Development of Addiction

Addiction can be seen as a cycle, which is progressive; however, the progression is not necessarily linearly.

This is based on addiction as a Primary, Progressive, Chronic, and often Fatal Disorder.

Addiction proceeds in stages:
1) Initial experience/exposure
2) Binge and intoxication
3) Maintenance of exposure
4) Withdrawal
5) Cue-Reactivity
6) Anticipation and Pre-occupation

Separate “brain systems” mediate these stages.

Learning and memory systems are crucial components of the addiction neurocircuitry.
The Cycle (Stages) of Addiction (Progression Through the Stages Isn’t Necessarily Linear)

1st
- Binge Intoxication

2nd
- Withdrawal
- Negative affect

3rd
- Preoccupation
- Anticipation

Neurocircuits → Synaptic systems → Molecules

Neuroadaptation

Koob et al., multiple publications

This neurocircuitry is just as relevant for other drugs of abuse (i.e., opiates/opioids).
Stages of Addiction and Associated Neuroanatomy

Koob et al., multiple publications
Koob et al., multiple publications
Learning and Memory

Learning Stages (Biographical/Contextual/Semantic)—Hippocampus/Amygdala
  Acquisition
  Consolidation
  Retrieval
  Rehearsal
  Re-Consolidation

Learning Stages (Habit/Motor/Episodic)—Caudate-Putamen/Ventral Striatum
  Acquisition
  Consolidation/Association
  Automatic Retrieval

Memory Stages
  Sensory Memory—Brain Stem
  Working Memory—Lateral Prefrontal Cortex
  Short-Term Memory—Amygdala
  Long-Term Memory—Hippocampus

Flash-Bulb Memories—Amygdala
  Emotion and Stress

Contextual Memory
  Stimulus-Response Learning—Nucleus Accumbens
Adapted from Bell et al.,
Glutamatergic projections and the recruitment of multiple memory systems in AUDs. Adapted from Bell et al.,
Adapted from Bell and Colleagues,
Addiction, Learning, and Memory

Multiple Memory Systems

1) **Hippocampus** mediates episodic/autobiographic and spatial learning and memory

2) **Amygdala** mediates fear and anxiety conditioning/learning and memory Basal-Lateral-Amygdala (BLA), Medial-Amygdala (MeA) and Central-Amygdala (CeA)

3) **Caudate-putamen** mediates stimulus-response/habit learning and memory *Dorsal Striatum*

4) **Nucleus accumbens** mediates reward conditioning/learning and memory (conditioned place preference)—*Ventral Striatum*

5) **Dorsal-lateral-prefrontal-cortex** (DLPFC) mediates ‘working’ learning and memory

Koob et al., multiple publications
The Opioid “System”

• Early research used “opioid” to identify endogenous/brain opiate ligands and receptors; whereas “opiate” was used to identify exogenous

• Later research and much of the public media now use “opioid” to indicate either endogenous or exogenous ligands

• Opioid receptors and their endogenous ligands are located throughout the body and highly expressed in the brain
General Opioid Receptor Function

• **Mu-receptor**
  – Analgesia (pain reduction)
  – Respiration (breathing)
  – Sedation (tired, listless, apathy)
  – Euphoria (feeling “high”)

• **Delta-receptor**
  – Analgesia
  – Dysphoric Affect (down-and-out)
  – Respiration
  – GI Motility (bowel movements)
  – Hormone release (e.g., Growth Hormone)

• **Kappa-receptor**
  – Analgesia
  – Dysphoric Affect
  – Sedation

• **Sigma-receptor** (binds non-opioid ligands as well)
  – Respiration
  – Dysphoric Affect
  – Psychotomimetic (Hallucinogen)
Opioid Receptors in the Brain

Distribution of Opiate Receptors

The distribution of opiate receptors in the brain of a guinea pig. Red areas = highest density; yellow = moderate density, blue, purple & white = low density.

https://www.slideshare.net/vacagodx/drugsandthe-brain-part3-opiates
MOR = μ-receptor density

DOR = δ-receptor density

Erbs et al., 2014 in *Brain Structure and Function*
Another Look at Relative Opioid Receptor Density As Well As Overlap with Other Neurotransmitters

Lutz and Kieffer, 2013 in Trends in Neuroscience
Functional Neuroanatomy and Opioid Receptor Localization

Erbs et al., 2014 in *Brain Structure and Function*
Opioids/Opiates and Nociception (Pain) As Well As Anti-nociception (Analgesia)

CNS
Opioids bind to central μ-opioid receptors to provide analgesia

Endogenous opioids
met-enkephalin leu-enkephalin β-endorphin, and dynorphin (localized in neurons of myenteric and submucosal plexus and in endocrine cells of mucosa)
Exogenous opioids (eg, morphine and codeine)

Gastrointestinal tract opioids bind to peripheral μ-opioid receptors which inhibits bowel function

Peripheral opioid antagonists do not cross the blood–brain barrier. Please note, oral prolonged release naloxone component in Targin® does cross the blood–brain barrier but most (>97%) undergoes first pass metabolism in the liver and so does not interfere with analgesic efficacy

Peripheral opioid antagonist
Reduction in adverse gastrointestinal effects

Peripheral opioid antagonist dislodges opioid from μ-opioid receptors in gastrointestinal tract

Figure 2 Mechanisms of action of opioid agonist/antagonist combinations to counteract opioid-induced bowel dysfunction development.

Abbreviation: CNS, central nervous system.

Leppert, 2014 in Drug Design, Development and Therapy
Opioids/Opiates and Nociception (Pain) As Well As Anti-nociception (Analgesia)

https://www.studyblue.com › ... › Pain Management, Analgesia
Alterations in Neurofunction Associated with Chronic Pain

Kuner and Flor, 2016
Putative Neurofunctional Circuits Associated with Phantom Limb Pain

Flor and Andoh, 2017 in Neuroforum Organ der Neurowissenschaftlichen Gesellschaft
Putative Role for Opioid Receptors in Neurocircuits Mediating Mood Disorders

Lutz and Kieffer, 2013 in *Trends in Neuroscience*
Opioids/Opiates and Eating/Feeding/Alimentary Behavior

Lee et al., 2012 The Neurobiology of Overeating EMBO Reports

Volkow et al., 2011 Curr Top Behav Neurosci Food and Drug Reward

Adan, 2013 TRENDS in Neurosciences
Supplementary Slides