Determinants of Nicotine Dependence: Bio/Psycho/Social Factors

Module Description

Until relatively recently, nicotine dependence was not recognized as a legitimate disorder, in part because its manifestations do not appear to be as severe and as potentially disruptive to everyday functioning as dependence on other drugs. However, closer study has revealed that nicotine dependence shares many features with other drug dependence, notably similar biological actions on brain reward and withdrawal circuitry, compulsive use, tolerance, etc. Moreover, because tobacco, the primary source of nicotine, is legal, availability is not a barrier. Nicotine dependence has an insidious onset, but once entrenched, takes addictive hold of the tobacco user, such that repeated efforts to quit are often met with failure, resulting in a lifetime of tobacco addiction.

This module will provide the knowledge base for understanding the biological, psychological and social basis of nicotine dependence. This will include learning about the basic brain processes that determine drug dependence in general and the development and maintenance of nicotine dependence in particular. We will look at how nicotine is absorbed, distributed and eliminated and review the diagnostic criteria for nicotine dependence and withdrawal.

Goal of the module

Provide tobacco treatment specialists with knowledge of the biological, psychological and social as determinants of nicotine addiction so they can better understand and treat tobacco users.

Learning objectives

1. Describe the prevalence and etiology of nicotine dependence.
2. Discuss Biological, Psychological and Social factors related to nicotine dependence and cessation.
3. Describe assessments of nicotine dependence.
The Biology of Nicotine Dependence

Supplemental Information

Originally developed by Raymond Niaura, Ph.D. May 18, 1999.
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Objective: Identify and Describe Brain Regions and Neuronal Pathways Associated with Drug Dependence

Basic Biology

Introduction to the brain: We will review how the brain basically works and how and where drugs such as cocaine and nicotine work in the brain. We will discuss the concept of "reward" which is the property that is characteristic of many addictive drugs.

The brain and spinal cord: The central nervous system is composed of the brain and the spinal cord. The brain is a functional unit; it is made up of billions of nerve cells (neurons) that communicate with each other using electrical and chemical signals. The spinal cord conducts information from the brain to other parts of the body to facilitate both voluntary (moving a hand) and involuntary (moving food through the digestive system) actions.

Brain regions and neuronal pathways: Certain parts of the brain govern specific functions. Areas such as the sensory, motor and visual cortex highlight their specific functions. The cerebellum mediates coordination and the hippocampus is involved in memory. Nerve cells or neurons connect one area to another via pathways to send and integrate information. The distances that neurons extend can be short or long. Neuronal connections are reinforced with use or activation. For example, the reward pathway is activated when a person receives positive reinforcement for certain behaviors ("reward"). This happens in response to natural survival behaviors or when a person takes an addictive drug. As another example, the thalamus structure receives information about pain coming from the body, and passes the information up to the cortex.

A simple reflex circuit: Pathway for sensing and reacting to pain: This is a long pathway in which neurons make connections in both the brain and the spinal cord. What happens when one slams a door on one's finger? First, nerve endings in the finger sense the injury to the finger (sensory neurons) and they send impulses along axons to the spinal cord. The incoming axons form a synapse with neurons that project up to the brain. The neurons that travel up the spinal cord then form synapses with neurons in the thalamus, which is a part of the midbrain. The thalamus organizes this information and sends it to the sensory cortex, which interprets the information as pain and directs the nearby motor cortex to send information back to the thalamus. Again, the thalamus organizes this incoming information and sends signals down the spinal cord, which direct motor neurons to the finger and other parts of the body to react to the pain (e.g., shaking the finger or screaming "ouch!"). Addictive behaviors can become reflexive, with the person having no conscious awareness of their behavior (e.g., patting a pocket or chain smoking).
Neuronal Structure, Synaptic Transmission

**Neuronal structure:** Signaling pathways are made up of neurons. Actual neurons from the thalamus can be photographed by injecting them with a fluorescent dye and viewing them through a microscope. The anatomy of a neuron consists of the cell body (soma), dendrites and axon. At the end of the axon is the terminal; each terminal communicates with another neuron through chemical signals.

**Impulse flow:** Neuronal signaling involves sending information by electrical impulses down the axons to the terminals of the nerve cell. Chemical signals are used to transfer the signal from one nerve cell to another nerve cell. The electrical impulse travels down the axon toward the terminal. This is called an action potential. When the action potential reaches the terminal of this presynaptic neuron, it makes a “connection” with the dendrite of a neighboring postsynaptic neuron by passing on chemical information. The chemicals, called neurotransmitters, are transferred across a short space between the nerve cells. The short space is called the synaptic cleft, and the area of “connection”, is called the synapse. While the synapse between a terminal and a dendrite is quite typical, other types of synapses exist as well. For example, a synapse can occur between a terminal and a soma or axon.

**The synapse and synaptic neurotransmission:** If we take a closer look at the synapse and the process of chemical neurotransmission, we see that as an electrical impulse arrives at the terminal, it triggers vesicles containing a neurotransmitter, such as dopamine, to move toward the terminal membrane. The vesicles fuse with the terminal membrane to release their contents. Once inside the synaptic cleft (the space between the two neurons) the dopamine can bind to specific proteins called dopamine receptors on the membrane of a neighboring neuron.

**Dopamine neurotransmission and modulation**

**Dopamine neurotransmission and modulation by endogenous opiates:** If we take a closer look at a synapse involved in dopaminergic signaling, we see that dopamine is synthesized in the nerve terminal and packaged in vesicles. Neurotransmission involves the vesicle fusing with the membrane and releasing dopamine. The dopamine molecules can then bind to a dopamine receptor. After the dopamine binds, it comes off the receptor and is removed from the synaptic cleft by reuptake pumps (also proteins) that reside on the terminal of the signaling neuron. This reuptake process is important because it ensures that not too much dopamine remains in the synaptic cleft at any one time. Neighboring neurons may release other chemicals called neuromodulators. These neuromodulators help to enhance or inhibit neurotransmission that is controlled by neurotransmitters such as dopamine. One example of a neuromodulator is an "endorphin". Endorphins bind to opiate receptors, which can reside on the postsynaptic cell or, in some cases, on the terminals of other neurons. Endorphins are destroyed by enzymes rather than removed by uptake pumps. GABA, or γ-aminobutyric acid, is an inhibitory neuromodulator: it decreases or inhibits dopamine signaling. Glutamate acts as a neuromodulator in that it causes neurons that have been exposed to addictive drugs to increase the release of dopamine during the next dose or exposure to drug. Glutamate also plays a role in learning and memory. This is important for nicotine dependence and will be discussed below.
Objective: Describe How Activation of Key Neuronal Pathways Predisposes Toward Nicotine Addiction in Terms of Reward and Withdrawal

Neural Circuitry

The reward pathway and addiction: Humans, as well as other organisms engage in behaviors that are rewarding; the pleasurable feelings provide positive reinforcement so that the behavior is repeated. There are natural rewards as well as artificial rewards, such as drugs.

Natural rewards: Natural rewards such as food, water, sex and nurturing allow the organism to feel pleasure when eating, drinking, procreating and being nurtured. Such pleasurable feelings reinforce the behavior so that it will be repeated. Each of these behaviors is required for the survival of the species. They activate the reward pathway and are experienced as pleasurable and they are encoded in memory so they will be repeated. Important note: there is a neuronal pathway in the brain that is responsible for remembering and repeating rewarding behaviors and this serves to ensure survival.

The reward pathway: When the brain is cut down the middle, we can view the major structures of the reward pathway: the ventral tegmental area (VTA), the nucleus accumbens and the prefrontal cortex. The VTA communicates with both the nucleus accumbens and the prefrontal cortex via this pathway and it sends information to these structures via its neurons. The neurons of the VTA contain the neurotransmitter dopamine, which is released in the nucleus accumbens and in the prefrontal cortex, an area of the brain involved in judgment. This pathway is activated by a rewarding stimulus. Dopamine is the main neurotransmitter of the Reward Pathway. The increase in dopamine results in the subjective experience of pleasure (I FEEL GOOD!). Note: the VTA – nucleus accumbens – prefrontal cortex is known as the Reward Pathway, however it is not the only pathway activated by rewards. Other structures and signaling pathways, such as those involved in memory, are also activated. We will discuss briefly some of these other pathways below.

Activation of the reward pathway by an electrical stimulus: The discovery of the reward pathway was achieved with the help of animals such as rats. Rats were trained to press a lever for a tiny electrical jolt to certain parts of the brain. When an electrode is placed in the nucleus accumbens, the rat keeps pressing the lever to receive the small electrical stimulus because it feels pleasurable. This rewarding feeling is also called positive reinforcement. When the electrode is placed in an area of the brain close to, but not within the nucleus accumbens, the rat will not press the lever for the electrical stimulus because stimulating neurons in a nearby area (even within one millimeter) that does not connect with the nucleus accumbens does not activate the reward pathway. The importance of the neurotransmitter dopamine has been determined in these experiments because scientists can measure an increased release of dopamine in the reward pathway after the rat receives the reward. And, if the dopamine release is prevented (either with a drug or by destroying the pathway), the rat won't press the bar for the electrical jolt. So with the help of the rats, scientists figured out the specific brain areas as well as the neurochemicals involved in the reward pathway.
**Biology of Addiction;** We will now summarize some of the neural circuits involved in addiction. The reward pathway is located close to the hypothalamus, an area involved in responses to stress. The locus ceruleus is separate from the reward pathway, and uses norepinephrine as the signaling neurotransmitter. The locus ceruleus is thought to be involved in withdrawal.

**Addiction;** Addiction is a state in which an organism engages in a compulsive behavior, even when faced with negative consequences. This behavior is reinforcing, or rewarding. A major feature of addiction is the loss of control in limiting intake of the addictive substance. The most recent research indicates that the reward pathway may be even more important in the craving associated with addiction, compared to the reward itself. Scientists have learned a great deal about the biochemical, cellular and molecular bases of addiction. There are different stages of addiction that are characterized by neuronal and signaling changes. For example, dopamine is associated with initiation and establishment of addictive behaviors whereas glutamate is associated with maintenance of addiction, cravings and relapse to an addiction. Following will be an example of the interaction between drugs that are addictive, their cellular targets in the brain, and the reward pathway.

**Example: The Action of Cocaine**

**The action of cocaine;** A lot of research has been done on the effects of cocaine on the brain. Cocaine is an addictive drug, and like heroin, not all users become addicted. With the advent of crack cocaine (the free base), the rate of addiction to cocaine increased considerably. The example of crack cocaine is used because its stimulant effects and method of administration (smoking) is very similar to nicotine. It also serves to demonstrate the extremely addictive nature of nicotine dependence.

**Snorting vs. smoking affects addictive liability;** Historically cocaine abuse involved snorting the powdered form; however, when cocaine is processed to form the free base, it can be smoked. Smoking gets the drug to the brain more quickly than does snorting. Snorting requires that the cocaine or nicotine travel from the blood vessels in the nose to the heart, where it gets pumped to the lungs to be oxygenated. The oxygenated blood carrying the cocaine or nicotine then travels back to the heart where it is pumped out to the organs of the body, including the brain. The drug travels from blood to heart to lungs to heart and then to the brain. However, smoking bypasses much of this and therefore delivers drug to the brain more quickly: the cocaine or nicotine goes from the lungs directly to the heart and up to the brain. Lungs to heart to brain! The faster a drug with addictive liability reaches the brain, the more likely it will be abused. The time between taking the drug and the positive reinforcing or rewarding effects that are produced determine the likelihood of abuse. This holds true for nicotine delivered by various forms of tobacco.

**Dopamine binding to receptors and uptake pumps in the nucleus accumbens; the action of cocaine;** Cocaine binds to sites in areas of the brain that are rich in dopamine synapses such as the VTA and the nucleus accumbens. When cocaine binds to receptors at a synapse, dopamine (inside the terminal) is released into the synaptic cleft. The dopamine binds to dopamine receptors and then is taken up by uptake pumps back into the terminal. When cocaine is present, it binds to the uptake pumps and prevents them from transporting dopamine back into the neuron terminal. So more dopamine builds up in the synaptic space and is free to activate more
dopamine receptors. This results in increased dopamine signaling, and increased sense of pleasure (I FEEL REALLY GOOD).

With repeated use, the body relies on this artificial stimulus to maintain rewarding feelings. The person is no longer able to feel the positive reinforcement or pleasurable feelings of natural rewards (i.e. food, water, sex); the person is only able to feel pleasure from the drug. Thus the addicted person becomes dependent and when drug is no longer present, anhedonia (inability to feel pleasure) and depression emerge as part of a withdrawal syndrome. To avoid this, the substance dependent person goes back to using the drug. The natural mood state becomes reset to a more negative level. As an addictive drug, nicotine also increases dopamine concentrations, and it does so even more due to inhibition of GABA (γ-aminobutyric acid), a neurotransmitter that naturally acts to block dopamine signaling.

Summary; addictive drugs activate the reward system via increasing dopamine neurotransmission; The reward pathway is activated by drugs that have addictive potential. Just as heroin (morphine) and cocaine activate the reward pathway in the VTA and nucleus accumbens, other drugs such as nicotine and alcohol activate this pathway as well, although sometimes indirectly (e.g., the globus pallidus, an area activated by alcohol that connects to the reward pathway). While each drug has a different mechanism of action, each drug increases the activity of the reward pathway by increasing dopamine transmission. The faster a drug activates the reward pathway, the greater the risk of dependence. Smoked tobacco delivers nicotine to the brain in about 7 seconds! Because of the way our brains are designed, and because these drugs activate or hijack the brain pathway for reward, they have the ability to be abused. Thus, addiction is truly a disease of the brain. As research delineates more about the pathways and neurotransmitters involved in addiction, new and more effective treatment strategies will be available to help people beat addiction.

Withdrawal Pathways

Central noradrenergic withdrawal circuit; In addition to the neural circuits involved in reward, it is also important to consider the circuits involved in states of drug withdrawal. This is important because withdrawal states can also lead individuals back to using the drug, for example, to alleviate withdrawal discomfort. There is a specific nicotine withdrawal syndrome, which we review a little later. Different drugs have somewhat different withdrawal circuits, but several, including alcohol, opiates, and the psychostimulants including nicotine, are thought to involve activity of the central noradrenergic system. The locus coeruleus (LC) is a densely compacted region of cells that pulse like a heart beat. This pulsing determines the activity (firing rate) of noradrenergic (norepinephrine) neurons, which have projections to different brain areas and the autonomic nervous system. The faster the LC pulses, the more noradrenergic firing, which is related to, among other things, increased feelings of anxiety, restlessness, and irritability, which are classic nicotine withdrawal symptoms. The drug clonidine is an antihypertensive agent, which directly reduces the pulsing actions of the LC; it has been shown to help alleviate alcohol, cocaine, opiate, and nicotine withdrawal. There are three main mediators of relapse to dependence: environmental cues to use, reexposure to drug, and stress. When the nervous system is on overload as in withdrawal, the risk of stress-induced relapse is high.
Another factor in withdrawal is the glutamate circuit. Glutamate signaling is primary during end stage or maintenance addiction. When drug is withdrawn, glutamate continues to trigger dopamine release in the reward pathway, causing an experience of craving for the drug that may lead to relapse or redosing.

**Actions on Memory Systems**

*Schematic representation of involvement of some memory systems underlying addiction:* This is a little bit complicated, but serves to illustrate in part that many neural circuits are involved in developing drug dependence, not only reward and withdrawal pathways. Norman White has discussed a few neural circuits that are thought to be particularly important in explaining and contributing to development of dependence. Through the reward pathway, repetitive use of addictive substances causes changes in memory. The natural rewards are remembered because they are necessary for survival. Once drugs hijack the reward pathway, they also become encoded in memory as a necessity for survival. Memory circuits affect drug-seeking behaviors, affective or emotional response to drugs, and integrating information about drugs that makes it easier and easier to use them over time. There are three primary memory systems involved. (1) The amygdala system mediates memory for approach and interaction with drug-related cues, such as the paraphernalia involved in taking drugs, and the settings in which the drugs are used. In a sense, this is the memory system that works with activation of the reward and reinforcement (dopaminergic and glutamatergic) systems, to ensure that this experience is efficiently stored in memory so that drug cues will automatically, and often unconsciously, prompt drug seeking. (2) The caudate-putamen circuit is thought to help store information related to behaviors surrounding drug use itself. In this case drug cues activate this circuit to promote repetition of prior behaviors performed in the presence of drug-related stimuli. This can occur outside of conscious awareness (e.g., lighting up more than one cigarette at the same time), and is thought to be particularly important in nicotine dependence because these sorts of memories do not extinguish easily over time. (3) The declarative memory system, mediated by activity of the hippocampus, is where everything comes into conscious awareness, including cue-provoked memories of the affective states and other reinforcing effects associated with prior nicotine use. This is also the circuit that helps focus conscious processes (e.g., attention) on drug-related stimuli, and how to obtain drugs (the next cigarette).

**Disease of learning and memory:** Drug use leads to acute (short-term) and chronic (long-term) changes in the brain regions involved in learning and memory, which act to support the continuation of use or relapse after abstinence. Recent research has identified a potential mechanism for the development and maintenance of addiction. The neural systems responsible for motivation and choice have been linked to addiction. Internal motivation is required to obtain rewards. Hunger and thirst lead to eating and drinking. Pleasant food odors trigger hunger. When we are hungry, we are more motivated to obtain food, and the food tastes better. The neurotransmitters dopamine and glutamate are involved in establishing memories. Behaviors that cause rewards initially are encoded in the brain by pulses of dopamine that then trigger glutamate release. Glutamate signaling pathways link the environmental cues with behaviors and the evoked emotional response, and communicate this information to the prefrontal cortex, the center for judgment, where decisions are made about which rewarding behaviors take the highest priority. Eventually, dopamine signaling decreases and glutamate signaling takes over to maintain the behaviors leading to natural reward the behavior is learned.
Addictive drugs hijack the neural circuits involved in learning and memory, namely the reward pathway and the reinforcement of reward-seeking behaviors mediated by dopamine and glutamate in the prefrontal cortex and amygdala. Cues become associated with drug use, and craving becomes associated with more intense rewards. Initial drug use causes substantially higher release of dopamine than natural rewards, and it does so more reliably and consistently than natural rewards. Because drugs produce stronger and more consistent dopamine release, drug use becomes highly overrated as a reward and becomes the top priority, overpowering the choice for alternative natural rewards. This bias leads to the loss of control over drug use that is characteristic of addiction. The glutamate signaling pathway has become another target for development of treatments for addiction. N-acetylcysteine is a drug that reestablishes proper glutamate function in the nucleus accumbens and has been shown to decrease drug-seeking behavior in rats. Additionally, mice with a deletion of a glutamate receptor gene (mGluR5) have shown reduced responsiveness to cocaine. The full picture is more complicated, and the role of glutamate is still under investigation. However, one outcome of this line of research is a clinical study currently underway, in which N-acetylcysteine is being investigated as a treatment to prevent relapse.

**Molecular and Cellular Basis**

**Acute, chronic drug states; short/long-term abstinence;** It is important to consider the cellular and molecular basis of dependence in relation to changes that occur over time both quickly and gradually, and that may be related to characteristics of dependence. For example, in the acute drug state, there is the experience of reinforcement or reward. As noted previously, this experience is mediated primarily by activation of the mesolimbic dopaminergic brain circuit, although other circuits, such as the serotonin and glutamate systems, are also activated. As the user moves toward chronic nicotine use, we observe development of tolerance (need more of the drug to attain the same effect) sensitization (nicotine use increases the sensitivity of the dopaminergic systems to the effects of nicotine, and dependence (inability to limit or control drug use). There may be permanent adaptations in brain neuroreceptors, in this case nicotinic receptors, as well as corresponding changes in signal transduction pathways and gene expression, which we will not discuss in detail here. In short-term abstinence, there is an increase in withdrawal symptoms mediated by changes in glutaminergic, noradrenergic, and dopaminergic activity. Increased noradrenergic activity is thought to play a prominent role in nicotine withdrawal. Dopaminergic and serotonergic systems may become less active and responsive, which could account for symptoms of depression that often accompany nicotine withdrawal. In long-term abstinence, the formerly dependent smoker still encounters persistent craving, and stress-induced relapse. These phenomena may have to do with relatively long-lived or even permanent changes in the brain (e.g., synaptic remodeling which impacts on learning and memory processes that reactivate addiction circuits when the smoker comes into contact with situations or cues previously associated with smoking – the glutamate pathways described above). There may also be relatively long-term changes in stress-response systems, making ex-smokers more reactive to stress and more prone to smoke to relieve stress and therefore susceptible to relapse.
**Nicotine’s Actions in the Brain**

**What is nicotine?**

*Chemical structure and major characteristics of the nicotine molecule;* Nicotine is a tertiary amine and a highly lipid soluble alkaloid that is found primarily in the tobacco plant. It can be synthesized, but virtually all nicotine is obtained from tobacco plants, including the nicotine used in nicotine replacement therapy products. Tobacco contains about 90% S-nicotine, the most potent form, and about 10% R-nicotine, which is physiologically less active. Nicotine is a weak base. At physiological pH, about 31% is un-ionized and can readily cross cell membranes. The bioavailability of nicotine can be manipulated by controlling the pH value of tobacco. Nicotine binds specifically to acetylcholine receptors at autonomic ganglia, the adrenal medulla, neuromuscular junctions, and the brain. Nicotine readily crosses the blood-brain and placental barriers. Within the brain, binding of nicotine is diffuse, but is most concentrated in the hypothalamus, hippocampus, thalamus, midbrain, brain stem, cerebral cortex, and the nigrostriatal and mesolimbic dopaminergic neurons.

*Sample receptor in mesolimbic neurons;* Nicotine in tobacco exerts its actions on physiology and behavior by binding to nicotinic receptors in the brain. These receptors are large proteins spanning nerve cell membranes that normally translate the external signal of the neurotransmitter acetylcholine into an electrical signal that affects processes inside the nerve cell. These nicotinic acetylcholine receptors (nAChRs) can affect nerve cell function because they act to increase ion flow in the nerve cell, which then results in an electrical signal, the action potential that then causes increased release of neurotransmitters at the terminal. Outside of the brain, nicotinic receptors are found in muscle and nerve cells of the autonomic nervous system (flight or fight), which also contribute to the physiological responses to tobacco. The nAChRs are made up of subunits that determine their activity. There are two general classes: muscle nAChRs and brain nAChRs, the latter of which concern us here. Despite the many different subunits expressed in the brain, experiments indicate that brain receptors are mostly composed of alpha-4 and beta-2 subunits. One important question is which of the effects of nicotine on the central nervous system are mediated through nAChRs containing the beta-2 unit. It is known that the alpha-7 unit is present at high levels in the hippocampus, an area of the brain involved in learning and memory. It is also known that many nicotinic subunits, including beta-2 and to a lesser degree alpha-7 are present in the mesolimbic dopamine system.

Experiments with gene knockout mice have indicated that the beta-2 and alpha-7 subunits are implicated in nicotine dependence. Scientists have been able to genetically alter mice so that they do not have any beta-2 nicotinic brain receptors. These mice show no stimulation of dopamine by nicotine, nor do they learn to self-administer nicotine compared to mice who have these receptors. This information is important because it might help us to understand individual differences in response to nicotine and therefore nicotine dependence (e.g., those smokers with more or less of the specific nicotinic receptors), and it might help in tailoring new pharmacologic approaches to treatment.
treatments that specifically target these receptors (e.g., by blocking or antagonizing their function, making nicotine less reinforcing).

**Dynamics of receptor function:** It is also important to understand the dynamics of receptor function in relation to smoking and blood/brain nicotine levels. Neuroreceptors can become more sensitive for various reasons and they can also proliferate, both of which can be referred to as upregulation. Typically, one observes upregulation of receptors when the level of a neurotransmitter is low, in order to compensate for this. Downregulation refers to the opposite, reduced sensitivity or fewer receptors, which in turn serves to compensate for excess levels of a neurotransmitter. In the case of nicotinic receptors, the story is a little more complicated, and can be explained as follows (Dani & Heinemann, 1996): Upon smoking a cigarette, a small pulse of nicotine activates nAChRs that directly or indirectly induce dopamine release that provides a pleasurable effect. With continued use, nicotine builds up to a slow steady-state concentration that causes significant nAChRs desensitization and over time inactivation. There is evidence that nicotinic receptor turnover decreases following inactivation, leading to an increased number of nAChRs. In between cigarettes, during sleep, or under conditions of abstinence while attempting to stop smoking, nicotine levels drop and a portion of the inactive nAChRs recover to a responsive state. Because of the increased number of nAChRs that have now become responsive, some cholinergic systems become hyperexcitable to acetylcholine, contributing to the drive for the next cigarette. Thus smokers may medicate themselves with nicotine to regulate the number of functional nAChRs. Note that this is still only a theoretical model, but it explains the powerful reinforcement experienced when smoking after a period of abstinence, even overnight. Understanding receptor function can also explain the rapid development of acute tolerance to nicotine’s effects, which would drive continued smoking.

**Central Nervous System Effects of Nicotine**

**Release of neurotransmitters and their actions**

**Neuropharmacologic effects of nicotine:** We have focused primarily on the actions of nicotine in terms of its effect on activating nicotinic receptors in the mesolimbic system, which promotes release of dopamine. It is also important to note that nicotine has many effects on different neurotransmitter systems, probably due to the fact that nicotinic receptors of all kinds are distributed throughout the brain. For example, release of norepinephrine can promote stimulation and arousal; acetylcholine has effects in terms of improving short-term memory and cognition (attention); glutamate affects memory and cognition. Nicotine also stimulates activity of endogenous opioids, possibly contributing to its stress-reducing and analgesic effects.

**Non-nicotine-related effects of smoking that may be related to dependence: MAO:** Recent studies have examined the role of monoamine oxidase A and B (MAO A & B) in the human brain. MAO breaks down neurotransmitters such as dopamine, serotonin, and norepinephrine. Using neuroimaging techniques, it has been shown that cigarette smokers have a reduction in brain MAO B of about 40% relative to nonsmokers and former smokers. Smokers have a 28% reduction in brain MAO A relative to nonsmokers. MAO A and B inhibition is associated with enhanced activity of dopamine, so inhibition of MAO could be reinforcing. This could also account for higher rates of smoking among individuals with symptoms of depression.
Interestingly, nicotine does not inhibit MAO at physiologically significant levels, so some other as yet unknown compounds in tobacco smoke have this property. Currently, clinical trials are underway to evaluate the efficacy of MAO inhibitors for smoking cessation.

Objective: Describe Nicotine’s Pharmacologic Properties, Including its Primary Physiological and Psychological Effects, as Well as its Pharmacokinetic Properties that Predispose Toward Development of Nicotine Dependence

Nicotine pharmacology; Nicotine was used by Langley & Dickinson as early as 1889 to explore the functions of the autonomic nervous system by applying nicotine to post-sympathetic ganglia, resulting in release of norepinephrine or acetylcholine. This discovery sparked a revolution in the field of physiology in terms of understanding the actions of autonomic functioning and neurotransmitters. Ironically, research on physiological effects and pharmacological properties, in particular with reference to understanding the reinforcing value of nicotine, was neglected until the past 20 years and really, the past decade. This is in part attributable to the fact that nicotine was not even recognized as a psychoactive compound capable of producing dependence until relatively recently. This may have had something to do with the tobacco industry’s continuing attempts to portray smoking as merely a pleasurable habit, at worst.

Nature of tobacco products

Production and modification of nicotine yields; As early as the 1950s, internal tobacco industry documents indicate that the industry considered the cigarette to be a sophisticated nicotine delivery device. The tobacco industry has the ability to carefully titrate the amount of nicotine in cigarettes. In the process of picking the leaves from the stalk of the tobacco plant, supervisors use a four or five tier system, literally how high the leaves are up on the stalk, to control nicotine yield. Nicotine is more concentrated in the upper leaves, so by mixing the proportion of upper and lower leaves the yield of nicotine can be manipulated very effectively. It is also worth mentioning that nicotine yield as indexed by the “smoke machine” method can be quite deceptive. For example, low tar cigarettes may contain more nicotine than high tar cigarettes. More important in terms of treatment is the smokers’ tendency to compensate for the manufacturing processes that make cigarettes low yield (e.g., faster burn, less tobacco, ventilation holes) by learning to smoke these cigarettes more effectively by blocking filter holes, smoking more of the cigarette, puffing more frequently, etc. This is referred to as nicotine regulation.

Primary physiological and psychological effects of nicotine

Peripheral Effects of Nicotine; Some of the peripheral effects include the following: Heart rate; Blood pressure; Cardiac output; Vasoconstriction; Metabolic rate; Lipolysis; Skeletal muscle relaxation; Appetite suppression; EEG desynchronization; ACTH → Adrenal steroids. Some of these peripheral effects may also reinforce continued use, such as effects on metabolism, and increased circulation of adrenal steroids (e.g., cortisol).

Primary psychological effects of nicotine: As noted before, tobacco, and more specifically nicotine, exerts a wide variety of psychological and behavioral effects. These include, among others, stimulation, arousal, improved memory and attention (short term), increased speed of cognitive processing, relaxation, stress reduction, analgesia, mood improvement (in particular
alleviation of depressed mood), suppression of appetite, and social facilitation (e.g., at a social gathering). There is some controversy about whether some of these effects are the result of relief of acute withdrawal or direct effects. Studies with non-smokers suggest that some of these effects are actual enhancements. Whether these are direct effects or relief of withdrawal, these effects constitute an important source of reinforcement for smokers.

**Implications for addiction:** Multiple reinforcing effects of tobacco mean that individuals come to depend on nicotine to reliably produce these effects and may rely increasingly on nicotine to produce these effects as a substitute for obtaining reinforcement in other ways. In other words, nicotine replaces natural rewards. This is partly a functional definition of dependence: what smoking does for an individual. When people use nicotine, they FEEL GOOD! It is also important to note that: (1) These reinforcing effects may be very short-lived (i.e., only a few seconds or minutes in duration), and (2) Tolerance may develop to these effects. This means that smokers who have come to depend on nicotine to produce these effects may continually “chase” these effects as they are less reliably produced in an acute sense. There is also the possibility that smokers selectively remember the most “reinforcing” smoking experiences in these terms, driving smoking behavior to re-experience these peak experiences.

**Pharmacokinetics and Nicotine Metabolism**

**Absorption of nicotine:** Nicotine is distilled from burning tobacco, carried on tar droplets that are inhaled, and deposited in the small airways and alveoli in the lungs. The absorption of nicotine across biologic membranes depends on pH. The pH from flue-cured tobacco found in most cigarettes is acidic (pH 5.5). At this pH the nicotine is primarily ionized and does not cross cell membranes rapidly. Hence there is little absorption by the tissues lining the mouth and throat. However, when tobacco smoke reaches the small airways and alveoli of the lung, nicotine is absorbed rapidly regardless of the pH of the smoke. By contrast, the pH of smoke from air-cured tobacco, such as that found in pipes, cigars, and some European cigarettes, is alkaline (pH 8.5). Smoke from such products is absorbed easily in the mouth. There is also considerable variability in the amount of nicotine that may be absorbed from these products. For example, it is currently unknown how much nicotine is absorbed from cigars, but the little research that has been conducted suggests the levels may be considerable.

**Plasma nicotine concentrations as a function of smoking a cigarette, nasal spray, vapor inhaler, and nicotine gum:** The time-course of absorption of nicotine from various tobacco and nicotine replacement products clearly show that cigarettes offer the most efficient delivery, with the most rapid uptake, due to first pass entry into the circulation from the lungs to the heart. Blood concentrations rise quickly during smoking and peak at its completion. The bolus effect refers to the spike in blood nicotine levels that occurs with each puff of a cigarette. Using heart rate as a marker, it has been shown that rapid nicotine dosing (i.e., by smoking) produces a much greater effect than does slower administration of a similar dose of nicotine. Likewise, the subjective effects of smoking a cigarette are greater than the subjective effects after nicotine exposure from nicotine gum, which is in turn greater than after transdermal patch delivery of nicotine. It is thought that this rapid exposure to the bolus of nicotine has direct and powerful effects on neuronal receptors in the mesolimbic dopaminergic system, and can therefore be particularly reinforcing. Abuse liability of nicotine delivery systems appears to be directly
related to the rapidity with which nicotine is delivered: faster delivery equals more likely to be abused.

**Absorption of nicotine:** The smoker can manipulate the dose of nicotine on a puff-by-puff basis (“finger tip control”). The intake of nicotine depends on such factors as puff volume, depth of inhalation, rate of puffing, and intensity of puffing. Because of this complexity, the dose of nicotine cannot be predicted from nicotine content of the tobacco product. Dose can only be determined through measuring blood levels and rate of elimination. There is wide variability in the amount of nicotine absorbed among smokers. One study found that the average intake was 37 mg/day (range 10-79); average intake per cigarette was 1.0 mg (range 0.37-1.56). For smokeless tobacco, these figures differ: absorption is slower with a peak concentration reached at 30 minutes, but there is persistent absorption for up to 60 minutes after the smokeless tobacco is removed. The average absorption per gram of moist snuff is 4.8 mg.

**Distribution of nicotine:** Smoking is a relatively unique form of systemic drug administration because it enters the circulation via the pulmonary rather than the portal or systemic venous circulation. There is similarity in this regard to smoking crack cocaine, which accounts in large part for crack cocaine’s ‘high’. Nicotine absorbed through the lungs reaches the brain more quickly than if it were injected intravenously. However, nicotine clears quickly from the brain as it is distributed into other body tissues. This rapid clearance from the brain could have something to do with the need for continuous rapid dosing of nicotine via smoking. Nicotine crosses the placenta easily and is found in the amniotic fluid and umbilical cord blood of newborns. Fetal exposure to nicotine has been associated with increased risk of sudden infant death syndrome, developmental problems, predisposition to attention deficit and conduct disorders, and even to later adult criminal behavior. It has also been linked to increased risk of smoking among youth and young adults, and to increased risk of nicotine dependence.

**Elimination of nicotine:** Nicotine is rapidly metabolized and is eliminated primarily (70-80%) by hepatic metabolism by way of C-oxidation (cytochrome P450) to cotinine, the major metabolite. About 10-20% of nicotine is directly excreted unchanged in urine. The half-life of nicotine averages about 2 hours, but there is considerable variability among individuals (range, 1-4 hours). The short half-life has important implications for smoking insofar as smokers need to maintain a steady level of nicotine in the blood, so they will work to constantly dose themselves when they are able. Cotinine has a relatively long half-life of about 16-20 hours. For this reason, it is commonly used as a measure of nicotine intake over the past few days, and is used to validate reports of nonsmoking in clinical trials. It has long been thought that cotinine was inactive, but recent studies indicate it might have some psychoactive properties and serve to reduce symptoms of nicotine withdrawal albeit only mildly.

**Factors influencing the elimination of nicotine:** Several factors influence the elimination of nicotine, which can have consequences for use and dependence. For example, if nicotine is cleared slowly from the body, there may be less need to re-dose quickly. If it is cleared rapidly, then the smoker may need to re-dose on a more frequent basis. The level of renal excretion depends on urinary pH and urine flow, and accounts for 2-35% of total elimination. More nicotine is excreted in acid urine. It has been proposed that the excretion rate and the pH of urine affect craving and addiction. Other factors influencing metabolism of nicotine include
gender (males may metabolize nicotine faster than females; consuming a meal (increases nicotine); ethnicity (African-Americans metabolize cotinine more slowly than Caucasian smokers); genetic effects (About 5% of the population are carriers of a defective CYP2A6 gene, which decreases the efficiency of nicotine metabolism in the liver. These carriers are less likely to become smokers, and if they smoke they are likely to smoke less than smokers without the gene defect). Essentially, any mechanism that decreases metabolism or elimination of nicotine leads to longer and higher plasma nicotine concentrations and less need to redoses. Slower metabolism means less addiction potential.

**Timecourse of nicotine in the body**

*Timecourse of nicotine in the body:* Smoking is considered to be a process of intermittent dosing of nicotine, which is relatively rapidly eliminated from the body. There is considerable peak-to-trough variability in blood levels from cigarette to cigarette. However, in a manner consistent with a half-life of two hours, nicotine accumulates over six to eight hours to form a plateau, and then drops off rapidly during sleep. Nicotine is almost completely eliminated from the body after overnight abstinence, although this varies with factors related to smoking pattern (e.g., amount) and metabolism, so that some smokers will have eliminated all nicotine after sleep and others will still have a significant amount in their body. One implication of the rapid drop off of nicotine after sleep is that the smoker will feel the acute need to re-dose as quickly as possible after awakening. This is a marker for nicotine dependence.

*Nicotine blood levels during tobacco use:* Steady-state blood nicotine levels range from 10-50 ng/mL, with an average of about 30-35 ng/mL. The increase in blood nicotine concentrations after smoking a single cigarette ranges from 5-30 ng/mL, depending on how the cigarette is smoked. Peak blood levels are similar in cigarette smoking and smokeless tobacco use, although the rate at which the nicotine level rises is slower in cigar smokers and users of snuff and chewing tobacco. The rise time of various nicotine delivery systems is thought to play a role in reinforcement and addiction, and may explain the more addictive potential of smoked tobacco products, especially cigarettes. Smokers generally work to keep blood nicotine levels within a relatively tight upper and lower boundary. This is easily accomplished because of the exquisite “finger tip” control smokers have over dosing. The lower boundary is related to breakthrough of withdrawal symptoms. The upper boundary is related to symptoms of nicotine toxicity (nicotine poisoning - nausea, palpitations, tremor, etc.). This may explain in part why many smokers smoke at a very constant rate and amount (e.g., 1 ppd): they smoke just often enough to keep themselves out of withdrawal, but not so often as to experience a nicotine overdose. There are also thought to be two general styles of smoking, both of which may relate to nicotine dependence: 1) peak seeking, and 2) trough avoidance. The peak seeking smokers are those who probably smoke more for the bolus effect; this may have to do with maintaining arousal or providing stimulation. The trough avoiders are those who smoke largely to avoid withdrawal symptoms; they strive to maintain a very steady blood nicotine level during the day. This may have implications for treatment of nicotine dependence. For example, trough avoiders may be treated adequately with slow delivery systems such as the nicotine patch, inhaler, or gum. Peak seekers might require treatment with rapid infusion nicotine replacement, such as the nicotine nasal spray.
Nicotine regulation

Nicotine regulation; Smokers work, consciously or unconsciously, to maintain blood nicotine levels within the “therapeutic window.” Evidence for this comes from studies of low tar, low nicotine cigarettes. Research has convincingly demonstrated that smokers will compensate for low nicotine yields by smoking more effectively - blocking filter holes to prevent ventilation of smoke; smoking more of the cigarette; inhaling more rapidly and deeply; smoking more. Thus, low tar, low nicotine cigarettes are both less safe (from the point of view of carcinogen exposure), and do not show less potential for addiction. In one study, the nicotine yield of cigarettes was manipulated by having smokers smoke through a filter that eliminated 75% of nicotine. Before and after this manipulation, blood nicotine levels were measured. The results indicated that smokers who maintained similar blood nicotine levels after the manipulation (those who worked harder to keep a steady blood nicotine level) were more prone to relapse when they tried to quit compared to smokers who could tolerate a drop in blood nicotine levels (those who did not work to increase their blood levels).

Timecourse of nicotine in the body; When blood nicotine concentrations are averaged over the course of a day, the concentration increases rapidly with the first few cigarettes, is maintained throughout the day at a relatively constant level, and drops off rapidly during sleep.

Blood nicotine levels smoking 1 cigarette per hour; There is a notable pattern of peaks and troughs that occur in nicotine levels when someone smokes a cigarette each hour. Blood levels are near zero in the morning, and the average level as indexed by the trough values, increases gradually over the day. There is considerable variability in actual levels because of the peak effects associated with acutely smoking each cigarette. The peak and trough levels may each have significance for maintaining smoking.

Tolerance

Definition; Smoking more to achieve the same effects as were achieved previously at lower doses.

Types of tolerance; There are several different types of tolerance, a few of which will be described here. Acute or short-term tolerance refers to development of tolerance over a very brief period of time. In the case of smoking, this can develop between the first few cigarettes smoked during the day (e.g., heart rate boosts peak after the first few cigarettes, and do not change much thereafter if smoking rate is held relatively constant). Acute tolerance can even develop within smoking a single cigarette. There is abundant evidence for this sort of tolerance in smokers. Chronic tolerance refers to tolerance that is not lost between smoking episodes, or even after relatively long periods of abstinence. This is a kind of residual tolerance. Metabolic tolerance refers to the body clearing nicotine more actively as a result of prior exposure to nicotine. This would result in less nicotine and therefore less effects of nicotine. There is some evidence that smokers metabolize nicotine more quickly than nonsmokers. Functional tolerance
refers to some adaptations that may take place to counter the anticipated effects of nicotine. These could be conditioned (learned) effects. For example, when the individual anticipates that smoking will take place, heart rate is decreased to counteract the boost in heart rate that occurs with smoking. There is also evidence for functional tolerance in smoking. Functional tolerance has a lot to do with the smoker’s familiar environment (smoking cues) that might trigger adaptation mechanisms.

**Factors influencing development of tolerance:** Included among the several factors influencing development of tolerance are: exposure to nicotine (both duration and amount); pattern of exposure (e.g., intermittent vs. steady); learning/environmental factors (pairing of certain stimuli with smoking).

**Motivational significance of tolerance:** The motivational significance of tolerance lies in the possibility that smokers need to smoke more to attain the same desired effects as achieved previously with a lower dose, or that acute desired effects wear off quickly so that the smoker constantly tries to recapture the immediately prior experience. However, tolerance is not easily assessed (e.g., typically by self-report) and so is probably not very accurate. Moreover, research has not established a significant relationship between tolerance and outcomes among smokers trying to quit.

**Withdrawal**

**Nicotine Withdrawal: DSM IV Signs and Symptoms**

**DSM IV Criteria for Nicotine Withdrawal:** Along with tolerance, withdrawal is thought to be a hallmark of physical dependence. Some models of drug dependence hold that you cannot have dependence without tolerance and withdrawal. Signs and symptoms of nicotine withdrawal were not well characterized until the late 1970s and 1980s. Part of the reason for this was that many believed that the nicotine withdrawal syndrome was nonexistent or so mild as to be meaningless. When compared to withdrawal from alcohol or opiates, this may seem to be the case. However, more careful research has demonstrated that nicotine withdrawal is essentially a coherent syndrome. There appear to be important individual differences in the intensity and temporal patterning of the syndrome, with some individuals experiencing very intense and incapacitating symptoms. It makes sense to think that withdrawal will drive smoking behavior; smokers smoke in part to relieve symptoms of withdrawal. There is some controversy about whether withdrawal is related to relapse among smokers trying to quit. More reliable studies indicate that increases in craving and sadness specifically are related to subsequent relapse. The timecourse of symptoms also seems to vary, with most symptoms subsiding within two weeks on average; but craving and appetite increases seem to persist for much longer periods of time.

**Some characteristics of nicotine withdrawal:** A key feature of physical dependence on a drug is a withdrawal syndrome. Individuals experience differences both in the intensity and the timing of their withdrawal symptoms.

**Individual differences in withdrawal profiles over time:** There is considerable individual variability in the timecourse of symptoms. For example, different groups of smokers were found to experience different patterns of withdrawal symptoms: (1) a classic pattern; withdrawal
peaked and then declined after a few days, and (2) an atypical pattern; withdrawal peaked much later, at around 30 days. The latter pattern was more predictive of relapse, which may have to do with the surprise and discouragement involved in experiencing a sudden increase in withdrawal symptoms after doing well for some time. The clinical implications are that withdrawal symptoms should be monitored carefully, and treated as they arise on an individual basis. There are no hard and fast rules about what to expect when someone quits, although a past history of withdrawal symptoms may be informative.

**Summary of smoking-body weight relationship:** Women tend to gain more weight than men when they quit smoking (3.8 vs. 2.8 kg). A subset of both men and women (9.8% and 13.4%) are likely to gain a major amount of weight when they quit smoking (i.e., in excess of 13 kg). However, amount of weight gain is influenced by several factors including race (blacks > whites), age (younger > older) and smoking rate (heavier > lighter). Fear of weight gain is an important deterrent to smoking cessation among women. Women report that they are less willing than men to tolerate weight gain if they quit smoking. Moreover, concerns about post cessation weight gain are particularly salient in younger and overweight women. Some evidence suggests that weight gain during smoking cessation predicts early relapse to smoking. Paradoxically, however, other studies suggest that longer-term abstinence is associated with greater weight gain. Behavioral weight control interventions coupled with smoking cessation treatment appear to impede smoking cessation. However, vigorous exercise programs and pharmacologic adjunctive treatments such as nicotine gum or serotonergic agents may hold some promise in preventing post-cessation weight gain.

**Objective:** Describe the nature of nicotine dependence in terms of diagnostic criteria and the functional significance of the criteria

**Definitions and manifestations of nicotine dependence:**

**Evidence for Nicotine Dependence: Psychoactive Effects:** The 1988 Surgeon General’s report on Nicotine Addiction emphasized psychoactive effects as being an important feature of nicotine dependence.

**Evidence that nicotine has psychoactive, pleasurable effects (as indicated by subjective liking of morphine, buprenorphine, pentazocine, amphetamine, nicotine, cannabis, pentobarbital, chlordiazepoxide, and zomiperac):** Studies done with drug addicts who were also smokers have shown that nicotine can be perceived as having psychoactive qualities, most notably pleasurable effects. Addicts who were injected with various drugs, but did not know what they were receiving, and had to rate their subjective experiences, rated nicotine very highly.

**Evidence that method of administering nicotine has implications for pleasurable effects (as shown by comparisons in subjective liking of cigarette, IV nicotine, nasal spray, vapor inhaler, nicotine patch, and nicotine gum):** The method of delivery of nicotine (i.e., smoking vs. gum, vs. inhaler, etc) can have profound effects on subjective pleasurable sensations. This could have important implications in terms of the addiction potential of different delivery methods.

**Comparison of nicotine with other drug addictions:** Drug addicts who were also smokers were asked which drug was hardest to give up. Most replied nicotine.
**DSM IV Criteria for Psychoactive Substance Dependence;** Let us take a moment to review specifically the criteria as laid out in DSM IV. It is important to note that not all criteria are a good fit with nicotine. For example, “important social, occupational, or recreational activities are given up or reduced because of substance use” has become more relevant with recent bans of smoking in public buildings. The criterion having to do with a great deal of time spent in activities necessary to obtain the substance is not a great fit with smoking or other tobacco use, largely because tobacco is legal and readily available. These may become more discriminating criteria as more restrictions are placed on use of tobacco products, e.g., in public places, and as tobacco itself may become more regulated and harder to obtain. There are additional problems with these diagnostic criteria. Three or more of the criteria need to be met to achieve a diagnosis of nicotine dependence, but this is an arbitrary number. Factor analyses suggest that the criteria do not form a uniform scale, and therefore may not represent a uniform syndrome. There is a tendency for too many smokers to be diagnosed as dependent using these criteria. Despite these problems, the advantage of using the DSM IV system is that it provides for a common language so that clinicians and researchers can communicate better. It is a tool that may be used to guide treatment (although more research needs to be done on this). It legitimizes the disorder, allowing (hopefully) for improved chances for reimbursement for treatment.