Nicotine: Addiction, Effects on the Adolescent Brain and Electronic Cigarettes

Neal L Benowitz MD
Professor of Medicine
University of California San Francisco
Neurobiology of Nicotine Addiction
WHAT IS DRUG ADDICTION?

• The essence is loss of control of drug use.

• A disease of brain reward centers (Dackis and O’Brien, 2005)
NICOTINE

ACETYLCHOLINE
Structure of Nicotinic ACh Receptors

acetylcholine

pore

ion

muscle type nicotinic receptor

neuronal type nicotinic receptors

Picciotto M. Emerging neuronal nicotinic receptor targets. SRNT 9th Annual Meeting; February 2003; New Orleans, La.
NICOTINE

- DOPAMINE: Pleasure, Appetite Suppression
- NOREPINEPHRINE: Arousal, Appetite Suppression
- ACETYLCHOLINE: Arousal, Cognitive Enhancement
- GLUTAMATE: Learning, Memory Enhancement
- SEROTONIN: Mood Modulation, Appetite Suppression
- BETA-ENDORPHIN: Reduction of Anxiety and Tension
- GABA: Reduction
Nicotine Addiction: Reinforcing Behavior

- Nicotine activates nAChRs on DA and GABA neurons (VTA) and Glu neurons
- Net result of stimulatory and inhibitory effects and differential desensitization of nAChRs is enhanced DA release in the n. accumbens
- Studies in transgenic mice: crucial role of a4 and b2 nAChR subunits
RAPID RISE IN ARTERIAL BLOOD NICOTINE LEVELS WHILE SMOKING
BLOOD NICOTINE LEVELS THROUGHOUT THE DAY
Nicotinic Receptor Upregulation In Smokers
Tobacco Abstinence Symptom Clusters
(Gross and Stitzer)

- PSYCHOLOGICAL DISTRESS:
  Irritability, Anger, Impatience, Anxiety
- DIFFICULTY CONCENTRATING:
  Cognitive and Performance Impairment
- HUNGER AND EATING:
  Weight Gain
- TOBACCO CRAVING
MAO A Activity

Figure
MAINTAINING NICOTINE ADDICTION

• Positive reinforcement –
  Liking a drug is part of addiction

• Physical dependence –
  Avoiding withdrawal symptoms
NICOTINE ADDICTION CYCLE

CIGARETTE SMOKING

NICOTINE ABSORPTION

AROUSAL MOOD MODULATION PLEASURE

CRAVING FOR NICOTINE TO SELF-MEDICATE WITHDRAWAL SYMPTOMS

DRUG ABSTINENCE PRODUCES WITHDRAWAL SYMPTOMS

TOLERANCE AND PHYSICAL DEPENDENCE
BIOLOGY OF NICOTINE ADDICTION

TOBACCO PRODUCT

ENVIRONMENTAL INFLUENCES

SMOKING BEHAVIOR

NICOTINE IN BODY

NICOTINIC CHOLINERGIC RECEPTORS

NEUROTRANSMITTER RELEASE

VULNERABILITY FACTORS
- Age
- Gender
- Genetics
- Psychiatric Disease
- Substance Abuse

METABOLISM

TOLERANCE

REINFORCEMENT
- Enhanced Performance
- Mood Modulation
- Lower Body Weight
- Reversal of Withdrawal Symptoms
- Self-Medication
Nicotine and Adolescent Brain Development
Adolescent Behavior and the Brain

- Increased risk-taking, impulsivity, novelty-seeking
- Increased vulnerability to initiation and subsequent addiction to drugs
- Incomplete development of the prefrontal cortex: decision making, impulse control and executive function
Temporal Aspects of Brain Development

Motor & Sensory System

Temporal & Parietal Association Areas

Prefrontal Cortex

Basic Survival Skills

Language and Attentional Skills

Higher order Association skills
Nicotinic cholinergic system and cognitive function

• Important for learning, memory, attentional processes
• Cholinergic NS in PFC involved in executive function
• Nicotine acutely increases activity in PFC, but regular smokers have reduced activity in response to attentional tasks
• Nicotine acutely activates but chronically desensitizes nAChRs
Nicotine interferes with maturation of the prefrontal cortex

- Neuroplasticity
  - Intracellular signaling
  - Gene expression
  - Structural changes
- Synaptic pruning
- Myelination of axons
Nicotine effects on prefrontal cortex functions

• Nicotine in adolescent rats results in long-term cognitive impairment (accuracy, impulse control)
• Adolescent smokers show reduced PFC activity, including memory and attention
• Adolescent smoking associated with later life behavioral disturbances, including substance abuse and mental health problems
Reduced Prefrontal Attentional Network Activity in Smokers

Musso, Psychopharm (2007)
Prefrontal Activation Decreases with Duration of Smoking

Musso, Psychopharm (2007)
Long-lasting nicotine effects on adolescent rat brain

• Persistent increase in mRNA expression for α5, α6 and β2 nAChR subunits
• Greater up-regulation of a4b2 and a7 nAChRs
• Persistent changes in DA release
• Anxiogenic phenotype in adulthood
• Persistent deficit in cognitive function
• Enhanced acquisition of cocaine self-administration in adulthood (gateway?)
A

nAChR Binding in Midbrain

percent change from control

PN37

PN65

0.6 mg/kg/day

6 mg/kg/day

* p < 0.0001

* p < 0.03

B

HC3 Binding in Cerebral Cortex

percent change from control

PN37

PN45

PN65

0.6 mg/kg/day

2 mg/kg/day

6 mg/kg/day

* p < 0.01

* p < 0.0002
Vulnerability of adolescent brain to substance abuse

- Rodents: greater rewarding effects of drugs of abuse; increased self-administration of nicotine; greater nicotine-mediated DA and serotonin release
- Early onset human substance abuse, including tobacco use, associated with greater severity of addiction as adult
Nicotine self-administration in adolescent vs adult rats

• Increased self-administration at lower doses
• Greater brain DA response to nicotine
• Acetaldehyde and MAOI facilitate nicotine self-administration in adolescent rats
Enhancement of Nicotine Self-Administration by Tranylcypromine Pretreatment

(a) Adolescents (P27)
(b) Adults (P90)
Nicotine withdrawal in adolescents vs adults

• Some but not all studies show less severe withdrawal in adolescent rats
• No increase in intracranial self-stimulation threshold in adolescent rats
• However, adolescent smokers report symptoms after smoking only a few cigarettes
Caveats in interpreting human causation

- Most data on nicotine and brain development from studies in rats
- In people, difficult to distinguish effects of nicotine/tobacco from genetic and social environmental influences
Electronic Cigarettes as a Nicotine Delivery Device
What is an electronic cigarette?

- Heats a nicotine solution to create an aerosol for inhalation
Main components of EC aerosol

- Nicotine
- Propylene glycol
- Glycerine
- Flavorants
Possible reinforcing effects of E-cigarette use

• Nicotine self-administration
• Sensory effects of particulates/flavorants
• Hand-to-mouth/ritualistic behavior
• Coping response to conditioned smoking cues
Nicotine Delivery
Puffing behaviors: Electronic vs Conventional Cigarettes

• More puffs in a typical use (15 vs 8); 100-300 puffs per day
• Some people puff continuously all day
• Greater resistance to inhalation
• Longer puff duration (4.4 vs 2.1 sec)
• 30 puffs or more to deliver the nicotine equivalent to one tobacco cigarette
Particle distribution of e-cigarette vapor vs. conventional cigarette smoke

Fuoco et al. Envir. Poll. 2014
Systemic Delivery of Nicotine from E-cigarettes

• Early reports – very low plasma concentrations of nicotine
• Vansickel & Eissenberg 2011 – plasma nicotine levels similar to cig smokers in experienced EC users using tank style devices
• Etter & Bullen 2011 – saliva cotinine 322 ng/ml (range 13-852) in 31 EC users with no tobacco use for 48 hrs
Nicotine levels and effects after e-cigarette use

E-cigarette use Suppresses Craving in Abstinent Smokers (Vansickel 2012)

1A
Plasma Nicotine

ng/ml

BL 1 2 3 4 5 6

1B
Heart Rate

Beats per minute

BL 1 2 3 4 5 6

1C
QSU Factor 2

Score

BL 1 2 3 4 5 6

1D
Urge to Smoke a Cigarette

Subject Ratings (VAS)

BL 1 2 3 4 5 6
E-cigarette use Reduces Desire to Smoke Independent of Nicotine Delivery

Change from baseline desire to smoke

Time from product use (mins)
E-cigarette Reinforcement: Conclusions

• E-cigarettes reduce cigarette craving & tobacco withdrawal symptoms, although not as well as conventional cigarettes

• Nicotine contributes to rewarding effects, but may not be essential to all users

• Sensory effects, flavorants and hand-to-mouth behaviors are likely important factors in reinforcement
Conclusions

• Nicotine alters the structure and function of the brain and is highly addictive
• Animal studies demonstrate that the adolescent brain is sensitive to nicotine and results in long-lasting neurochemical and behavior changes
• Early initiation of smoking is associated with a higher level of addiction in adulthood
Conclusions 2

• Electronic cigarettes can deliver as much nicotine as cigarettes, but this depends on the device and the experience of the user.

• EC use is reinforced by several mechanisms, including sensory effects and hand-to-mouth behaviors such that nicotine is not necessary for some users.

• The reinforcing effects of nicotine are enhanced by tobacco specific toxicants: acetaldehyde and MAOI.

• Whether EC use is a pathway for initiation of nicotine addiction and later tobacco use is as yet unknown.