Drug-related Deaths …

Some Notable People Who Have Died From Drug-related Causes.


Whitney Houston (1963–2012) Singer and Actress. "a combination of Xanax and other prescription drugs mixed with alcohol"

450 others….
Heroin users who didn’t make it

Charlie Parker 1920-1955
Hillel Slovak 1962-1988
Kristen Pfaff 1967-1994
Sid Vicious 1957-1979
Janis Joplin 1943-1970
Johnny Thunders 1952-1991
Pete Farndon 1953-1983
Jimi Hendrix 1942-1970
John Belushi 1949-1982
River Phoenix 1970-1993
Gram Parsons 1946-1973
Keith Moon 1947-1978
Addiction

- A state in which an organism engages in a compulsive behavior
- Loss of control in limiting intake
- Behavior is reinforced (rewarding or pleasurable)
The Reward Pathway
Natural Rewards

- Food
- Water
- Sex
- Nurturing
These brain circuits are important for natural rewards such as food, music, sex, etc.
Neuronal Physiology
Postsynaptic Mechanisms

Illustration by Carol Donner, Tucson, Arizona
Postsynaptic Neuron

Nicotinic Receptors (Ligand-gated)

ACh
Drugs Modulate The Release/Uptake Of Endogenous Neurotransmitters At Synapses In The Brain...
The Action of Opioids
Heroin
Morphine
**OPIATES & BRAIN**

- Endorphins
- Enkephalins
- Heroin
- Morphine
- $\mu$, $\kappa$, $\Delta$, orphan
Opioid receptor activation triggers different responses in different parts of the brain.
μ & κ- opioid receptors

Ortiz-Miranda, 2011
µ-opioids inhibition of voltage-gated channels

Voltage-gated K⁺ channels
Voltage-gated Na⁺ channels
Voltage-gated Ca²⁺ channels
Opiate Receptor

K⁺ currents
- Before
- After
- Subtracted Current

Ca²⁺ currents
- Control
- 200nM DAMGO
- 70mV to 10mV (60 sec)

Ortiz-Miranda, 2011
Opioid Intracellular Mechanisms

μ- vs. κ- Opioid Receptor Pathways:
- Different Ca-channel Subtype Targets
- Diffusible 2nd Messenger Vs. Membrane-Delimited?
- Role Of Intracellular Calcium
- c-ADPR is 2nd Messenger For Oxytocin?
The Action of Alcohol (EtOH)
**Cortex:** Main area involved in thinking, decision-making, emotions, and all five senses. EtOH impairs clear thinking, sensory signals (vision), lowers inhibitions (aggression).

**Cerebellum:** Main area involved in motor coordination. EtOH decreases reflexes and balance.

**Medulla:** Controls breathing. Excess EtOH can shut down the activity in this area leading to a coma.

**Spinal Cord:** EtOH slows down the transmission of signals between peripheral and central nervous systems.

**Hippocampus:** Controls memory processes. Excess EtOH impairs memory consolidation (blackout). Long-term use causes learning impairments.

**Hypothalamus:** Controls heart rate, thirst and hunger sensations. EtOH slows down heart rate and can make you hungrier & thirstier.
ALCOHOL & BRAIN

Vasopressin Effects...
Voltage-gated K⁺ currents

Voltage-gated Na⁺ channels

Voltage-gated K⁺ channels

Voltage-gated Ca²⁺ channels

EtOH

Ca²⁺

AVP

Knott et al., Molecular Pharmacology July 1, 2002 vol. 62 no. 135-14
Knott et al., Molecular Pharmacology July 1, 2002 vol. 62 no. 1135-14
Tolerance

Knott et al., Molecular Pharmacology July 1, 2002 vol. 62 no. 135-14
EtOH causes K⁺ channel internalization

EtOH causes Ca\textsuperscript{2+} channel mobilization toward PM

Ortiz-Miranda, et al., 2012
Withdrawal

Ortiz-Miranda, 2011
Opiates & EtOH: Common targets

- Voltage-gated Ca\(^{2+}\) channels
- Voltage-gated K\(^{+}\) channels
- Opioid Receptor
- EtOH
- AVP/OT

Ortiz-Miranda, 2011
14 days after ending EtOH consumption...

Knott et al., Molecular Pharmacology July 1, 2002 vol. 62 no. 1135-14
Long-term effects of alcohol...
### Males

**ALCOHOL IMPAIRMENT CHART**

<table>
<thead>
<tr>
<th>Drinks</th>
<th>Body Weight in Pounds</th>
<th>Approximate Blood Alcohol Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>0.00</td>
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<tr>
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<tr>
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<tr>
<td></td>
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<td>0.00</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>0.00</td>
</tr>
</tbody>
</table>

ONLY SAFE DRIVING LIMIT

- Impairment Begins
- Driving Skills Affected
- Possible Criminal Penalties
- Legally Intoxicated
- Criminal Penalties

Your body can get rid of one drink per hour.

Each 1 oz. of 80 proof liquor, 12 oz. of beer or 5 oz. of table wine = 1 drink.

(Chart from the Pennsylvania Liquor Control Board)

### Females

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(Chart from the Pennsylvania Liquor Control Board)
Activation of the reward pathway by addictive drugs
<table>
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<tr>
<th>Alcohol</th>
<th>Amphetamines</th>
<th>Caffeine</th>
<th>Cocaine</th>
<th>Marijuana</th>
<th>1,4-Butanediol</th>
<th>Hallucinogenic Mushrooms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>Inhalants</td>
<td>LSD</td>
<td>Rohypnol</td>
<td>1,4-Butanediol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>Ecstasy</td>
<td>PCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHB</td>
<td>Barbiturates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heroin & reward pathway

- Frontal cortex
- Striatum
- Substantia nigra
- Nucleus accumbens
- VTA
- Hippocampus

Functions:
- reward/salience
- pleasure, euphoria
- motor function (fine tuning)
- compulsion
- perserveration
Heroin modifies the action of dopamine in the nucleus accumbens and the ventral tegmental area of the brain—these areas form part of the brain’s ‘reward pathway’. Once crossing the blood-brain barrier, heroin is converted to morphine, which acts as a powerful agonist at the mu opioid receptors subtype. This binding inhibits the release of GABA from the nerve terminal, reducing the inhibitory effect of GABA on dopaminergic neurones. The increased activation of dopaminergic neurones and the release of dopamine into the synaptic results in sustained activation of the post-synaptic membrane. Continued activation of the dopaminergic reward pathway leads to the feelings of euphoria and the ‘high’ associated with heroin use. Morphine is a weak agonist at the opioid kappa and delta receptor subtypes and activation of these receptors has a weak activating effect on the dopaminergic reward pathway.
When the cortex has received and processed a sensory stimulus indicating a reward, it sends a signal announcing this reward to a particular part of the midbrain—the ventral tegmental area (VTA)—whose activity then increases. The VTA then releases dopamine not only into the nucleus accumbens, but also into the septum, the amygdala, and the prefrontal cortex. The nucleus accumbens then activates the individual’s motor functions, while the prefrontal cortex focuses his or her attention. These regions are connected by what is called the pleasure or reward bundle. In neuroanatomical terms, this bundle is part of the medial forebrain bundle (MFB), whose activation leads to the repetition of the gratifying action to strengthen the associated pathways in the brain.

First described by James Olds and Peter Milner in the early 1960s, the MFB is a bundle of axons that originates in the reticular formation, crosses the ventral tegmental area, passes through the lateral hypothalamus, and continues into the nucleus accumbens as well as the amygdala, the septum, and the prefrontal cortex. The MFB is composed of ascending and descending pathways, including most of the pathways that use monoamines as a neurotransmitter. The mesocorticolimbic dopaminergic system is one of its main components. Consequently, the reward circuit and the punishment circuit can be said to supply most of the necessary motivation for most of our behaviours.
STOP!
Before You Drop!

Don't Take The First Step