reidar Hagtvedt | Diane Kunyk | Barend Sonnenberg | Vernon G Lappi | Sebastian Straube

View authors' declarations of interest

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012299.pub2/abstract

Bottom line

'There is no high-quality evidence to show how well high doses of opioids work, or what side effects there are, when these medications are used for the treatment of chronic pain that is not due to cancer in adults.'

Pain

Which statement is not correct?

a) Pain refers to the neural process of encoding noxious stimuli, i.e. stimuli causing tissue damage.

b) Pain is the main cause of disability in the UK.

c) Opioids can reduce pain by disinhibiting a descending pain pathway that inhibits pain.

d) Opioids can reduce pain by inhibiting signal transmission in the ascending pathway.

Opioid treatment to reduce pain

Which statement is best supported by available evidence?

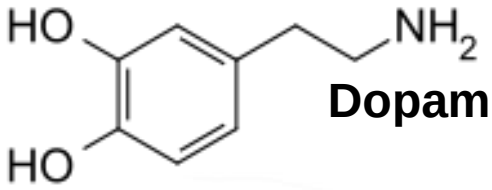
a) Opioids should not be prescribed to reduce pain.

b) Opioids are useful to reduce the intensity of acute pain.

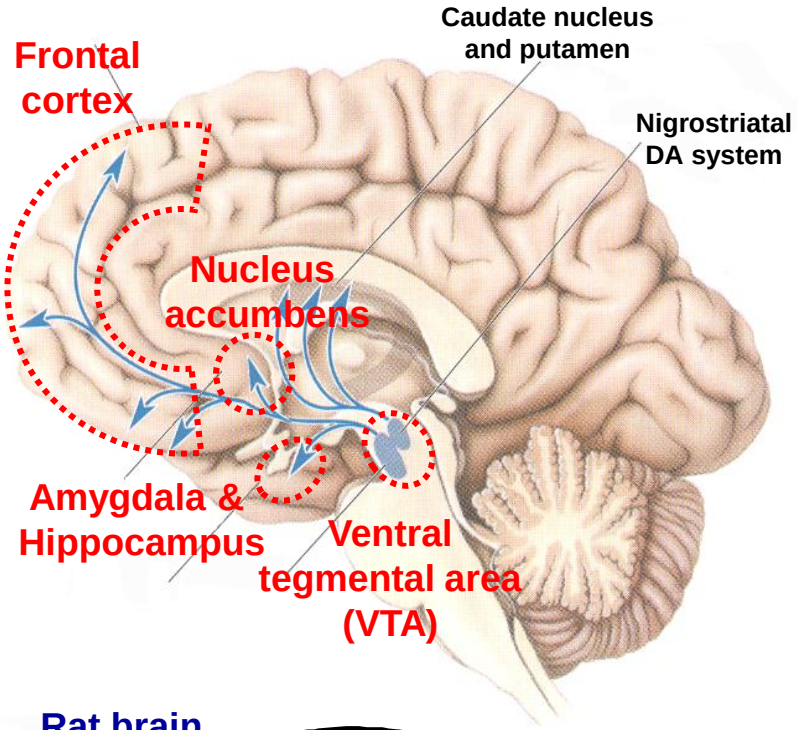
c) Opioids are useful to reduce the intensity of chronic pain.

d) Both b) and c).

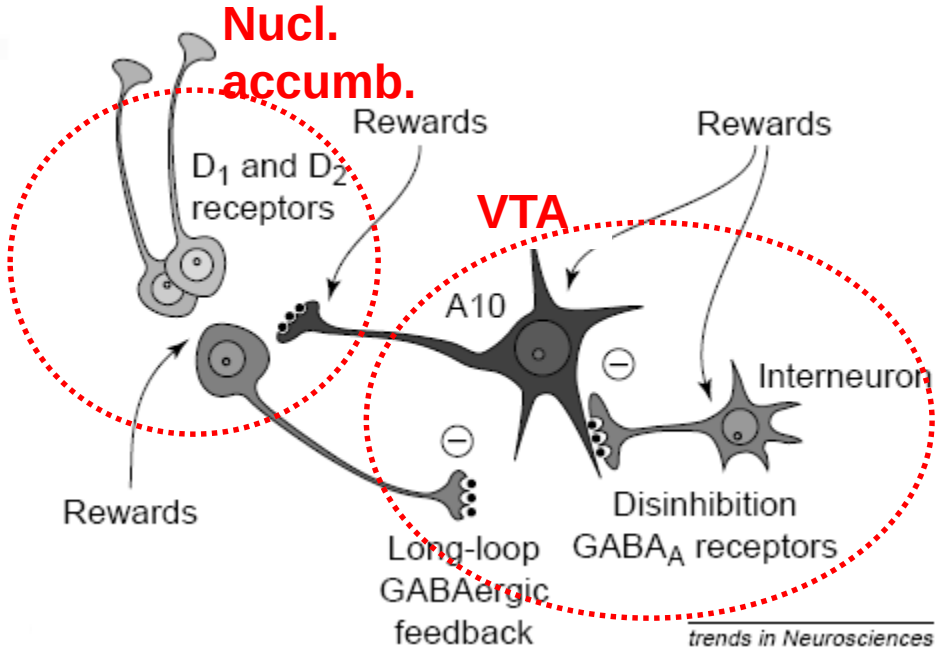
Meso-corticolimbic dopamine system and reward

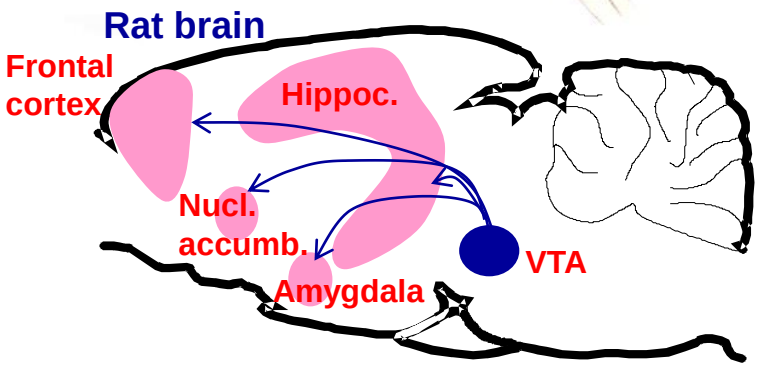


Dopamine



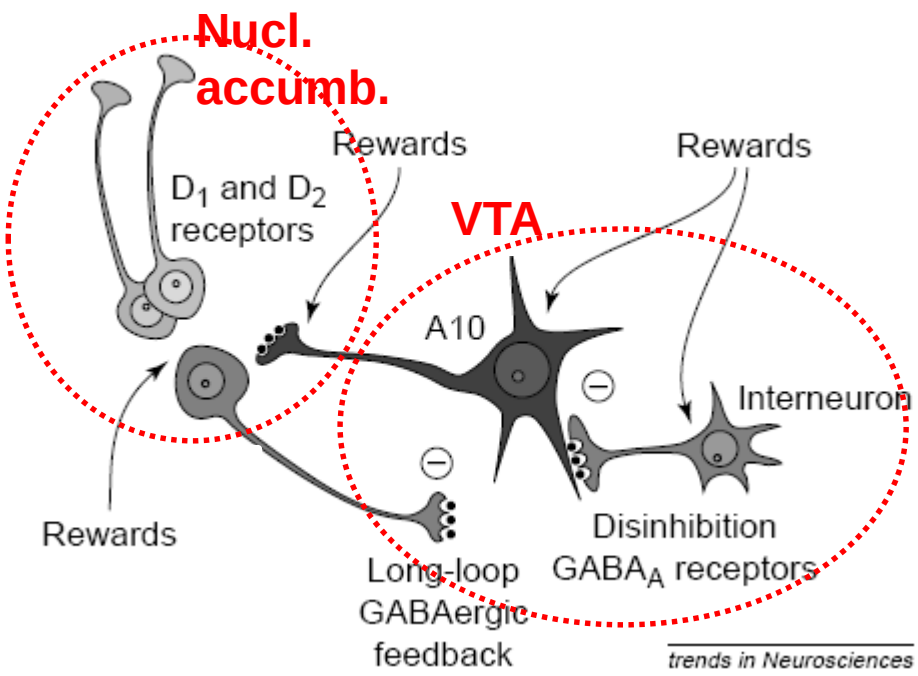
Rewards activate meso-corticolimbic dopamine transmission





For critical review see:
Spanagel & Weiss (1999) *Trends Neruosci.* 22:521

How may opioids increase dopamine release within the nucleus accumbens?



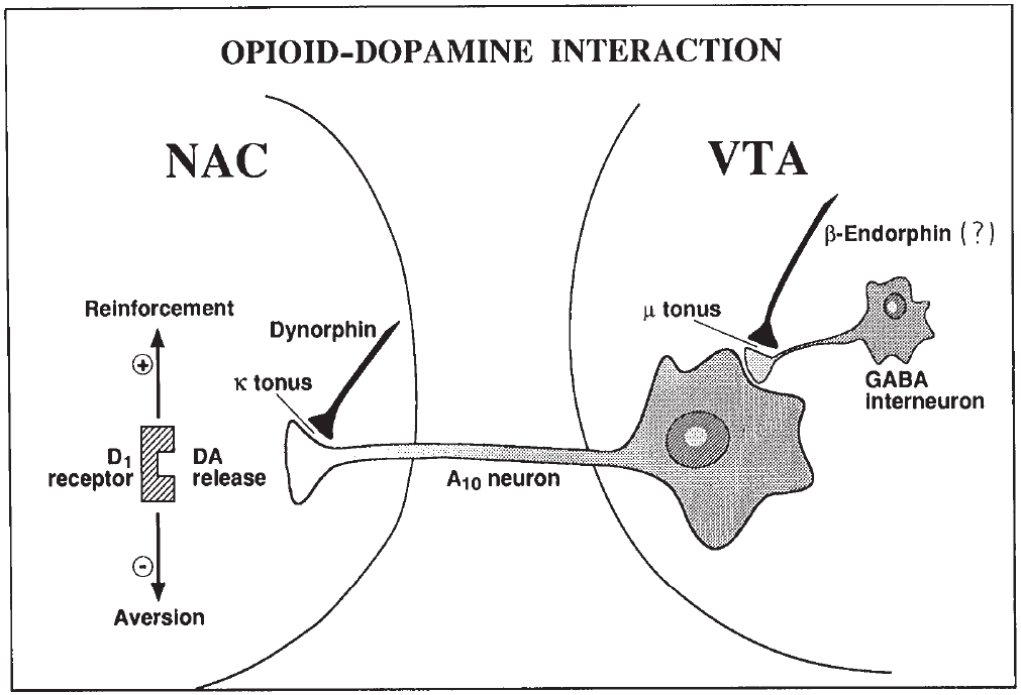
a) **Disinhibition of dopaminergic neurons in the VTA: opioids stimulate opioid receptors of GABA neurons, inhibiting GABA release by these neurons, thereby allowing an increase of dopaminergic VTA neurons**

b) **Inhibition of dopaminergic neurons in the VTA: opioids stimulate opioid receptors of the dopamine neurons, thereby reducing the firing rate of these neurons.**

c) **Excitation of dopaminergic neurons in the VTA: opioids stimulate opioid receptors of the dopamine neurons, thereby increasing the firing rate of these neurons.**

d) **Presynaptic inhibition of dopamine terminals in the nucleus accumbens: opioids stimulate opioid receptors on dopamine terminals in the nucleus accumbens, thereby inhibiting dopamine release from these terminals**

Opioid modulation of meso-corticolimbic dopamine system



•Opioids can increase NAC dopamine release via mu-opioid receptors in the VTA.

•Opioids with preferential action on kappa-receptors can act presynaptically on dopamine terminals in NAC to reduce dopamine release.

Herz (1998) *Can. J. Physiol. Pharmacol.* 76: 252-258

Which method could we use to measure if opioid administration increases dopamine release in the nucleus accumbens?

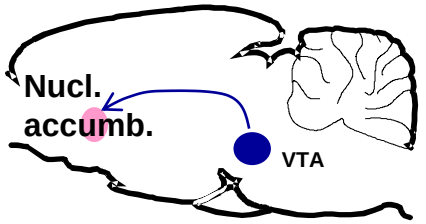
a) Functional MRI

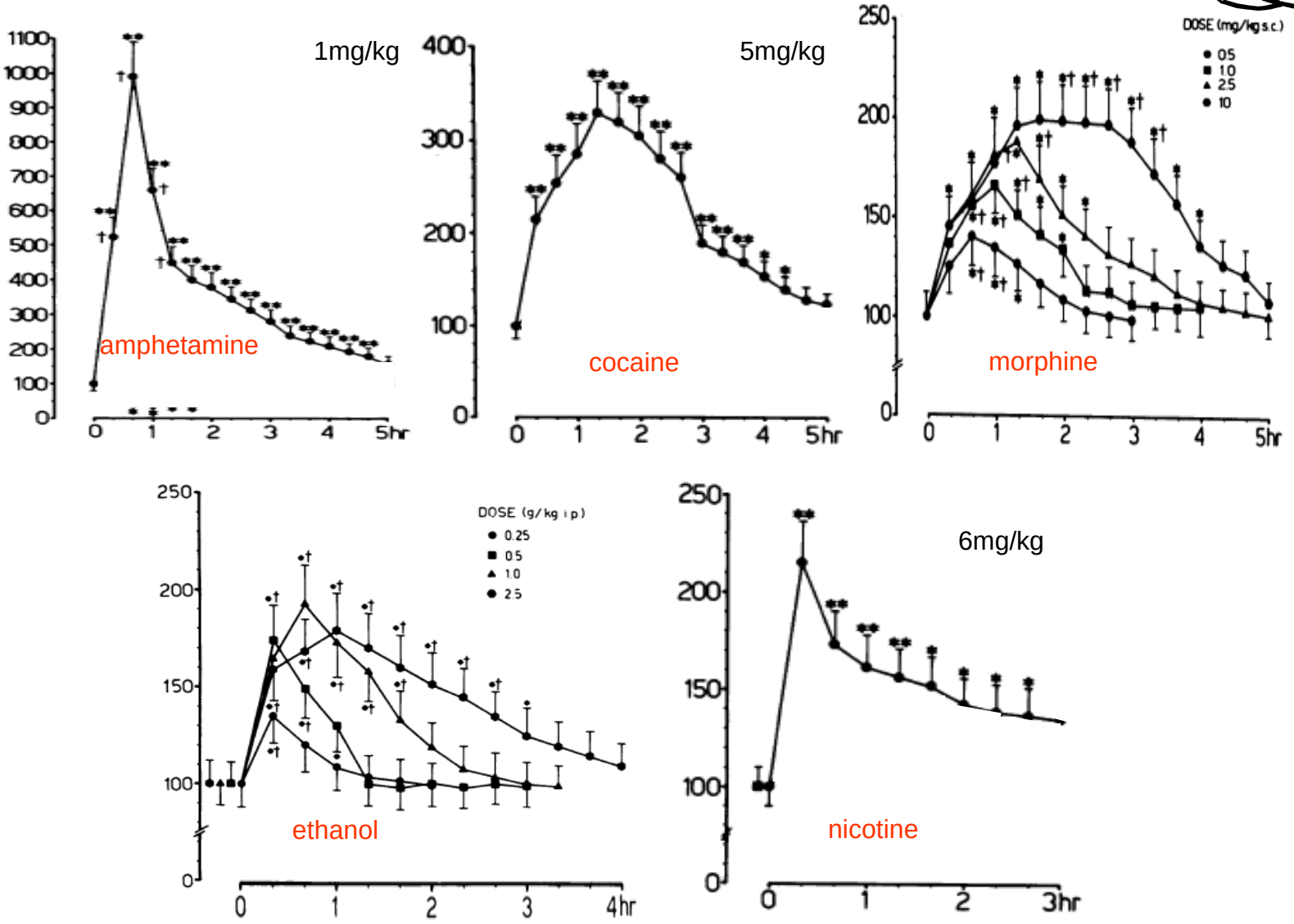
b) Microdialysis

c) Electrophysiology

d) All of the above

Drugs of abuse, including opioids, increase accumbal dopamine levels





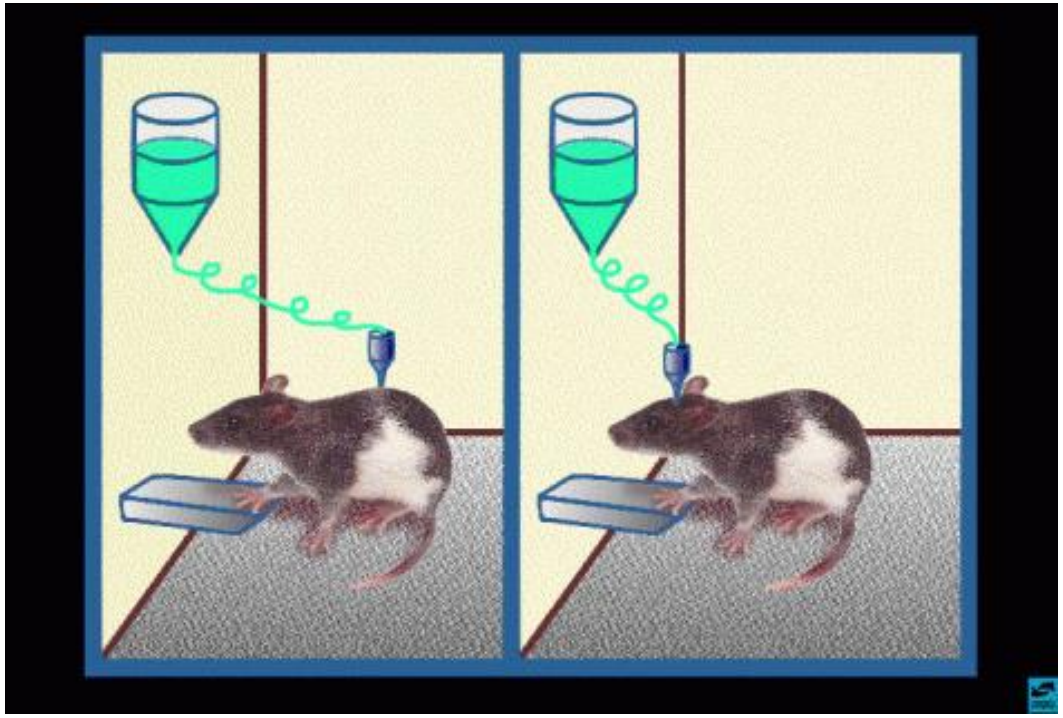
Dichiara & Imperato (1988) *Proc. Natl. Acad. Sci.* 85:5274

Measuring the rewarding properties of a drug

Operational definition of reward

Reward = something we and other animals work for

Drug self-administration procedure



https://www.drugabuse.gov/publications/teaching-packets/brain-actions-cocaine-opiates-marijuana/section-ii-introduction-to-reward-system/1-reward-drug-

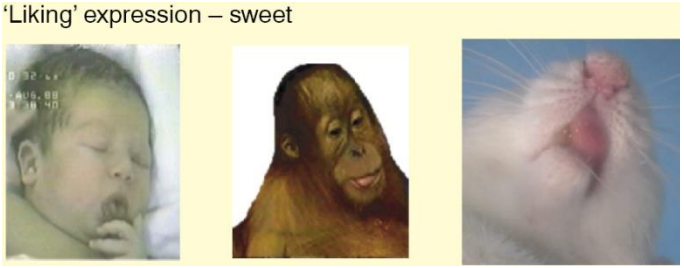
Rats self-administre a wide range of opioids intravenously and intracranially, including into VTA (Devine & Wise, 1994, J Neurosci 14(4):1978-1984).

Opioids and 'pleasure'

Distinction between reward and pleasure/liking

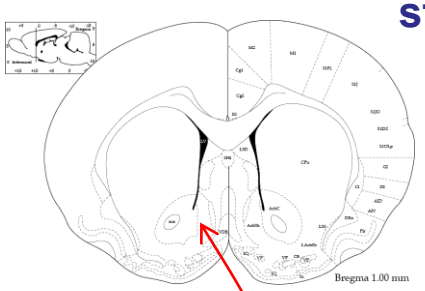
How much a subject works for reward may not directly reflect the 'liking' or 'pleasure' induced by the reward, but rather 'wanting' of or 'desire' for the reward.

Facial expressions to sweet or bitter tastes as measures of 'liking'

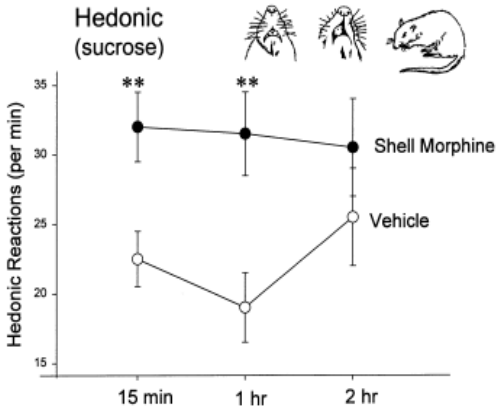


Berridge & Robinson (2003) *Trends Neurosci* 26:507

Nucleus accumbens shell: stimulation of opiod receptors increases 'liking', whereas stimulation of dopamine receptors reduces 'liking'

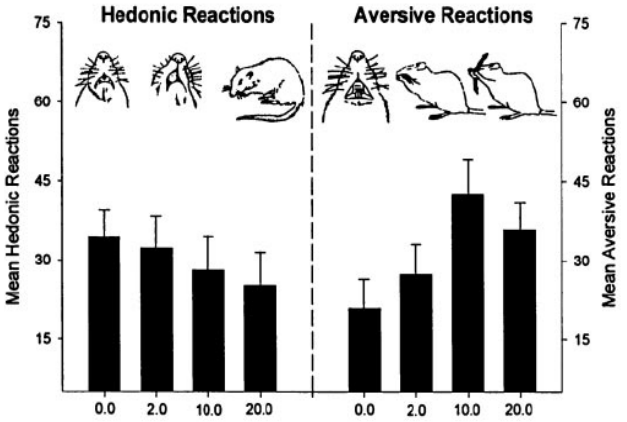


Morphine increases 'liking'



Pecina & Berridge (2000) *Brain Res* 863:71

Amphetamine decreases 'liking'



Wyvell & Berridge (2000) *J Neurosci* 20:8122

Opioid dependence

Substance dependence occurs when the drug fulfills the criteria for abuse and also includes:

development of tolerance;

physiological or cognitive signs of withdrawal at abstinence;

frequent desire and effort to reduce drug use;

preoccupation with securing, consuming, and recovering from drug use so that most daily activity is directed by the drug.

Source: American Psychiatric Association, 1994.

Neuropharmacological adaptations to repeated opioid use contribute to dependence:

- **Tolerance** in response to repeated use leads to reduced acute effects (which may lead the user to increase dose or take a stronger opioid)
- **Long-term compensatory changes** in neural mechanisms in response to repeated opioid use lead to **withdrawal symptoms**

-Compensatory changes are opposed to acute opioid effects

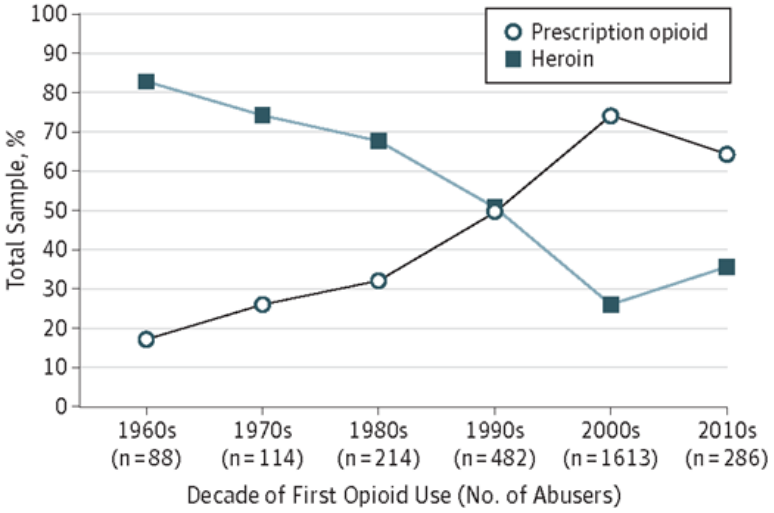
TABLE 11.2 Acute Effects of Opioids and Rebound Withdrawal Symptoms

Acute action	Withdrawal sign
Analgesia	Pain and irritability
Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation
Flushed and warm skin	Chilliness and "gooseflesh"

PSYCHOPHARMACOLOGY 2e, Table 11.2

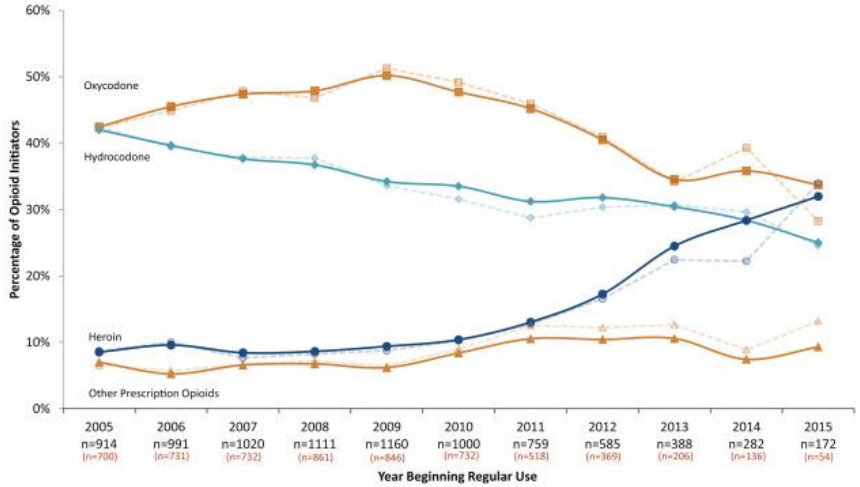
Prescription opioids may initiate users to heroin abuse and dependence (data from US studies)

Since the late 90s early 2000s, heroin dependent patients in the US have mainly initiated opioid abuse with a prescription opioid



Cicero et al. (2014) *JAMA Psychiatry* 71(7):821

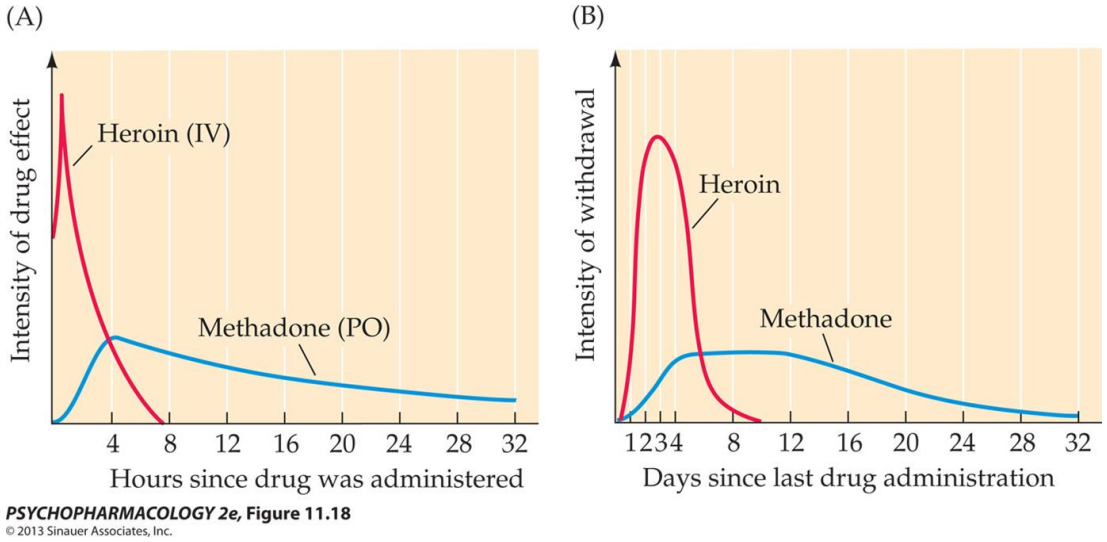
More recently, with reduction in supply of prescription opioids, heroin again gains in importance as initiating drug



Cicero et al. (2018) *Add Behav* 87:267

Treatments of opioid dependence

- Detoxification, usually assisted by substitution with a long-acting opioid drug – methadone or buprenorphine –, which has lower highs and less pronounced withdrawal symptoms.



PSYCHOPHARMACOLOGY 2e, Figure 11.18

- Maintenance with methadone or buprenorphine

- Reduces mortality from overdose and other causes (Sordo et al., 2017, BMJ 357:j1550)

- However, substitution drugs have adverse effects, too, and interfere with normal life; the partial agonist buprenorphine may have reduced adverse effects compared to methadone, but high-quality evidence that this significantly improves patients' life is lacking (Matticket al., 2014, Cochrane database of systematic reviews 2).

- Treatment for full abstinence with opioid antagonist (e.g., with naloxone): antagonist will make opioid administration ineffective; typically very low adherence and requires highly motivated patients.

Schuckit (2016) New England Journal of Medicine 375(4): 357-368.

Reward and pleasure

Which statement is incorrect?

a) All rewarding stimuli increase pleasure.

b) Rewarding stimuli reinforce behaviour.

c) Pleasure can be measured using facial expressions.

d) How rewarding a stimulus is can be measured using self-administration procedures.

Opioids, reward and pleasure

Which is correct?

a) Opiods inhibit dopaminergic neurons in the ventral tegmental area.

b) Opiods are rewarding and increase pleasure/liking in rats and cause euphoria in people.

c) Morphine reduces dopamine release in the nucleus accumbens.

d) a) and c).

Opioid withdrawal

Which is correct?

a) Opioid withdrawal symptoms resemble the acute effects of opioid administration.

b) Opioid withdrawal symptoms can be treated by the opioid antagonist naloxone.

c) Respiratory depression is one of the symptoms of opioid withdrawal.

d) Increased sensitivity to pain is one of the symptoms of opioid withdrawal.

Treatment of opioid dependence

Which statement is incorrect?

a) Methadone and buprenorphine are used for substitution and maintenance treatment of opioid dependence.

b) Methadone and buprenorphine induce stronger withdrawal symptoms than heroin.

c) Methadone and buprenorphine have a longer duration of action than heroin.

d) Overdoses of methadone and buprenorphine can be deadly.

Some questions for revision

- What is: pain, chronic pain, nociception?

- What are the ascending and descending pain pathways?

- In principle, how do opioids modulate pain?

- How can we measure ‘reward’ and ‘pleasure’? Are opioids rewarding, do they increase ‘pleasure’?

- What are the symptoms of opioid withdrawal and the underlying neuropharmacological mechanisms?

- How can we treat opioid dependence?

The MCQs related to opioids will all be based on the material dealt with in my two lectures on opioids. If you understand the material, so that you can answer the lecture MCQs and revision questions well, you should have no difficulties with the exam MCQs.

Selected reading – Opioids 2

***Textbook chapter*:**

Chpt. on opioids – for general overview

Selected overviews of topics discussed today:

Nutt, David. Drugs - without the hot air : Minimising the harms of legal and illegal drugs, UIT Cambridge Ltd., 2012.
https://ebookcentral.proquest.com/lib/nottingham/detail.action?docID=5285796

See chpt. 9 on Can addiction be cured?

All references given in lecture are available online via Nottingham University access.