“THEY TRIED TO MAKE ME GO TO REHAB”

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The spiraling distress/addiction cycle

**Preoccupation**

Wanting drug
certain psychological problem

**Positive Reinforcement**

**Binge Intoxication**

taken in larger
amounts than needed

**Withdrawal**

Persistent desire
tolerance withdrawal

**Spiraling Distress**

Addiction

**Negative Reinforcement**

Persistent negative affect

Adapted from Koob & Le Moal (2001) *Neuropsychopharmacology* 24, 97–129
Drug Effects Over Time

- Administration Phase
- Active Phase
- Metabolism Phase

Drug Effects vs. Time

active drug → metabolism → inactive drug
DOSE RESPONSE CURVE...
DOSE RESPONSE CURVE...

Magnitude of Drug Effect

Dose of Drug

Initial dose-response curve

Dose-response curve after drug exposure
Drug effect decreases with increased exposure.

Withdraw from drug.

Drug exposure leads to the development of adaptive neural changes that produce tolerance by counteracting the drug effect.

Withdrawal from drug leads to withdrawal effects opposite to the effects of the drug.

The magnitude of the withdrawal effect is proportional to the tolerance of the drug.
ALTERING THE FUNCTION OF NEUROTRANSMITTERS CAN CHANGE BEHAVIOR.

**Agonist**
- mimics or facilitates the release of dopamine
- More dopamine released

**Antagonist**
- oppose or blocks the release of dopamine
- Less dopamine released
MESOTelecephalic DA SYSTEM

- Nigrostriatal pathway
- Mesocorticolimbic pathway

- Limbic cortex
- Dorsal striatum
- Ventral tegmental area
- Corpus callosum
- Basal ganglia
- Prefrontal neocortex
- Nucleus accumbens
- Olfactory tubercle
- Amygdala
- Septum
- Substantia nigra

DA = Dopamine
PLEASURE CENTERS OF THE BRAIN...

ICSS: intracranial self-stimulation
INCREASE IN DA RELEASE IN N. ACCUMBENS...
Is there a common molecular pathway for addiction?

Eric J Nestler
Drugs of abuse

Diverse chemicals

Distinct targets & effects

Cause common effects:

acute

chronic

Characterized by:

Immediate reward → repeated use → addiction

Loss of control over drug use. Negative emotional symptoms withdrawal.
MESOTELECEPHALIC DA SYSTEM

- Nigrostriatal pathway
- Mesocorticolimbic pathway
All drugs of abuse affect the limbic system.

Mesocorticolimbic system → dopaminergic neurons in the ventral tegmental area → NAc.
Examples of common effects on the VTA-NAc.

- **Stimulants** directly increase dopaminergic transmission in the NAc.

- **Opiates** do the same (indirectly) they inhibit GABAergic interneurons in the VTA, which disinhibits VTA dopamine neurons.

- **Opiates also directly** act on opioid receptors on NAc neurons.

Highly simplified scheme of converging acute actions of drugs of abuse on the VTA-NAc.

“On the basis of these common acute actions, one would expect that chronic exposure to drugs of abuse would also cause common chronic functional changes in the VTA-NAc pathway. Indeed, numerous common chronic adaptations have been described, examples of which are discussed in the next sections. Consistent with common mechanisms of addiction are the observations that certain drugs of abuse, under particular experimental conditions, can induce cross-tolerance and cross-sensitization to one another with respect to their locomotor activating and rewarding effects⁹,¹⁰.”
Highly simplified scheme of some common, chronic actions of drugs of abuse on the VTA-NAc

Under normal conditions – there are glutamatergic inputs to both the VTA and NAc neurons.

Tolerance: homeostatic response to repeated drug activation of the system

“Chronic exposure to any of several drugs of abuse causes an impaired dopamine system”

It also becomes sensitized → more dopamine is released in response to the drug and its cues.

“Baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective.”

Addiction also involves powerful emotional memories.

More recent work has established that several additional brain areas that interact with the VTA and NAc are also essential for acute drug reward and chronic changes in reward associated with addiction. These regions include the amygdala (and related structures of the so-called ‘extended amygdala’), hippocampus, hypothalamus and several regions of frontal cortex, among others\textsuperscript{1,2,4,10–13}. Some of these areas are part of the brain’s traditional memory systems; this has led to the notion, now supported by increasing evidence, that important aspects of addiction involve powerful emotional memories\textsuperscript{2,4,5,11–13}.