

TOLERANCE AND DEPENDENCE

Drug Tolerance is a decrease in the effect of a drug as a consequence of repeated exposure.

- Change over *repeated exposures*.
- Different effects may show different tolerance.
- Tolerance is reversible.

Mechanisms of Tolerance

- Pharmacokinetic Tolerance
 - Enzyme Induction Effects.
- Pharmacodynamic Tolerance
 - NT depletion
 - Receptor Plasticity

Receptor Plasticity and Tolerance

- Drugs that are NT *agonists* can cause receptor *downregulation*.
- Drugs that are NT *antagonists* can cause receptor *upregulation*.

Pharmacodynamic drug tolerance can also affect “normal” synaptic transmission.

- Serious side-effect of drug use.

Mechanisms of tolerance continued...

Learned Tolerance - Learned behaviors compensate for drug effects.

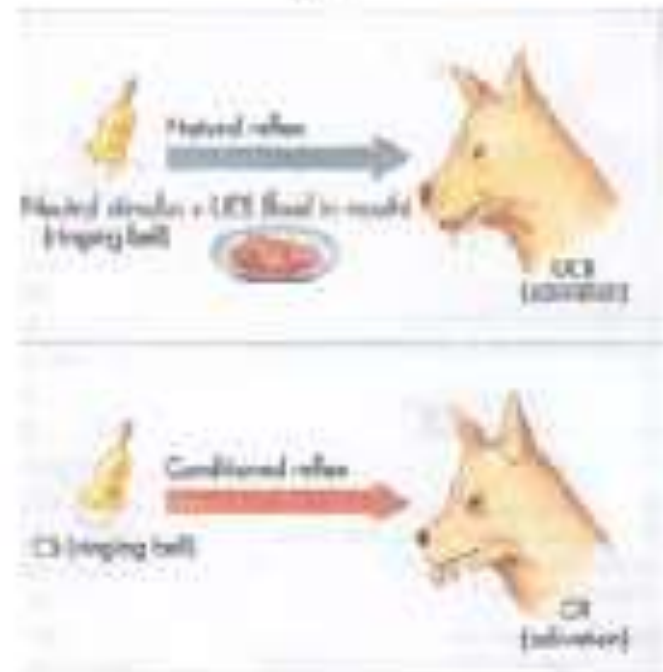
- Practice effects.
- Reward and punishment.

Context-Specific Tolerance

- Stimuli in the environment (context) become able to counteract the effects of a drug.

Pavlovian Conditioning

- A neutral stimulus paired with a biologically relevant stimulus becomes able to elicit a response.



Siegel et al. (1982) - Demonstrated that drug tolerance can be conditioned.

Group Control

15 injections of saline in distinctive room.

High dose of heroin in distinctive room on Day 16.

- Results: 96% died of overdose.

Group Same

15 injections of heroin in distinctive room.

High dose of heroin in distinctive room on Day 16.

- Results: 32% died of overdose.

Group Different

15 injections of heroin in distinctive room.

High dose of heroin in *new room* on Day 16.

- Results: 64% died of overdose.

Siegel's Theory:

- When an environment consistently *predicts* drug administration...
- ... the environment begins to elicit a “compensatory” response that is opposite to the drug’s effect.
- The compensatory response counteracts the drug’s effect.

Siegel's theory predicts:

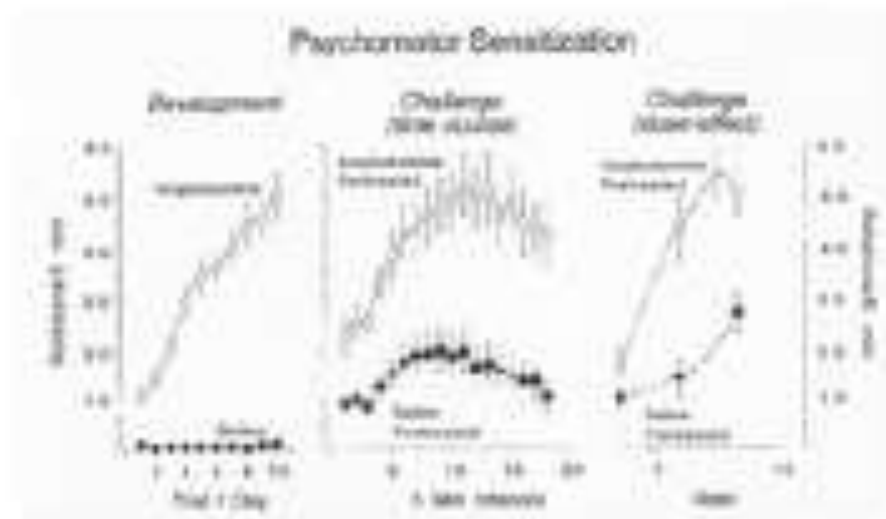
- Craving, withdrawal, and relapse.
 - “Drug environments” trigger compensatory response
 - Compensatory responses are aversive.
- Accidental overdose.

Other issues of tolerance.

- Acute tolerance
- Cross tolerance
 - Example: Cross tolerance between alcohol and valium.
- Cross tolerance can be due to
 - ...pharmacokinetic,
 - ...pharmacodynamic,
 - ...or learned tolerance.

Reverse Tolerance (sensitization)

- The drug becomes more effective with repeated doses.
- E.g., marijuana, stimulant psychomotor effects, drug-induced liver disease.
- Could be due to:
 - Learning
 - Pharmacokinetics
 - Pharmacodynamics



From Anagnostaras & Robinson (1996)

Drug Dependence

- As a consequence of previous use, the individual must continue to use the drug to avoid adverse consequences.



Two types of dependence.

- Physical Dependence
 - Presence of an abstinence syndrome (withdrawal).
 - Physical symptoms relieved by drug administration.

What causes withdrawal?

Opiate administration

Analgesia

Euphoria

Hypothermia

Decreased BP

Sexual Dysfunction

Constipation

Opiate Withdrawal

Hyperalgesia

Depression

Hyperthermia

Increased BP

Spontaneous Orgasm

Diarrhea

Withdrawal symptoms tend to be *the opposite* of drug effects.

Homeostatic Model of Drug Withdrawal.

- Homeostasis - systems of the body keep the internal environment in an optimal state.
- Drugs interfere with normal homeostasis.
- Over time, the body adjusts to the presence of the drug and homeostasis is restored.
- When the drug is removed, homeostasis is once again disrupted.

Two types of dependence continued...

Psychological Dependence

- Strong compulsion/desire to use the drug for reasons other than to eliminate withdrawal.
 - Craving
 - Drug Seeking Behavior
 - Inability to terminate drug use.
 - Use of drug despite negative consequences.
- **Physical and psychological dependence often occur simultaneously.**

Is psychological dependence less important than physical dependence?

- Absolutely not.
- Most relapse occurs *after* physical withdrawal has terminated.

Drug Addiction - The inability to discontinue use of a drug.

Theories of Addiction

- Physical dependence model – Withdrawal symptoms serve as negative reinforcers.
 - Problems:
 - Not all psychoactive drugs support withdrawal.
 - Is the individual “cured” once withdrawal has terminated?

Theories of Addiction continued...

Positive Reinforcement Model

- Addiction occurs because the drug stimulates “reward centers” of the brain.
- Positive reinforcement - A behavior followed by a pleasant outcome will become more common.

Evidence for positive reinforcement model

- Drugs can serve as positive reinforcers.
 - Drug Self-Administration Paradigm
- Stimulation of “reward centers” in the brain is reinforcing.





- Nucleus Accumbens - A natural reward center in the brain.
 - Activated by dopamine.

Evidence for positive reinforcement ctd...

- Addictive drugs affect dopamine transmission in the Nucleus Accumbens.
- Lesions of Nucleus Accumbens eliminate drug self-administration of stimulants.
- Drug addictiveness seems to follow rules of effective reinforcers.
 - Saliency and Immediacy.
 - What about negative consequences?
- Social factors might also act to reinforce addictive behavior.

Problems with positive reinforcement model:

- DA seems to mediate attention not pleasure.
- Addiction without pleasure?

Incentive-Sensitization Theory of Addiction (Robinson and Berridge, 1993)

- The acts of *liking* and *wanting* a drug are different.
- Addiction occurs due to sensitization of *wanting* pathway.
 - Drug-related cues trigger *wanting* by being paired with hedonic drug effects.

Diagnosis of Substance Abuse/Dependence

- DSM IV TR

Diagnosis of *Substance Abuse Disorder*.

- At least one of the following in the last 12 months:
 - Substance related failure to meet major role obligations.
 - Substance related physically hazardous behavior.
 - Substance related legal problems.
 - Continued substance use despite negative consequences.

Diagnosis of *Substance Dependence Disorder*.

- At least 3 of the following in the last 12 months:
 - Tolerance
 - Withdrawal
 - Substance taken more/longer than intended.
 - Desire to quit or unable to quit.
 - Substance use eliminates/reduces other important activities.
 - Substance used despite negative consequences.

Approaches to treat addiction.

Stages of Treatment

- **Stage 1: Detoxification**
 - Elimination of drug from the body.
 - Management of physical withdrawal.
 - Medical treatment might be necessary.

Stage II: Active Treatment

- Treatment Settings:
 - Residential versus Out-Patient
- Treatment Goals:
 - Abstinence versus Controlled use.
- Treatment for comorbid disorders.

Treatment Approaches

Psychotherapy

- Group therapy (structured and unstructured).
- Behavioral Therapy
- Cognitive- Behavioral Therapy

Pharmacotherapy

- To reduce impact of withdrawal.
- To reduce likelihood of relapse.

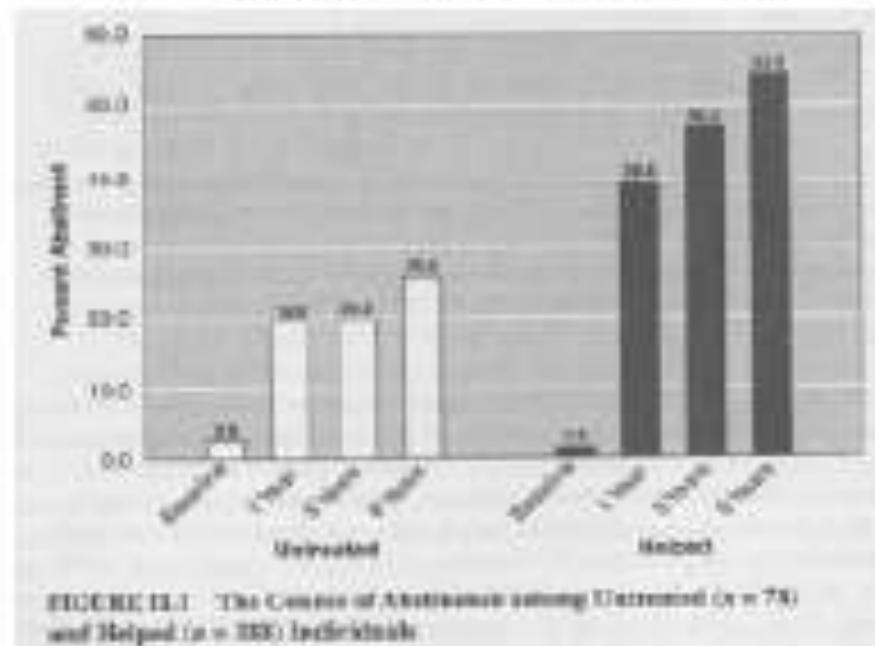
Stage III: Aftercare

- Long-term support against relapse.
 - Options:
 - Self-help Groups
 - Psychotherapy

Does treatment work?

- About 1/3 to 2/3 of clients have positive outcomes....

...improvement rates in untreated clients are about half as high.



Timko et al (2000)