# REWARD AND REINFORCEMENT II

**Neurobiological substrates of drug addiction**

*Pluck from the memory a rooted sorrow*
*Raze our the written troubles of the brain,*
*And with some sweet oblivious antidote*
*Cleanse the stuff'd bosom of that perilous stuff*
*Which weighs upon the heart*

William Shakespeare, MacBeth

Humans have used drugs for thousands of years to cure diseases, alleviate pain, relieve mental suffering, and produce pleasant subjective effects. We have often sought "some sweet oblivious antidote" to the hardships of living. Drug dependence is in fact a very old phenomenon found in many societies and cultures, and in all socioeconomic groups. Psychoactive drugs (including alcohol) have powerful subjective, reinforcing, and addictive properties. Indeed, substance abuse is a major health problem in the United States. In fact, if all costs to society are taken into account, in terms of death, disease, and injury attributable to alcohol and nicotine abuse alone, and the emotional toll on the lives of abusers and their families, it could be considered as **the** biggest public health problem. Abuse of alcohol, cigarettes, and other drugs results in nearly $200 billion annually in economic costs to society. Over 500,000 people a year die of drug, smoking, or alcohol-related illness, a truly staggering number. Yet paradoxically, our society tacitly condones drug use, since the two drugs that cause the most suffering, alcohol and nicotine, are the ones that are legal. What makes these substances so rewarding and addictive? Why do people risk their health and lives for a chemical substance? We will explore some of these questions in this lecture.

In the last lecture, we learned that there is a neural system in the brain that seems to be intimately involved with regulating goal-directed, appetitive behaviors, that is behaviors by an animal that are directed toward achieving specific goals. The ascending mesocorticolimbic dopamine system and its forebrain targets (nucleus accumbens and frontal cortex especially) are critical components of the brain's reinforcement system. Although drugs of abuse come in different classes and molecular structures, they all appear to have one critical property in common**:** they **activate** this system. Moreover, we are just now learning with the use of sophisticated neuromolecular probes, that drugs of abuse exert long-lasting alterations in gene expression, protein synthesis, and synaptic function; these changes may underlie their addictive properties.

It first may be useful to consider what we mean by addiction. The DSM-IV (Diagnostic and Statistical Manual of the American Psychiatric Association) criteria for psychoactive substance dependence emphasize clusters of symptoms or behavioral manifestations that clearly indicate distress or disability. There are three basic characteristics to this set of criteria: (1) loss of control over the use of the substance; (2) impairment in daily functioning and

continued use of substance despite adverse consequences; and (3) physical or emotional adaptation to the drug, such as in the development of tolerance or a withdrawal syndrome. It is sometimes helpful to think of the essentials of drug dependence being defined by the "three C's": **loss** of control regarding drug use, **continued** use in the face of adverse consequences, and **compulsion** (or need) to use the drug.

**Animals self-administer the same drugs as do humans**

One of most important models of drug dependence is that of the **animal self-administration model**. It has been known for over 25 years that monkeys, rats and other species will learn to perform an operant response (such as lever press) for intravenous delivery of a drug. Early experiments also showed that **physical dependence** (when a person cannot function normally without the repeated use of a drug; if the drug is withdrawn, the person has severe physical and psychic disturbances) was not a necessary condition for animals to self-administer drugs. This suggested that the positive reinforcing properties were sufficient for drug-seeking behavior to develop. Interestingly, all the compounds that humans use, with the exception of **hallucinogens** (LSD, mescaline), are avidly self-administered by animals: cocaine, amphetamine, nicotine, caffeine, alcohol, opiates (narcotics), and sedatives (barbiturates and benzodiazepines; Halcion, Xanax). This fact has provided the principal basis for studying the neural systems affected by these drugs. One of the more compelling demonstrations of self-administration has been shown with **cocaine**. If given unlimited access, animals will self-administer cocaine "to death", that is, they will forego food and water in order to get cocaine. (One monkey was recorded as pressing 6,000 times for one dose of cocaine). The parallels with severe addiction in humans, in which people will engage in destructive behavior in order to obtain the drug, are apparent.

**Dopamine is necessary for self-administration of stimulants, and is activated by many drugs of abuse**

It was shown many years ago that lesions (neurotoxic destruction) of **the mesolimbic dopamine system** resulted in reduction or abolition of responding for intravenous cocaine or amphetamine. Researchers infused the neurotoxin 6-OHDA (6-hydroxydopamine; a neurotoxin that kills dopaminergic cells and terminals) into the nucleus accumbens or VTA and found that lever pressing for the drugs was greatly **reduced**. Recent studies show that drugs that cause strong euphoria, such as cocaine and amphetamine, induce a large **increase** in the amount of synaptic dopamine. This occurs in a number of brain regions, but the increase in the nucleus accumbens appears to be critical for the euphoriant effects. *In vivo* microdialysis studies have shown that many drugs of abuse, despite belonging to differing chemical classes, were able to activate the accumbens dopamine system (morphine, methadone, alcohol, and nicotine; see Fig. 1). Drugs that rats do not self administer (press the bar to get the drug) do not have an effect on dopamine levels.

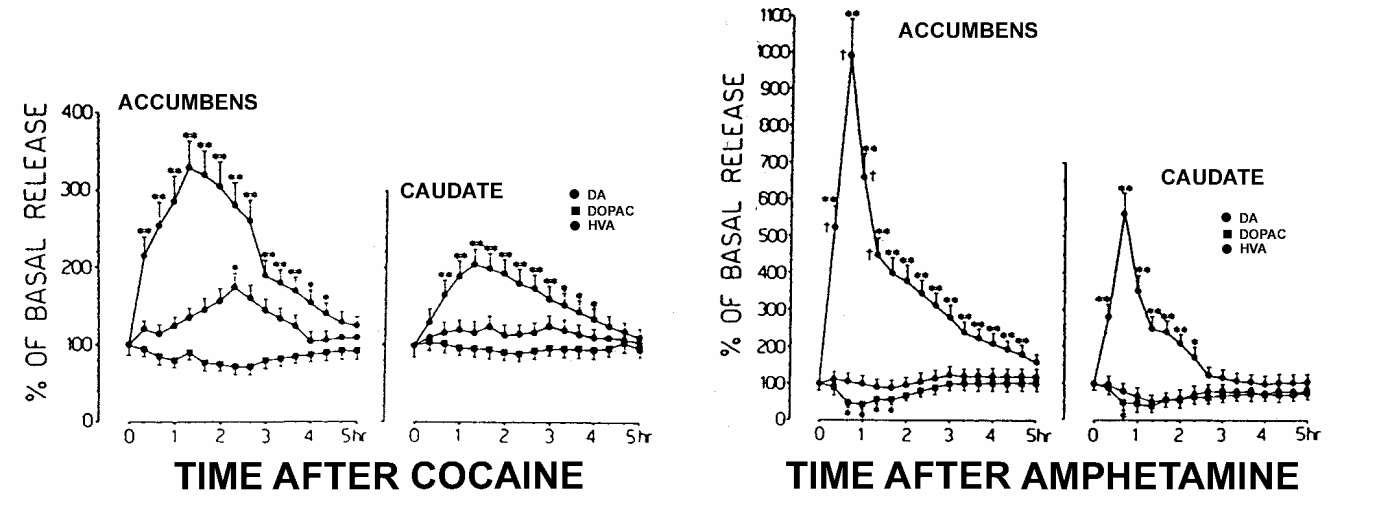


Fig. 1. With a microdialysis probe placed in the nucleus accumbens or caudate, the extracellular DA overflow was measured in animals receiving various drugs of abuse. Shown here are the effects of cocaine and amphetamine on DA release. (The other curves, DOPAC and HVA, are metabolites of dopamine). In the same study**, morphine**, **methadone**, **alcohol**, and **nicotine** were all found to significantly activate dopamine. Several control drugs that are not self-administered did not have effects on dopamine. From Di Chiara et al, 1988.

The mechanism of action of **cocaine** has been the focus of much research in recent years. It is now known that cocaine binds to the **dopamine transporter**, or re-uptake site. This site is a membrane-bound protein that is responsible for clearing dopamine from the synapse (taking it back up into the terminal) following release. When cocaine binds to the transporter, it **blocks** its action, resulting in greatly **increased** synaptic levels of dopamine. **Amphetamine** is also thought to utilize the **dopamine transporter** for its action.

The psychostimulant effect of cocaine and amphetamine was recently examined in knockout mice lacking the dopamine transporter both before and after cocaine or amphetamine treatment. In knockout mice, spontaneous locomotor activity is highly elevated in comparison to wild-type and heterozygote mice. In knockout mice, DA remains in the extracellular fluid 100 times longer than in wild-type mice, resulting in the **enhanced** locomotor behavior (no dopamine transporter for re-uptake). After administration of cocaine and amphetamine, both wild-type and heterozygote mice exhibited a pronounced **increase** in locomotor behavior. In contrast, knockout mice showed no increase in locomotor activity after drug administration. These results indicate that the **dopamine transporter** is a major molecular target of the psychostimulants **cocaine and amphetamine.**

While cocaine and amphetamines affect the DA transporter, alcohol is thought to use the **endogenous opiate** system to activate DA release. Thus, alcohol could bind directly to opiate receptors on cells in the VTA (=more DA release in accumbens) or affect the opiate pathways that reach the nucleus accumbens directly (=more DA release in accumbens; remember, there are opiate receptors on GABA processes that terminate on VTA terminals). **Nicotine** has been found to bind at multiple nicotinic ACh receptors on DA nerve cells and thus can increase dopamine levels. Heroin acts at mu opioid on cells

in the VTA and marijuana is thought by some to act on cannabinoid receptors (which are, however, few in number!) on VTA neurons.

**Conditioning and learning models of addiction**

The pleasurable states that drugs induce and the relief they bring to aversive withdrawal states are important factors underlying drug-seeking behavior. However, the greatest problem in substance abuse treatment is keeping the individual abstinent. Weeks, months or even years following successful detoxification, the patient may yield to uncontrollable drug cravings and may relapse. The conditioning and learning models provide a framework for understanding this aspect of substance dependence. These models embrace the notion that a **drug** is an **unconditioned stimulus (US).** Remember, Pavlov showed that a bell (CS) paired with a piece of meat (US) could eventually cause salivation when only the bell rang (CR). Interestingly, he also conditioned a dog to exhibit a drug reaction to a non-drug stimulus; he paired a tone with an injection of morphine and elicited restlessness and vomiting. The bell alone (CS) was then shown to elicit the restlessness and vomiting.

There are a number of lines of evidence to suggest that conditioned drug effects are different from, or opposite, those evoked by the drugs themselves. Thus, when a drug user is walking down the street and sees the neon sign outside a tavern where he/she has often taken drugs, the sign serves as a CS. This leads to respiratory depression, analgesia and increased temperature and drug seeking behavior to alleviate these symptoms.

At the Public Health Service Hospital in Lexington, Kentucky, in the early 1970s, Abraham Wikler was observing opiate addicts in a group therapy session. These particular patients had been free of drugs for several months, and there were certainly no signs of opiate withdrawal. However, when the patients began talking about drugs, Wikler noticed that some of them began to show signs of withdrawal, such as tearing eyes, runny nose, sweating, and yawning. He labeled this **phenomenon "conditioned withdrawal"** and also noted its occurrence when the former addicts returned to neighborhoods where they had previously used drugs. Wikler suggested that through classical conditioning, environmental stimuli acquire the ability to elicit the signs of withdrawal. Moreover, these **drug cues** or drug "reminders" induced craving for the drug and played an important role in triggering relapse.

There is considerable evidence, both from human studies and animal research, to support Wikler's theories. Presentation of drug-related stimuli to patients in treatment induces strong signs of physiological arousal and self-reports of drug craving. Research suggests that conditioned cues can elicit withdrawal-like symptoms that reinstate the overwhelming need for the drug. This may be true for a variety of psychoactive substances and situations. For example, passing a bar or arriving at a cocktail party may induce a strong desire for a drink (even in a social, moderate drinker), and the smell of smoke or sight of cigarettes can induce a strong craving in smokers trying to quit. PET

scanning studies show that cocaine addicts who are exposed to cocaine related cues show marked activation of critical brain regions, particularly the prefrontal cortex.

**Adaptation to drugs: tolerance and physical dependence**

**Neuroadaptation** refers to the complex biological changes that occur in the brain with repeated or **chronic** exposure to a drug. Drugs by their very definition induce some changes in the neurochemical environment of the brain; one exposure to a particular drug will cause a specific effect (for example, increased levels of a particular neurotransmitter). However, with repeated exposure, the brain often **adapts** to the presence of the drug. Over stimulation decreases the number of DA receptors, and the remaining receptors become less sensitive to dopamine. This process is called **desensitization** and is better known as **tolerance,** where exposure to a drug causes less response than previously caused. Tolerance reflects the actions of the nervous system to maintain **homeostasis,** a constant degree of cell activity in spite of major changes in receptor stimulation. The nervous system maintains this constant level in an attempt to keep the body in a state of equilibrium, even when foreign chemicals are present.

During desensitization progressively **more** drug is needed in order to obtain the same effect. Compared with inexperienced drinkers, people who regularly consume alcohol often show a **high degree** of tolerance to its behavioral effects. Tolerance may also be accompanied (although not necessarily) by **physical dependence**. Physical dependence is characterized by the need for the presence of the drug in **order to function normally**, and by the appearance of a **withdrawal syndrome** upon cessation of the drug. The **withdrawal syndrome** (also called abstinence syndrome) is usually characterized by **observable, physical signs** such as marked changes in body temperature or heart rate, seizures, tremors, or vomiting. Such a syndrome may occur, for example, following abrupt cessation of chronic heavy drinking. In opiate dependence, withdrawal signs include nausea, gastrointestinal disturbance, chills, dysphoria, and sympathetic arousal. It is important to note that in some forms of dependence, such as that associated with cocaine or nicotine, the so-called withdrawal syndrome **may not be easily observable**; it may take the form of severe depression, irritability or craving. It is also important to keep in mind that avoidance of withdrawal may be a major motivating factor for continued drug use, particularly with prolonged drug use. For example, early in the development of opiate drug use, positive reinforcement (i.e. the attainment of euphoria) might be dominant, whereas in later use, negative reinforcement, the **avoidance of withdrawal**, might be more important.

**Cellular and molecular effects of drug exposure**

There is now convincing evidence that exposure to drugs causes long-lasting neuronal changes in the brain. For instance, in a drug-addicted or drug-preferring animal, there is a **decrease** in the number of **neurofilaments** (NF) in the VTA cells; such cells **shrink** appreciable. This decrease in NFs may be associated with alterations in neuronal structure, decreases in axonal caliber, and/or decreases in axonal transport rate in these cells. Such a decrease in axonal transport could account for the fact that tyrosine

hydroxylase (TH) levels are increased in the VTA cell bodies but decreased in dopaminergic terminals in the nucleus accumbens. Decreased TH implies decreased dopamine synthesis, and may result in lower dopaminergic transmission to nucleus accumbens.

In the nucleus accumbens of the drug-addicted or drug-preferring state, G proteins, second messengers, protein phosphorylation, and nuclear transcription factors are affected and activate **intermediate early genes** (IEGs). These genes and their protein products may play an important role in regulating the activity and expression of many other genes and in cellular functioning. That is, **IEGs** are responsible for **long term** changes in cells. Researchers have also studied phosphorylated **CREB**. CREB (cyclic AMP response-element binding protein) is a nuclear transcription factor protein that when phosphorylated (via protein kinase A), activates a large number of target genes. Amphetamine also activates phosphorylation of CREB, and there is adaptation to this response with repeated treatment. It is interesting to note that CREB is believed to be an evolutionarily conserved component of long-term memory, from fruit flies to mammals. All of these findings indicate that drugs like cocaine and morphine can cause **long term changes in cells**.

There is still little known about the enduring molecular changes that may be associated with drug craving or conditioned effects, and with the process of long-term addiction. However, there are provocative findings. It has been demonstrated that conditioned stimuli (a tavern sign) associated with cocaine treatment, in the absence of the drug itself, can turn on IEG expression (a gene called **c-fos**) in certain brain regions, such as the **amygdala** and **prefrontal cortex**. This means that the pairing of the drug states with environmental cues has actually **changed cellular activity** in a long-term manner. A further area being extensively studied is the role of N-methyl-d-aspartate, (**NMDA)** receptors in long-term drug effects. NMDA receptors (a form of glutamate receptor that you learned about in Physiology) are a critical component of the brain's learning and plasticity mechanisms. A drug that **blocks** these receptors, **MK-801**, blocks many of the behavioral and neuronal adaptations observed following repeated exposure with addictive drugs. For example, amphetamine can activate the IEG **zif/268**, but this activation is entirely **blocked** by MK-801 (Fig. 2). It is noteworthy that **zif/268** has been implicated in long-term potentiation (important in memory), as have NMDA receptors. An intriguing hypothesis currently under investigation is that addictive drugs affect the same molecular processes responsible for the long-term synaptic modification that is necessary for learning and memory. In sum, **drugs of abuse induce long-term alterations in the internal biomolecular machinery of the cell**.

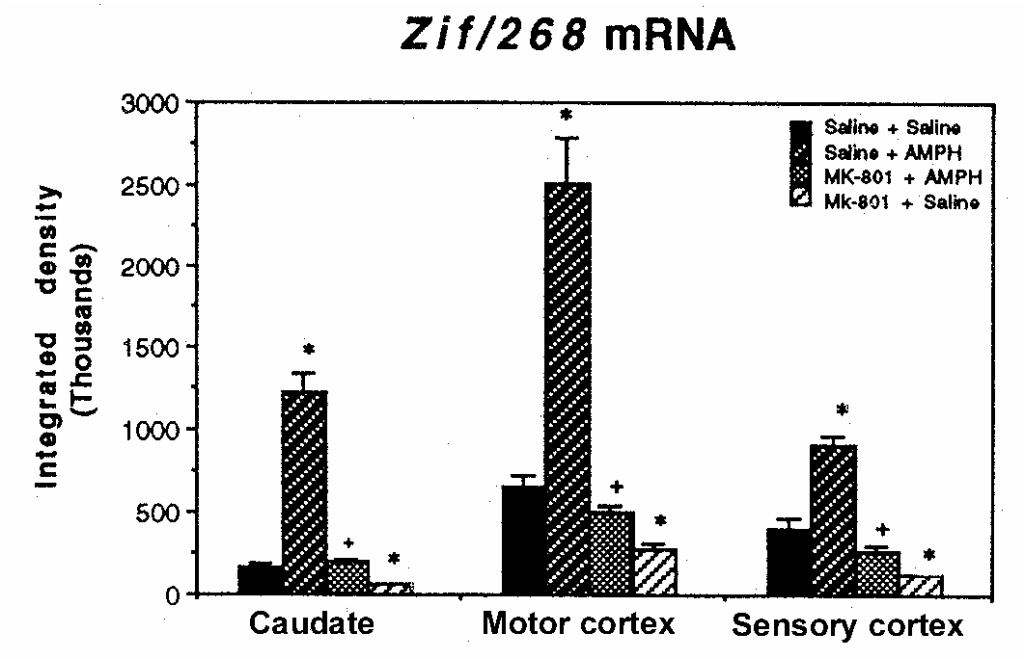


Fig. 2. Glutamate receptors are involved in the ability of amphetamine to turn on **zif/268** gene expression. Pretreatment of animals with the drug MK-801, a very selective NMDA receptor antagonist, blocked the induction of gene expression in several brain regions. **zif/268** is a transcription factor (a protein that binds to DNA and regulates expression of a gene) thought to be involved in sensory stimulation and synaptic plasticity. From Wang et al., 1994.

**Problem Solving**

1. Dopamine levels in the nucleus accumbens:
A. increase when you eat a donut
B. increase during sex
C. increase when you think of eating a donut
D. increase when you think about sex
E. all of the above are **TRUE**

2. Administration of MK-801 along with amphetamine:
A. has no effect on the IEG zif/268
B. blocks the activation of the immediate early gene zif/268
C. enhances the activation of zif/268
D. blocks the dopamine transporter
E. A and B are **TRUE**

3. Which of the following occur following long-term drug use in rats?
A. activation of IEGs in nucleus accumbens
B. increase in neurofilaments in VTA neurons
C. enlargement of cell bodies of VTA neurons
D. other inputs to the nucleus accumbens and VTA are affected
E. A and D are **TRUE**

4. Which of the following drugs are self-administered by animals?
A. cocaine
B. LSD
C. morphine
D. A and C
E. A, B, and C

5. Dopamine is released in the nucleus accumbens by:
A. alcohol
B. eating highly palatable food if you're hungry
C. nicotine
D. allowing a male rat to mate with a female rat
E. all of the above

6. Which of the following statement(s) is/are **TRUE**?
A. cocaine's mechanism of action is to bind to the acetylcholine re-uptake transporter
B. drugs of abuse from different chemical classes cause an increase in dopamine release in the nucleus accumbens
C. a conditioned stimulus cannot control drug-seeking behavior
D. both positive and negative reinforcement are involved in drug-seeking behavior
E. two of the above are **TRUE**

7. Drug-associated conditioned stimuli:
A. can activate the prefrontal cortex in addicts
B. can activate the nucleus accumbens
C. play a role in human but not animal drug-seeking behavior
D. do not evoke physiological arousal and drug craving
E. two of the above are **TRUE**

8. Which of the following statement(s) about the sequelae of chronic exposure to a drug of abuse is/are **FALSE**?
A. repeated exposure to drugs of abuse causes neuroadaptation in the brain
B. physical dependence includes the need for the drug to function normally
C. tolerance involves an increased response to a drug after it has been taken repeatedly
D. withdrawal signs can include seizures, nausea, and severe depression
E. during sensitization, progressively more drug is needed in order to obtain the same effect

9. Which of the following statement(s) about a heroin addict who quits using drugs "cold turkey" is/are **TRUE**?
A. he/she might experience gastrointestinal disturbance
B. he/she might experience chills
C. he/she might resume drug taking according to the principle of negative reinforcement
D. he/she might experience a runny nose and tearing
E. all of the above are TRUE

10. Brain systems involved in positive reinforcement:
A. are inactivated by acute administration of drugs of abuse
B. include norepinephrine transmission within the nucleus accumbens
C. undergo neuroadaptation with chronic exposure to drugs of abuse
D. can be similarly affected by primary and secondary reinforcers associated with either naturally rewarding stimuli or drugs of abuse
E. C and D are **TRUE**

**PROBLEM SOLVING ANSWERS**

1. E
2. B
3. E (A, D)
4. D
5. E
6. E (B, D)
7. E (A, B)
8. C
9. E
10. E (C, D)