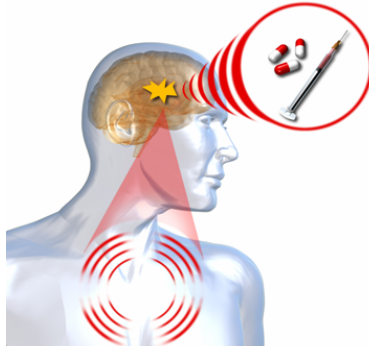


Lessons learned from placebo research in medicine

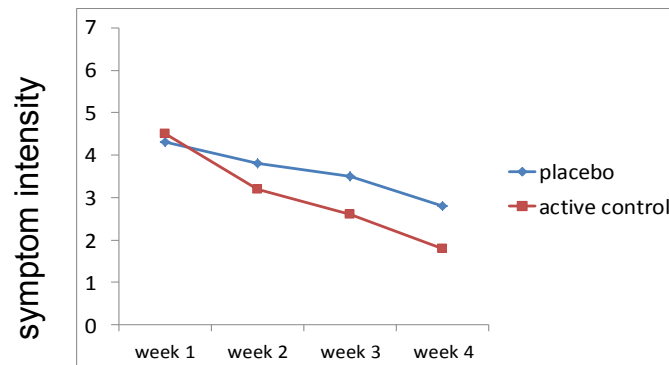


Prof. Ulrike Bingel
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Overview

- Definition and efficacy
- Psychological mechanisms and neurobiology
- Contribution to active treatments
- Clinical implications (→ tomorrow)

Definition placebo effect



Definition placebo effect



placebo treatment

natural course
co-intervention
treatment context

symptom
improvement

treatment context



expectation

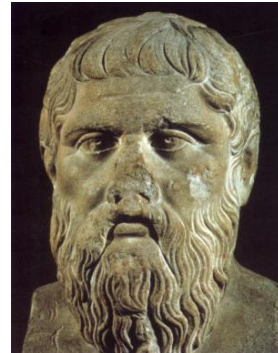
learning

patient-physician communication

Plato – substance and meaning: context matters

"when he asked me, whether I knew the remedy against headache ... [I answered] it is in fact a leaf, but in addition to the remedy a certain sentence had to be said, and only if that was spoken with its application, the remedy would cure completely, without the sentence however the leaf was useless....."

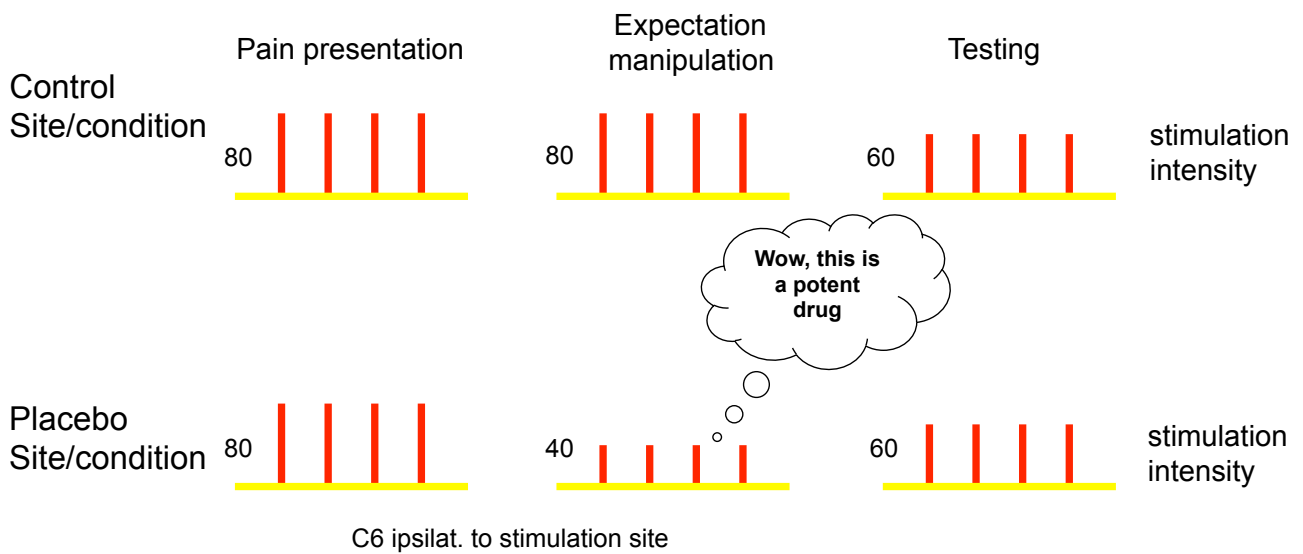
Platon * 428 v. Chr., Charmides



Psychological mechanisms



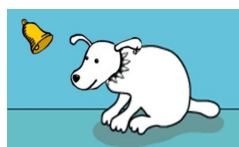
The learned placebo effect



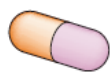
➔ **Learned (conditioned) placebo responses are stronger and more stable compared to those induced by verbal instruction only**

The learned placebo effect

pharmacological conditioning



Neutral stimulus

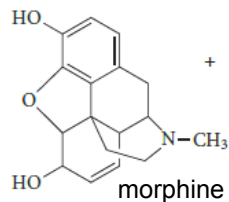


No response



Acquisition

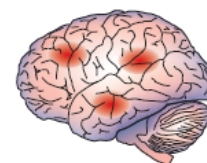
Unconditioned stimulus + neutral stimulus



+



Unconditioned response



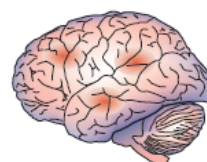
analgesia

Evocation

Conditioned stimulus



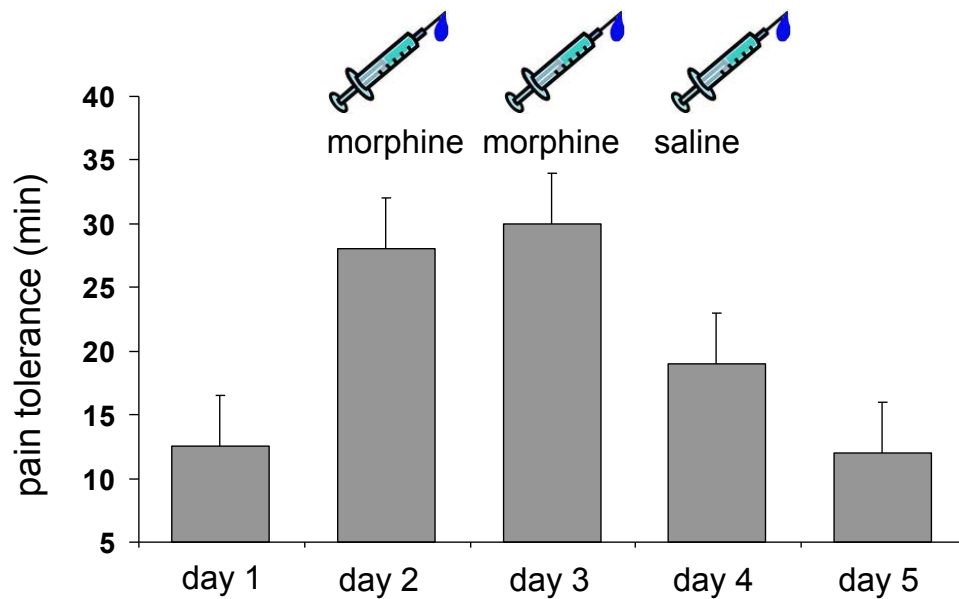
Conditioned response



analgesia



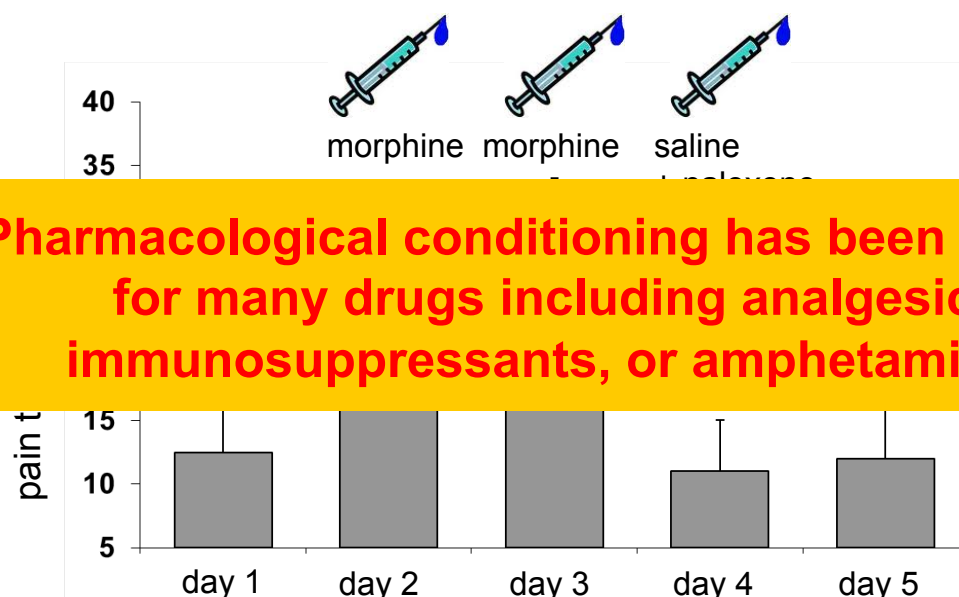
„pharmacological conditioning“



placebo without expectancy!

Amanzio & Benedetti 1999, J. Neuroscience

„pharmacological conditioning“



Pharmacological conditioning has been shown for many drugs including analgesic, immunosuppressants, or amphetamines

placebo without expectancy!

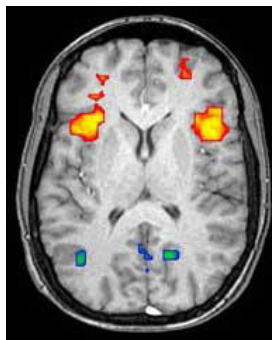
Amanzio & Benedetti 1999, J. Neuroscience

Overview

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- Clinical implications

Studying placebo analgesia

functional brain imaging



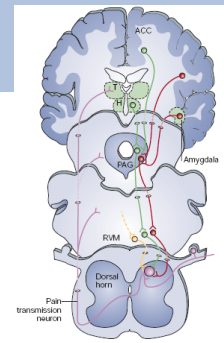
pain



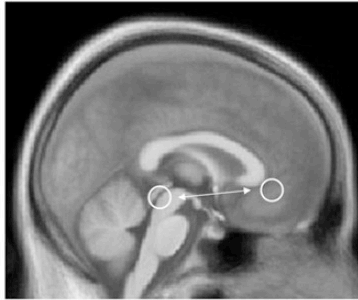
placebo procedure



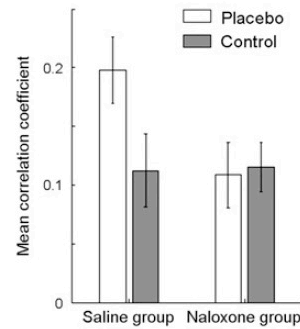
Role of the endogenous opioid system



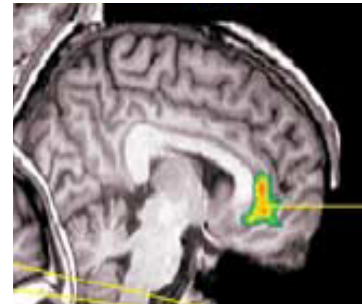
pharmacological modulation (naloxone)



Eippert et al. Neuron 2009



[11C]Carfentanil PET

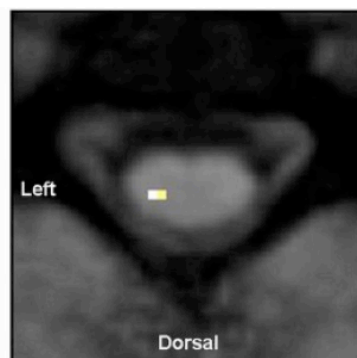
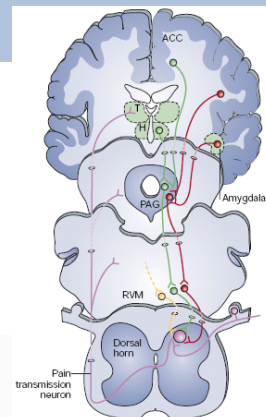


Zubieta et al. Science 2005

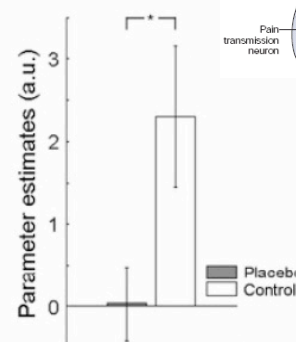


increased opioidergic neurotransmission
in the descending pain modulatory system

Placebo analgesia and the spinal cord

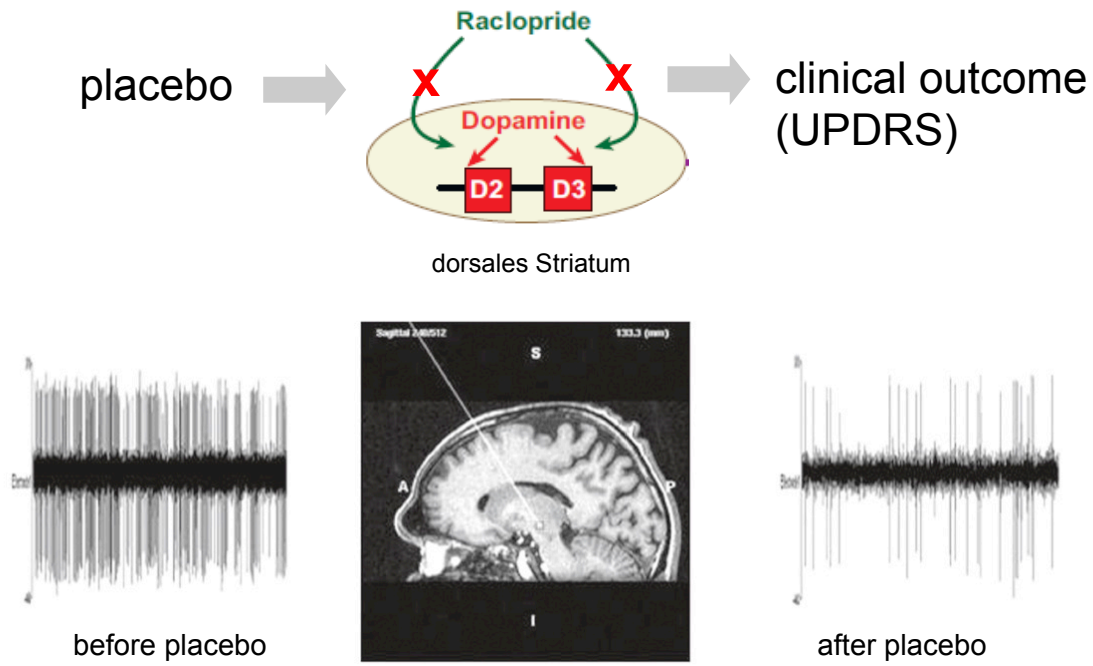


C6 ipsilat. to stimulation site



evidence for spinal cord involvement in placebo analgesia

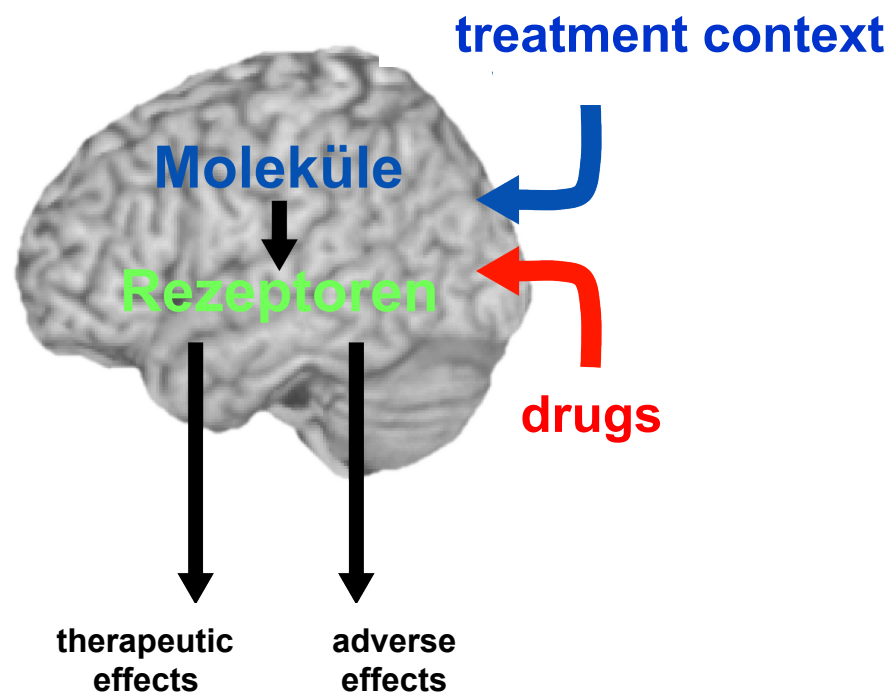
Placebo and Parkinsons disease



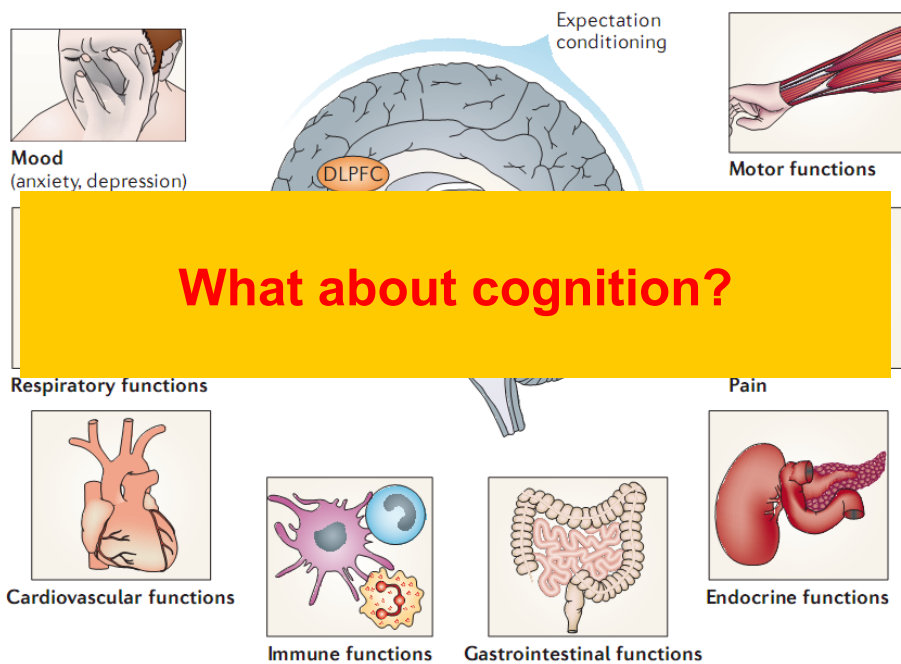
activation of the dopaminergic system and normalisation of abnormal activity patterns in the EPMS

Benedetti, Nature Neuroscience, 2004; de la Fuente-Fernandez, Science, 2001

Placebo: a psychoneurobiological phenomenon



Placebo effects



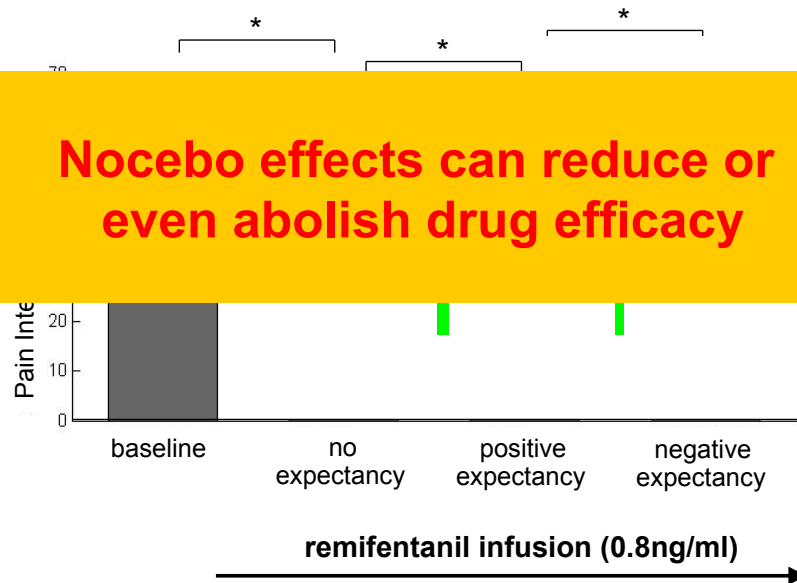
Enck & Bingel et al. Nature Reviews Drug Discovery (2013)

Overview

- Definition and efficacy
- Psychological mechanisms and neurobiology
- Contribution to active (pharmacological) treatments
- Clinical implications

Nocebo: treatment efficacy

remifentanil analgesia



Bingel et al. Science Translational Medicine 2011

Opioids and expectancy: neurobiology

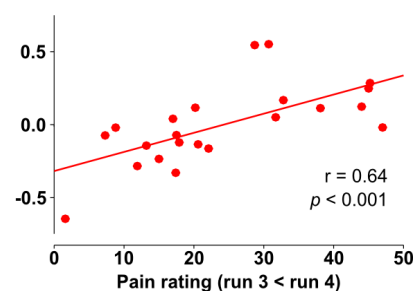
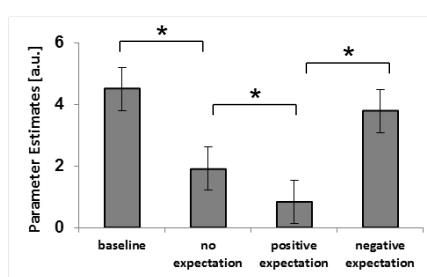
pain-related areas



endogenous pain modulation with positive expectancy



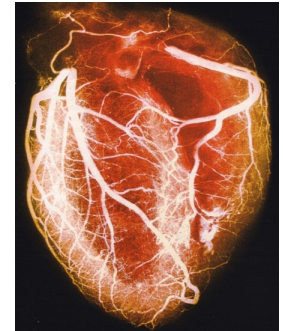
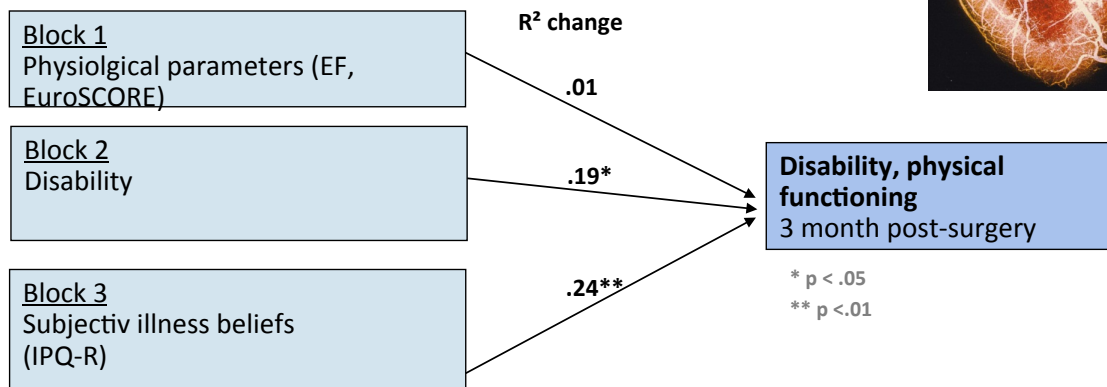
expectation modulates drug effect at neurobiological level



Bingel et al. Science Translational Medicine 2011

Expectancy modulates treatment outcome after heart surgery

hierarchical multiple regression



Jürgens, Rief, et al., J Psychosom Res, 2010

A medical emergency

- Emergency admission of A.M: 26 years, history of depression



expectation can have detrimental effects on health outcomes (nocebo)

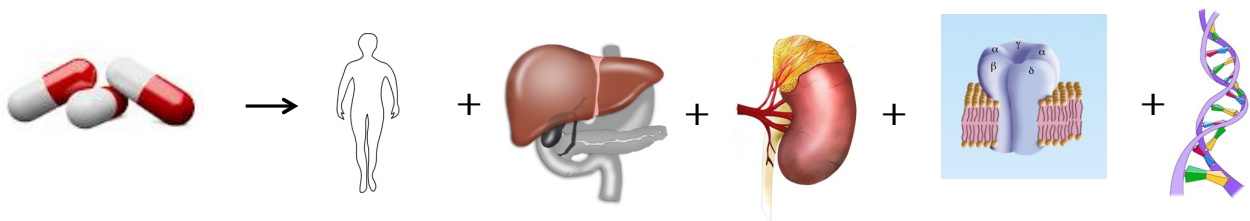
- Further inquiry reveals that patient was enrolled in an RCT on antidepressants
- Disclosure: patient was randomised to placebo group
- After debriefing: normalisation of vital signs, patient calms down

(Reeves et al., 2007 in Gen Hosp Psychiatr 29, 275-277)

Overview

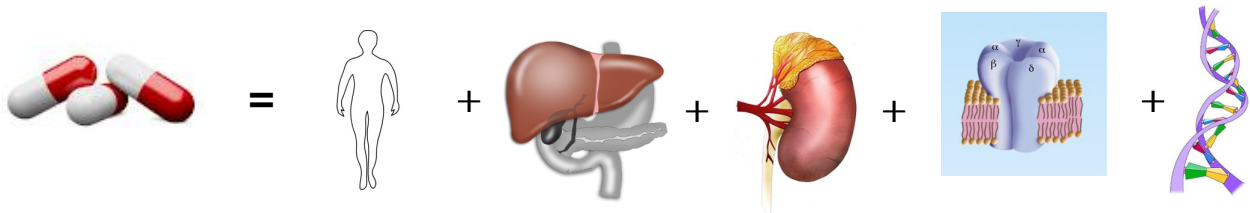
- Definition and efficacy
- Psychological mechanisms and neurobiology
- Contribution to active treatments
- Clinical implications

Determinants of drug effects



?

Determinants of drug effects



Expectation and learning mechanisms modulate the efficacy and tolerability of medical treatments



Summary

- Placebo effects involve specific CNS and peripheral physiological changes
- These effects also occur in the presence of active drug treatments and can improve (placebo) or reduce (nocebo) the overall therapeutic outcome.
- In clinical settings, placebo effects should be maximized by exploiting expectancy and learning mechanisms to improve therapeutic outcome
- Knowledge regarding placebo and nocebo effects and the impact of patient-physician communication should be reflected in the curricula of health care professionals
- and influence the design and interpretation of clinical trials