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Historical and Current Perspective on Tobacco use and Nicotine Addiction

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Abstract

Although the addictive influence of tobacco was recognized very early, the modern concepts of nicotine addiction have relied on knowledge of cholinergic neurotransmission and nicotinic acetylcholine receptors (nAChRs). The discovery of the “receptive substance” by Langley, that would turn out to be nAChRs, and “*Vagusstoff*” (acetylcholine) by Loewi, coincided with an exciting time when the concept of chemical synaptic transmission was being formulated. More recently, the application of more powerful techniques and the study of animal models that replicate key features of nicotine dependence have led to important advancements in our understanding of molecular, cellular, and systems mechanisms of nicotine addiction. In this Review, we present a historical perspective and overview of the research that has led to our present understanding of nicotine addiction.

Introduction

Tobacco use spread around the world from its origins in the Americas (Box 1). Early anecdotal accounts of tobacco’s captivating influence and of associated health consequences inspired research into its addictive properties. However, our present molecular and cellular concepts of nicotine addiction (Glossary) arising from tobacco use are relatively recent. The specific investigation of nicotine addiction arose from a long history of basic cholinergic research. It is valuable, captivating and, for some of us, even romantic to look back at the early work that laid the foundation for our present understanding of nicotine addiction. The early discovery of autonomic cholinergic transmission and nicotinic acetylcholine receptors (nAChRs) spurred physiological characterization of the neuromuscular junction (NMJ). Those studies served as guideposts, or they may more appropriately be called points-of-reference, for the more recent investigations that revealed surprisingly different and diverse mechanisms of nicotinic cholinergic transmission in the brain. Most commonly, humans self-administer nicotine using an exquisite dosing device, the cigarette. Acting directly and mainly through nAChRs, nicotine impinges upon neural circuitry that shapes short-term and

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long-term behavior. This review provides a compact summary of tobacco use and the scientific advances that led to the modern research into nicotine addiction. We hope this brief article and the referenced review publications and books will inspire both novices and experts to explore these fascinating historical events further.

Brief History of Nicotinic Cholinergic Signaling

While tobacco use spread around the world (Box 1), interest in the active ingredients and their effects stimulated scientific investigation. Early in the 20th century, nicotine had been synthesized and the classic studies of drug action by John Newport Langley and his colleagues had begun¹. These initial efforts with nicotine culminated in the 1905 study in which Langley refers to the “receptive substance” that would eventually turn out to be nAChRs².

As the concepts of specific receptors, drug pharmacology, and synaptic transmission were being formulated and advanced (Figure 1), Otto Loewi published the results of his most famous experiment, indicating the importance of neurotransmitters in chemical neural communication³ (Figure 2). Two frog hearts were separately bathed in saline solutions, and the vagus nerve was stimulated to slow the beat of one frog heart. When solution was taken from that bath and applied to the second bath, it slowed the beat of the second frog heart. This *Vagusstoff*, as Loewi termed it, was identified by Henry Dale with his colleagues to be acetylcholine (ACh). They identified ACh from ergot extracts and, then, demonstrated that it had inhibitory action upon the heartbeat⁴.

The mechanistic and quantitative analysis of nicotinic synaptic transmission began at the NMJ and was catapulted forward by the works of John Eccles, Bernard Katz, and Stephen Kuffler⁵. As the concepts of nicotinic cholinergic quantal release and postsynaptic response were being delineated^{6, 7}, biochemical and structural characterization of the nAChR was aided by the extremely dense expression of muscle-like receptors in the *Torpedo* electric organ and by the high affinity binding of the snake toxin, α -bungarotoxin⁸. The kinetics of the muscle nAChRs were finally examined in detail using single-channel electrophysiological approaches^{9, 10}. The sequences of the *Torpedo* and the muscle nAChRs were revealed as the subunits were cloned¹¹. The structure of nAChRs was progressively delineated (Figure 3)^{8, 12}, leading to an understanding of ACh binding and gating that was critically advanced owing to images from 2-dimensional nAChR crystals^{13, 14} and from the crystal structure of the molluscan ACh binding protein¹⁵.

Although behavioral effects of nicotine had been recognized and described hundreds of years earlier, the physiological roles and importance of neuronal nAChRs in the brain were not widely appreciated until as recently as the early 1980s. Cloning of neuronal nAChR subunits¹⁶ and their identification throughout the central nervous system (CNS) by *in situ* hybridization¹⁷ generated more attention to nAChRs within the brain. Neuronal nAChRs were found to be much more diverse than the several kinds of muscle nAChRs. Neuronal subunits formed heteropentameric nAChRs in combinations of (2–6) and (2–4). Some subunits (7–9) also were found to form homomeric nAChRs, and 10 formed a heteromeric channel with 9 subunits^{8, 18, 19} (Figure 3). Consequently, the number and diversity of neuronal nAChRs were remarkably large.

The functional progress began by characterizing nAChR currents from neuronal cells mainly cultured *in vitro* and later using *in vitro* brain slices^{8, 18, 20–25}. The modality of nicotinic synaptic transmission differs significantly between the peripheral and the central nervous systems. Muscle and ganglionic nAChRs commonly mediate fast, direct nicotinic synaptic transmission at the NMJ and autonomic ganglia (Figure 4A). In the mammalian brain, however, sparse diffuse cholinergic innervation more commonly provides a slower signaling

that arises as ACh diffuses away from the immediate release site^{25, 26}. This type of neurotransmitter signaling is often called volume transmission, as a convenient short hand.

Nicotinic receptors operate in the brain using a wide variety of mechanisms. The most well studied process is modulation of neurotransmitter release by presynaptic nAChRs (Figure 4B)^{22, 23, 25, 27–29}. The activity of presynaptic nAChRs initiates a direct and indirect intracellular calcium signal that enhances neurotransmitter release^{22, 30–36}. Properly localized calcium signals mediated by nAChRs initiate intracellular signalling that is known to modify synaptic transmission^{37, 38}. Furthermore, properly timed presynaptic nAChR activity, arriving just before electrical stimulation of glutamatergic afferents, boosts the release of glutamate and enhances the induction of long-term synaptic potentiation^{39, 40}.

Nicotinic receptors also have different patterns and levels of expression at preterminal, axonal, dendritic, and somatic locations where they modulate excitability and neurotransmitter release^{18, 24, 25, 41, 42}. Preterminal and axonal nAChRs located before the presynaptic terminal indirectly affect neurotransmitter release by activating voltage-gated channels and initiating local action potentials (Figure 4C)^{41, 43}. Somatodendritic receptors initiate or modulate synaptic inputs to the soma, and thereby modulate plasticity and information flow. Postsynaptic nAChRs also contribute to the depolarization and intracellular calcium signal normally assigned to glutamatergic synapses^{39, 40}. Because ACh spreads from synaptic and possibly non-synaptic release sites²⁶, nAChRs at non-synaptic locations influence not only the excitability of neurons but also their overall electrical and chemical responsiveness²⁵.

Brief History and Scientific Advances of Nicotine as an Addictive Drug

Although the modern concepts of tobacco or nicotine addiction are relatively recent, the captivating influence of tobacco was known by Native Americans and was quickly documented by Europeans⁴⁴. For example, Francis Bacon, an English philosopher, statesman, and Renaissance scientist, observed the spread of tobacco and wrote: “*In our time the use of tobacco is growing greatly and conquers men with a certain secret pleasure, so that those who have once become accustomed thereto can later hardly be restrained therefrom.*” – Francis Bacon, *Historia vitae et mortis* (1623) quoted by others⁴⁴.

Scientific progress indicating that tobacco smoke is addictive post-dates the first evidence in the early 1950s that smoking was associated with a substantially increased incidence of lung cancer^{45, 46}. Initially, tobacco smoking was seen as a habit, but by 1971 researchers were beginning to recognize that many smokers were addicted to nicotine present in tobacco smoke^{47, 48}. Much of the work focused on the evidence that chronic or repeated exposure to nicotine results in a withdrawal effect if the drug is precipitously withheld. By the 1980s, the validity of the nicotine dependence hypothesis was becoming more widely accepted, and the concept of using nicotine replacement therapy to aid successful cessation attempts had moved to the fore^{49–51}. This period also saw the development of tests that could measure the degree of tobacco dependence. The best known is the Fagerstrom Test of Nicotine Tolerance & Dependence^{52, 53}, which remains the standard measure of tobacco dependence. This test allowed researchers to evaluate anti-smoking treatments and, then, to relate the cessation outcomes to the ways in which people smoked and their level of dependence.

Intracranial self-stimulation and nicotine self-administration

The idea that nicotine caused dependence also influenced work with animal models. Although some early animal studies on nicotine pre-dated the wide acceptance of nicotine dependence in humans^{54, 55}, the results with humans largely spurred research with animal models. Dependence upon nicotine is characterized by compulsive drug-seeking and drug-

taking behavior. The psychological and neurobiological factors that underlie drug taking and the reinforcement of that behavior have been most directly examined experimentally using animals trained to self-administer nicotine through indwelling venous catheters (Figure 5A). Nicotine self-administration was difficult to establish when compared to other drugs, such as cocaine⁵⁶. The difficulty arose, at least in part, because the dose of nicotine had to be optimized to a restricted range. If the nicotine dose was too low, the positive reinforcing aspects were not initiated, but if the dose was too high, peripheral and central aversive effects dominated. Thus, the nicotine dose dependence followed a tightly restricted inverted-U relationship, and only the optimal doses near the top of the inverted U supported nicotine self-administration (Figure 5B).

Singer and colleagues^{57–59} were among the first to show that experimental animals could be trained to self-administer small intravenous doses of nicotine. However, the seminal studies of Corrigan and colleagues⁶⁰ were the first to describe a robust methodology for studying nicotine intravenous self-administration in rats. This methodology was a pivotal development since it allowed researchers to investigate both the psychological and neurobiological substrates that influence nicotine reinforcement. Subsequent studies showed that nicotine reinforcement in this self-administration model depends upon the stimulation of the mesocorticolimbic dopamine (DA) neurons^{61, 62}. Since the earliest studies of intracranial electrical self-stimulation (Figure 5C), cortical and limbic structures of the brain have been identified as mediating reward. In particular, the mesocorticolimbic DA system plays an important role in intracranial self-stimulation, in drug self-administration, and in processing environmental reward.

The landmark studies of the brain reward circuitry predated the initial nicotine self-administration advances, but those fields of reward circuitry and drug addiction later converged⁶³. In the 1950's, James Olds and his colleagues showed that particular neural nuclei and fiber tracts supported intracranial electrical self-stimulation (Figure 5C)^{64, 65}. Rats worked to the exclusion of other goals to self-administer intracranial electrical stimulation when delivered to “rewarding” regions of the brain^{66–68}. In this same time period, Arvid Carlsson and his colleagues showed that DA was a neurotransmitter⁶⁹, and midbrain DA systems had an important role in brain self-stimulation^{70–72}. Self-stimulation of the medial forebrain bundle facilitated DA release, and DA receptor antagonists or DA neuron lesions inhibited brain self-stimulation^{70, 73, 74}. The DA efferents originating from the midbrain ventral tegmental area (VTA) and targeting the prefrontal cortex and nucleus accumbens (NAc) of the ventral striatum became recognized as paramount neural structures shaping reward-related behavior^{75–78}. These mesocorticolimbic DA pathways became the major focus of research into reward-motivated behavior and drug addiction.

Mesocorticolimbic dopamine system

The studies of brain reward circuitry and mesocorticolimbic DA signaling preceded the demonstration that nicotine self-administration depended upon the stimulation of DA neurons^{61, 62}. Nicotine injection into the whole animal induced an increase in DA neuron firing (as measured by *in vitro* and *in vivo* electrophysiological recordings)^{79, 80}, and elevated DA concentrations particularly in the NAc (as measured by *in vivo* microdialysis)⁸¹. The increased DA release in the NAc shell was thought to mediate the reinforcing properties of the drug, and this process drove the acquisition and maintenance of responding for the primary reinforcer^{82, 83}. Subsequent studies suggested that the DA projections to the shell and core subdivisions of the NAc mediated differential and complementary components of nicotine dependence^{81–88}.

Recent studies showed that long-lasting DA neuron activity was driven by nicotine-induced synaptic potentiation of excitatory glutamatergic afferents onto DA neurons^{25, 89}. Nicotine

has multiple actions upon synaptic events and circuitry within the midbrain DA centers. By activating presynaptic nAChRs (Figure 4B), nicotine boosts glutamate release, and by activating postsynaptic nAChRs at glutamate synapses, nicotine boosts the postsynaptic depolarization and calcium signal mediated by glutamate receptors. Both of these actions enhance the likelihood of initiating synaptic potentiation that increases DA neuron activity. In addition to its direct effects on midbrain DA neurons, nicotine also alters DA signaling in the NAc itself^{90–94}. Taken together, these results implicate the mesocorticolimbic DA system and indicate that nicotine has behavioral and neurobiological properties that are like those of other psychostimulant addictive drugs^{95–97}.

Withdrawal from nicotine

Much of the early work on nicotine addiction in animals focused on measures of withdrawal to assess the level of dependence. The work of David Malin and his colleagues was seminal in this regard. They were the first to describe a nicotine abstinence syndrome in rats, which they argued models important components of the abstinence syndrome experienced by many smokers when they first quit⁹⁸. More recent experimental studies have employed a withdrawal model in which rats or mice are constantly infused with nicotine for a week or more before the drug is precipitously withdrawn or antagonized by the administration of a nAChR antagonist. The abstinence syndrome evoked in this model is attenuated by the re-administration of nicotine (which is comparable to nicotine replacement therapy in humans). The abstinence syndrome also is attenuated by pharmacotherapies (e.g., the atypical antidepressant, bupropion) that treat tobacco dependence in humans⁹⁹. Some behavioral consequences of nicotine withdrawal in this paradigm are mediated by the periphery, but there also is a CNS component^{100–102}. For example, CNS withdrawal effects are accompanied by decreased brain reward function that is estimated by measuring the threshold for intracranial self-stimulation of brain reward pathways¹⁰³ (Figure 5C). Stimuli or drugs, such as nicotine, reduce the threshold current for self-stimulation. By contrast, nicotine withdrawal evokes a robust increase in the threshold current, which is thought to reflect anhedonia (a reduced ability to respond to pleasurable stimuli), a core symptom of tobacco withdrawal¹⁰³. These methodologies continue to be used to the present day as a measure of the somatic and central symptoms of nicotine withdrawal¹⁰².

The anhedonia associated with nicotine withdrawal has been associated with reduced extracellular DA in the NAc shell¹⁰⁴. A number of brain regions that innervate the NAc and VTA have been implicated in the expression of drug withdrawal¹⁰⁵. Recent studies have begun to focus on the neurons that project to the VTA from the lateral habenula. Those projections can inhibit mesoaccumbens DA neurons, providing a source for negative reward^{106, 107}. In addition, the medial habenula is particularly rich in $\alpha 3$ and $\alpha 4$ subunits that are sometimes expressed in combination with the less common $\alpha 5$ subunit. In addition, a direct target of the medial habenula, the interpeduncular nucleus, expresses $\alpha 2$ subunits. All of these subunits contribute to nAChRs that have been implicated in the expression of the somatic symptoms of the nicotine withdrawal syndrome^{108, 109}. These nAChR subtypes also are implicated in the aversive effects (negative reward) experienced at higher doses of nicotine¹¹⁰. Their action in the medial habenula and interpeduncular nucleus contribute to the decrease in nicotine self-administration seen at higher nicotine doses. Thus, receptors comprised of $\alpha 2$, $\alpha 3$, $\alpha 5$, and $\alpha 4$ subunits contribute to the falling arm of the inverted-U dose-response curve for nicotine self-administration (Figure 5B).

Up-regulation of nAChRs

Another important advance toward understanding the effects of chronic nicotine came in the early to mid-1980's. After prolonged exposure to nicotine there is an "up-regulation" of nicotine binding sites. Of the many drug-induced neuroadaptations caused by chronic

nicotine, this up-regulation is the most widely appreciated, but its mechanistic importance is still actively under investigation. The nAChR up-regulation is observed in rodent animal models^{111, 112} and in postmortem tissue from the brains of smokers as increased radiolabelled nicotine binding^{113–115}. The results suggest that prolonged exposure to a smoker's concentration of nicotine increases the binding and possibly the number of excitable nAChRs. However, the up-regulation is not uniform; there is variation in the up-regulation across locations of the brain and among the nAChR subtypes. For example, the presynaptic regulation of catecholamine release appears to be enhanced by nAChR up-regulation, and this action may enhance the responses to a subsequent challenge with nicotine¹¹⁶. It also is hypothesized that nAChR up-regulation contributes to the development of sensitization: as more nAChRs become available to respond to the same nicotine dose, less nicotine is needed to cause the same effect. On the other hand, continuous exposure to nicotine caused by smoking throughout the day produces desensitization (Figure 3C) of particular nAChR subtypes, which may contribute to acute forms of tolerance. That is, more nicotine is needed to achieve the same effects because many nAChRs are desensitized and unable to respond, owing to maintained low concentrations of nicotine. During longer periods of smoking abstinence, such as overnight or during attempts to quit, when nicotine is not present, the up-regulated nAChRs recover from desensitization. Then, reactivation of an increased excitable population of nAChRs may play an early role in the expression of the nicotine abstinence syndrome^{117–119}.

Tobacco associated environmental cues and learning

Although the addictive properties of tobacco smoke clearly depend upon the presence of nicotine, the powerful addictive properties of tobacco reflect a complex interaction between the drug and the context in which it is delivered. When compared with other addictive drugs, nicotine alone in animal models does not seem to be as powerfully addictive as tobacco experienced by many smokers. Increasingly, researchers have begun to consider the role of the tobacco smoke vehicle in which nicotine is most commonly delivered. An early study showed¹²⁰ that the satisfaction experienced by smokers who inhale tobacco smoke is substantially diminished if the upper airways are anaesthetized with a local anesthetic. Rose and colleagues¹²⁰ concluded that the sensory components of tobacco smoke contribute to the satisfaction experienced by the smoker. In this case, the drug-associated sensory cues become conditioned (learned) reinforcers associated with smoking tobacco.

As the addiction process progresses, neural plasticity and neuroadaptations throughout the brain are influenced by the drug experience. Environmental stimuli become conditioned cues as they are paired with the unconditioned rewards arising from the nicotine dose delivered by tobacco use^{121–124}. For example, rodent studies have shown that pairing a sensory cue (normally a tone or light) with delivery of the drug in a self-administration paradigm enhances the reinforcing properties of nicotine¹²⁵. By repeated association with nicotine, the cue acquires reinforcing properties in its own right^{125, 126}.

In a similar manner, memories associated with addictive behaviors become internal motivational drives to continue drug use^{25, 127–129}. Learned associations arise as nicotine acts locally upon memory-related circuits¹³⁰ while also inducing DA release from midbrain centers¹²⁴. The cellular mechanisms underlying these system level effects arise in part from the ability of nicotine to alter local GABAergic inhibition, thereby, enhancing synaptic mechanisms that underlie systems-level learning^{124, 130}. The results indicate that nicotine induces a DA signal that serves to increase the probability and strength of synaptic potentiation that underlies drug-associated learning.

Because nicotine acts throughout the brain and influences synaptic mechanisms that normally mediate the neural plasticity of learning, cues associated with smoking come to

elicit neuronal activity in regions linked to attention, memory, emotion, and motivation¹³¹. Consequently, nicotine-associated cues reinstate extinguished nicotine-seeking behavior, contributing to relapse^{132, 133}. Inhibition of DA receptors significantly attenuates the magnitude of cue-elicited reinstatement of nicotine-reinforced behavior¹³⁴, and that result is consistent with a DA contribution during the associative learning linked to drugs of abuse¹²⁴.

In addition, other components of tobacco smoke may influence the addictive properties of nicotine by interacting with the neural responses to the drug. Although not addictive on their own, monoamine oxidase inhibitors, which slow the breakdown of monoamines such as DA, may affect the overall motivational impact of nicotine¹³⁵. Although it has been consistently established that nicotine has the behavioral and neurobiological properties of an addictive drug, environmental associations and components of the tobacco smoke vehicle play a pivotal role in the severity of the dependence developed by some smokers.

Future perspectives

The decreasing cost of sequencing the human genome has brought human genetic diversity into the forefront of mental health and addiction research. Genome-wide association analysis of single nucleotide polymorphisms (SNPs) has already linked nAChRs to tobacco use and health problems. For example, the CHRNA5-CHRNA3-CHRNA4 gene cluster, which encodes the 5, 3, and 4 nAChR subunits, has been implicated in various aspects of nicotine dependence and cigarette-related health issues¹³⁶. Individuals homozygous for the less common SNP, rs16969968, of the CHRNA5 gene are more likely to be heavy smokers and nicotine dependent^{137, 138}. Future efforts will expand the genetic links to various aspects of smoking, such as the initiation of use, the difficulty in quitting, and the risk for relapse. This research will indicate mechanistic pathways for more detailed animal studies that will ultimately indicate further targets for therapeutic interventions to aid smoking cessation.

The future holds more powerful experimental tools. New approaches are continually being added (Box 2) to the arsenal of methodologies used to study cholinergic mechanisms and addiction. One such advance toward understanding the roles of nAChR subtypes within the addiction process is the creation of genetically engineered mutant mice lacking specific subunits or containing gain-of-function subunits^{8, 139–142}. Studies with such mouse models have shown that 2-containing (α2) nAChRs mediate much of the reinforcing influence of nicotine^{143, 144}, and those receptors potently regulate DA release in the NAc^{92, 145}. Mutant knockout mouse models also helped to show that nAChRs containing the 5, 3, 2, and 4 subunits are implicated in the somatic manifestations of nicotine withdrawal^{108, 109, 146}. The next level of sophistication is rapidly entering the nicotinic field. Conditional knockout models and re-expression of a subunit on the null background have demonstrated the important nAChR subunit and its neural location for tasks involving reinforcement and cognition¹⁴⁷, passive avoidance¹⁴⁸, locomotion¹⁴⁴, and nicotine dosing¹¹⁰. Another significant advance is the ability to control the activity of specific neurons by introducing light-activated molecules (i.e., optogenetics). For example, channelrhodopsin-2 introduced into “cholinergic” habenula neurons was recently used to show that glutamate was co-released with acetylcholine¹⁴⁹. Yet another ever-expanding capability is the increased power of *in vivo* recordings from freely-moving animals¹⁵⁰. Dozens of neurons can be separately recorded from multiple areas of the brain while an animal performs a behavioral task.

In the future, the convergence of these powerful approaches will provide unprecedented data. Molecular, cellular, systems, and behavioral approaches will be combined to study the various animal models created as discussed above, as well as those models based on human

genetic association studies. As interesting and exciting as the past has been, the future promises even more innovation and surprises (Box 2).

Box 1. Brief history of tobacco use

Tobacco as we know it originated in temperate climates of America. The native populations chewed and smoked the leaves, and they spread the plant throughout the Americas^{44, 46}. By the time of Columbus's landing on San Salvador in 1492, tobacco had reached across the continent and nearby islands, and the leaves had become a form of barter. Through the 1500's tobacco use began to spread as Spanish, Portuguese, and later English sailors introduced its use at ports (Borio, G., 2007, The Tobacco Timeline; http://www.tobacco.org/resources/history/Tobacco_History.html). Early on, court physicians studied and fostered the plant. Jean Nicot de Villemain, the French ambassador to Lisbon, learned about the "medicinal" properties of tobacco, and introduced the plant to the French court. Eventually his name was used for the plant that has become the most widely cultivated tobacco, *Nicotiana tabacum* (Figure I), and for the addictive alkaloid, nicotine⁴⁴.

In 1612, John Rolfe began cultivating tobacco in Jamestown, the earliest successful English settlement in the present day United States. Within a few years, he married Pocahontas, the daughter of a Native American chief, and their relationship was later romanticized into American folklore. Very rapidly, tobacco became the primary cash crop and even a currency of the colonies and the early United States. In 1880 James Bonsack invented the cigarette-rolling machine, and commercial cigarettes became widespread. By the beginning of the 1900's, billions of cigarettes and cigars were sold yearly.

Through the early 20th century, cigarette use grew, scientific advances accelerated, and resistance to smoking began to grow. In 1950, epidemiological studies linked smoking to lung cancer and other diseases, and thereby extensively publicized the hazards of tobacco^{45, 46}. Shortly after, Ernst Wynder and colleagues induced tumors in mice by painting cigarette tar onto their exposed skin¹⁵¹. Those epidemiological and experimental studies spurred other research that led to the general scientific and government acceptance of a causal link between cigarette smoking and ill health. In 1965, when the US Congress passed the Cigarette Labeling and Advertising Act requiring a warning label on every pack of cigarettes, 42% of adults in the United States smoked¹⁵². Smoking rates have generally fallen in developed countries, and in 2006 about 21% of the adults in the US smoked (Rock, V.J., *et al.*, Cigarette Smoking Among Adults---United States, 2006. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5644a2.htm>). Demographic estimates for the early 2000's indicated, however, that there were more than 1.2 billion smokers worldwide, and 80% were in less developed countries. Presently, 5.4 million deaths worldwide are attributed to tobacco use, accounting for about 9% of deaths globally (WHO 2007 Report)^{153, 154}.

Box 2. Rapid progress in nicotine addiction studies

The general field of addiction and specific field of nicotine addiction arising from tobacco use have seen transformational advances in recent times. Like many areas of scientific research, the progress seems to be accelerating. Behavioral advances are being linked to underlying mechanisms, providing targets for therapeutic and prophylactic developments. Increasingly powerful techniques and experimental approaches enable scientists to address questions that were unapproachable only a decade ago. The excitement, energy, and progress seem unique to our time, but our impressions were

expressed well by Henry Dale more than 50 years ago. Dale, who identified ACh, when in his 80's wrote to his friend Thomas R. Elliott, who also had made seminal contributions toward understanding synaptic transmission⁴. An excerpt from Dale's 1958 letter expresses the dizzying rate of scientific advances he observed when visiting Bernard Katz's lab while Katz was in his astonishing prime: *"I feel almost bewildered by the kind of detail which such people are now elucidating with the aid of electron-ultramicroscopy, and also with an electrical recording which they can now achieve of the transmitted excitatory process at the motor end-plate of a single muscle fibre I find it really exciting to think of the contrast between physiology as we had it from Langley and Gaskell, and what it is becoming today. A great deal indeed has happened since you first suggested a chemical mechanism for the transmission of the excitatory process from a nerve ending; and it goes on happening with a constant acceleration."* – Letter, Dale to Elliott, 29 June 1958, Royal Society Archives quoted from Tansey (1991)⁴.

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Glossary

Addiction	A state in which drug taking is out of control. Chronic exposure to drugs of dependence evoke changes in the central and peripheral nervous systems that cause the behavioral and somatic signs of withdrawal when drug taking is terminated abruptly.
Anhedonia	A state in which the ability of the individual to experience and respond to pleasurable stimuli is blunted.
Conditioned cues/ stimuli	This refers to cues or stimuli that are paired repeatedly with the delivery of the addictive drug (or reward). The cues may be sensory (e.g., stimulus lights or tones) and applied within a behavioral chamber where they are tightly associated with the delivery of a drug of abuse (e.g., nicotine) or environmental contextual cues that relate to the availability of nicotine.
Mesocorticolimbic dopamine system	A neural pathway in the brain that projects from the midbrain to the cortex, the limbic structures, and extending to the striatum to include the NAc of the ventral striatum. The neurons release the neurotransmitter dopamine, which has been implicated in the rewarding/reinforcing properties of drugs of abuse.
Nicotine withdrawal	The somatic, emotional, and behavioral symptoms exhibited when nicotine is abruptly withdrawn following a period of chronic treatment or self-administration.
Receptor up- regulation	An increase in the density and/or function of the receptor evoked by chronic exposure to a drug. Chronic exposure to nicotine has been shown to cause up-regulation of nicotinic receptors in brains of both experimental animals and human smokers.

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Figure 1.

An historical pathway and representative contributors to our present use and understanding of tobacco. *1490's*: At their first encounter with Native Americans in 1492, Christopher Columbus and his crew of Spanish sailors were given merchandise, including dried tobacco leaves that they discarded because they had no use for them. Later, members of Columbus's crew were again given the highly prized leaves, and they were shown the process of smoking. *1560's*: As France's ambassador to Portugal, Jean Nicot sent tobacco products to the French court as a potential medicinal treatment in 1561. The tobacco plant, *Nicotiana*, and the addictive substance, nicotine, derived their names from him. *Early 1900's*: In the early 1900's, Henry Dale isolated acetylcholine and demonstrated that it was the parasympathetic neurotransmitter that Otto Loewi had called, *Vagusstoff*. *Mid-1900's*: In the 1950's, Ernst Wynder contributed to an epidemiological study linking smoking to cancer⁴⁵. Wynder and colleagues also painted cigarette tar onto the skin of mice during the first study using tobacco to induce cancer in a laboratory setting¹⁵¹. *Later 1900's*: Bridging from the 1960's to the present, Jean-Pierre Changeux has made important contributions to our understanding of the molecular and cellular properties and roles of nAChRs. Using genetically engineered mouse models, he and his colleagues also contributed detailed information about the roles of specific nAChR subtypes in the mesolimbic dopamine system during the nicotine addiction process.

Figure 2.

Didactic representation of Otto Loewi's most famous experiment, which was published in 1921³. The idea for the experiment came to him in a dream. Two beating frog hearts were isolated in containers of Ringer's solution. The vagus nerve was stimulated in one heart (A), slowing heart rate A. Fluid moved from container (A) and applied to the heart in container (B) slowed heart rate B. This demonstrated that a soluble substance released by the vagus nerve modulated the heart rate. He called the unknown substance *Vagusstoff*, and Henry Dale's lab later identified the chemical to be acetylcholine.

Figure 3.

Schematic representation of a generalized nAChR. (A) The arrangement of a single nAChR polypeptide subunit within the plasma membrane. The 4 transmembrane segments (M1–M4) of a nAChR subunit are oriented within the membrane, with both the amino and carboxyl ends being located extracellularly. (B) Many nAChRs are constructed from α and β subunits, with the most common nAChR subtype being the $\alpha 4 \beta 2$ nAChR in the mammalian brain. The $\alpha 7$ subunit forms the most common homomeric nAChR in the mammalian brain. More complex subunit combinations are possible, with more than one α and/or more than one β subunit combining to form other nAChR subtypes. Looking down on the receptor from above, the central water-filled cation-conducting pore is represented by the white circle in the center of the subunits. (C) A side cut-away view of the nAChR showing the subunits arranged around the central pore that passes through the membrane. There are 3 main conformational states of the nAChR: closed pore at rest, open pore with 2 acetylcholine (ACh) molecules bound to the agonist binding sites, and closed pore in the desensitized state with 2 ACh molecules bound.

Figure 4.

Didactic representations of nAChR subtypes at different synaptic locations. (A) Fast, direct, nicotinic cholinergic synaptic transmission is shown with ACh (green circles) being released from the presynaptic terminal vesicles. Only nAChRs (purple) are represented on the postsynaptic bouton in this simplified picture. (B) A representation of presynaptic nAChRs (light blue) intermingling with other presynaptic macromolecules. The nAChRs are positioned so they can influence the release of synaptic vesicles. Evidence indicates that nAChRs initiate a direct and indirect increase of calcium in the presynaptic terminal. The calcium then enhances the release of the neurotransmitter. Low levels of ACh (green circles) are represented to have diffused near to this non-cholinergic synapse from more distant

sources. (C) A representation of preterminal or axonal nAChRs (blue). The nAChRs are located in a position along the axon to indicate they could influence excitability along that fiber. Low levels of ACh (green circles) are represented to have diffused into the area from more distance sources.

Figure 5.

Schematic representations of nicotine self-administration in rodents, the inverted U-shaped dose-response curve, and electrical intracranial self-stimulation. (A) Nicotine self-administration by a rodent (e.g., a rat) is commonly through an intravenous catheter located in the jugular vein. By an operant act (e.g., pushing a level), the rat activates a pump that delivers a small nicotine infusion that is distributed throughout the body and brain. (B) Nicotine dosing in both humans and animals follows an inverted U-shaped dose-response curve. At the lower concentrations, nicotine has little influence, but there is increasing pleasurable or rewarding influence activated with increasing dose. At higher nicotine concentrations, aversive influences come into play. Smokers and animals during self-administration titrate their nicotine intake to experience the rewarding effects, while avoiding the aversive actions. (C) Intracranial self-stimulation by a rat is induced by activation of an electrical stimulator with an electrode placed within discrete areas of the brain that influence the reward circuitry, including the mesocorticolimbic dopamine (DA) system and targets such as the NAc. By an operant act (e.g., pushing a level), the rat activates the stimulator to deliver a brief shock to the areas of the brain where the electrode is positioned. The technique allows the experimenter to measure changes in brain reward function. The protocol has been used to show that nicotine increases brain reward function (measured as an increase in the sensitivity to rewarding stimulation within the brain) whereas nicotine withdrawal decreases brain reward function.

Box 1 Figure I.

A tobacco field of *Nicotiana tabacum* under a threatening sky. Photo credit: [iStockphoto.com](https://www.iStockphoto.com).