Neurobiology of Nicotine Addiction

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Outline

Addiction defined

• Nicotine absorption
• Nicotine neurophysiology
• Conditioning Cues
• Nicotine withdrawal
• Dealing with frustration
Frustration

• Patient viewpoint--ambivalence
  – 90% know cigarette smoking is harmful and want to quit.
  – Most smokers feel guilty and feel they have let themselves, their spouse, family and care provider down.
  – But most smokers are reluctant to quit and make only brief attempts to quit and often experience relapse if they do quit.
Frustration

• Health Care Provider viewpoint
  – Failure to help patient quit smoking may weaken care provider’s resolve to try again
  – Tendency to “blame” the patient for “non compliance”
  – Failure to understand the addictive physiology and consequences of nicotine addiction which promotes relapse
Psychoactive Substance Dependence DSM_IV

Three or more of the following:

• Tolerance

• Substance taken in larger amounts or over a longer period than intended

• Persistent desire or unsuccessful efforts to cut down or control use

• Great deal of time spent in activities necessary to obtain or use the substance or recover from its effects
Dependence diagnosis criteria (continued)

• Important social, occupational, or recreational activities given up or reduced because of use

• Continued use despite knowledge of having had persistent or recurrent problems caused by the substance

• Withdrawal symptoms when attempt to discontinue
Cigarette smoking—not a “habit”

- Habits = automatic routine, repeated regularly and without thinking
- Addictions are compulsions characterized by subjective distress when routine behaviors are forbidden.
Nicotine “hard-wired”

• Nicotine creates a motivation for the “target” behavior (smoking) that is rendered undeniable by the abnormal amplified negative emotional consequences of unresolved compulsion.

• This association becomes “hard-wired” and persists over time
Addiction—alternative view

• “Continued smoking could no longer be considered a manifestation of motivation deficit, but instead must be considered a disorder of an abnormally amplified motivation “NOT to quit”

• Cessation treatment should focus less on the consequences of tobacco use and more on the amplified motivations NOT to quit
Nicotine absorption
There seems no doubt that the “kick” of a cigarette is due to the concentration of nicotine in the blood-stream and this is a product of the quantity of nicotine in the smoke and the speed of transfer of that nicotine from the smoke to the blood-stream.

Nicotine is in the smoke in two forms as free nicotine base (think of ammonia) and as a nicotine salt (think of ammonium chloride) and it is almost certain that the free nicotine base is absorbed faster into the blood-stream.
Forms of Nicotine as a function of pH

Diprotonated

Monoprotonated

Unprotonated

Fraction of Each Species

pH of Solution

Distribution of protonated and unprotonated nicotine in solution at various pH increments.

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Nicotine state

• Protonated and free base
• Only the “free base” form can volatilize in gaseous form and be absorbed in the lungs
• Tobacco companies add ammonia to the tobacco leaf which by increasing pH increase nicotine conversion to “free base”
Cigarette-efficient nicotine delivery device

- Capable of producing very rapid peaks in the arterial concentration of nicotine
- Nicotine absorbed in alveoli of lung and circulates via pulmonary veins to Left heart. (bypasses the right heart)
- Nicotine circulates to brain within 7-10 seconds where nicotine receptors stimulate dopamine release
Cigarettes and Tobacco Dependence

- Cigarette is the most efficient delivery device for nicotine that exists—better than intravenous.
- Cigarette manufacturers have modified cigarettes over the past decades to maximize nicotine delivery to the brain.
- High doses of arterial nicotine cause upregulation of the nicotinic acetylcholine receptors.
- Genetic factors influence tobacco dependence.
- Left untreated 60% of smokers die from a tobacco-caused disease.

Hurt RD, Robertson CR JAMA 280:1173, 1998
The cigarette should be conceived not as a product but as a package. The product is nicotine.

Think of the cigarette pack as a storage container for a day’s supply of nicotine:

Think of the cigarette as a dispenser for a dose unit of nicotine:
“Low Tar Low Nicotine” Cigarettes

FTC Method

- Determines relative yield of individual cigarettes by smoking them in a smoking machine
- Machine draws 35ml puff of 2 seconds duration every minute
- Cigarette smoked down to 23mm butt length
- Cambridge filter collects the particulate matter
- Does not measure the gas phase “free nicotine”
- 2008 no longer used and as of June 2010 no longer can use “light” terminology
“Low Tar Low Nicotine” Cigarettes

Ventilation

• Ventilation holes one of key technologies to manipulate tar and nicotine yields
• Electrostatic or laser perforations of the filter or paper
• Ventilation holes in most brands are not visible
• 2/3’s of U.S. smokers are unaware of ventilation holes or that blocking then increases tar/nicotine yield
• Many smokers block (consciously or not) the ventilation holes with their lips on fingers
Carcinogens Excreted by Smokers of Regular or “Light” Cigarettes

• 150 smokers of regular or “light” cigarettes

• Nicotine metabolites—Serum cotinine and urine NNAL, NNAL-Gluc, and 4 aminobiphenyl hemoglobin adducts measured

• Essentially the same concentrations of were present in “light” as in regular cigarette smokers.
Nicotine effect on the brain

• Brain imaging studies show nicotine acutely increases activity in the prefrontal cortex, thalamus and visual system brain circuits—

• There is stimulation of central acetylcholine receptors (nAChRs) which results in release of several neurotransmitters most important - Dopamine
Mesolimbic system

- Ventral Tegmental area (VTA)-collection of nerve cells located midline on the floor of the midbrain
- Neurons of the VTA send projections to target the Nucleus Accumbens in the prefrontal region of the brain
- The Nucleus Accumbens –reward center for most drugs of abuse
Dopamine (DA) release in the nucleus accumbens is thought to be the “final common pathway” for the rewarding effects of most drugs of abuse.
Mesolimbic system

• VTA contains “dopaminergic neurons” that respond to external rewarding stimuli such as food, sex and social interaction as well as aversive stimuli and stress.
• VTA stimulation promotes a generalized behavioral arousal under both positive and negative stimuli.
• “seeking of safety”
Neurophysiology of nicotine

- VTA’s inputs are transmitted by cholinergic pathways and receptors.
- Nicotine “hijacks” these receptors and compels them to produce dopamine, creating a powerful but artificial “safety” signal.
- Most potent drug—more potent than cocaine, amphetamine and morphine to compel repetitive behavior.
Different types of nAChr

Two α4 and three β2 subunits form an α4β2 heteromeric nAChR

Five α7 subunits form an α7 homo-oligomeric nAChR
Nicotine addiction-animal study

• Powerful motivator of behavior
• Animal studies
  – Prolonged “foot shock” behavior extinction
  – Lever pressing of nicotine exposed monkeys
Nicotine Stimulates Release of Many Different Neurotransmitters

- 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 of Anxiety and Tension

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Nicotine actions

- Induces stimulation and pleasure
- Reduces stress/anxiety
- Improves concentration, reaction time and task performance
- Prevents withdrawal symptoms by keeping nAChRs in desensitized state
Smoking Saturates Nicotinic Receptors

• Radioligand allows for visualization of α4β2 nAChRs

• Position Emission Tomography (PET) Scans

• 11 smokers had 14 PET scan sessions

• Smoked: none, 1 puff, 3 puffs, 1 cigarette or 2-3 cigarettes (satiety)
Smoking Saturates Nicotinic Receptors

Results

• 1-2 puffs of a cigarette → 50% occupancy of α4β2 nAChRs for 3 hours after smoking

• One cigarette → 88% receptor occupancy and ↓ cigarette craving
Smoking Saturates Nicotinic Receptors

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Neuroadaptation

• Repetitive Nicotine exposure
  – Upregulation - Increase in nAChRs
  – Response to nicotine-mediated desensitization of receptors which may lead to tolerance/dependence
  – Daily smoking maintains near-complete saturation and desensitization of nAChRs
  – Avoids withdrawal
Conditioning

environmental factors (cues) contribute to urge to smoke (after meals, with coffee, with friends)

Cue often is to avoid “irritability

- Association between cues and anticipated drug effect drives urge
- May maintain nicotine use while nAChRs are desensitized
Nicotine Addiction

- Physical Dependence

Psychological Dependence:
- “Conditioned Response” to Cues
  - The Five Senses
  - Emotions (positive and negative)
- Cues trigger neurotransmitter release
- Anticipation of Nicotinic receptor activation and Dopamine release

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Withdrawal Syndrome or "Abstinence Syndrome"

Pathophysiologic disturbances which result when a drug to which an organism is physically dependent is stopped.
Craving

• An intense desire to fulfill an unsatisfied state
  – As opposed to ‘like’
• Positively correlated with relapse in two ways
  – Intensity during early quit
  – Momentary craving associate relapse long after initial quit
The experience:
Withdrawal Symptoms

- Insomnia
- Restlessness
- Anxiety, Irritability, Frustration, Anger
- Difficulty concentrating
- Sad, depressed mood, anhedonia
- Increased appetite
- Decreased heart rate
Other Common Withdrawal Symptoms

- Headache
- Mouth ulcers
- Nausea
- Constipation
- Diarrhea
Timeline of Nicotine Withdrawal
For most smokers, withdrawal symptoms last for a few weeks and then resolve. Cravings can be frequent and intense early, but become less intense and less frequent over time.
Medication: Effects on Withdrawal & Urges

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High Relapse

• Most people who smoke want to stop
• 80% of smokers who try to quit on their own relapse within 1 month
• Only 3% remain abstinent at 6 months

• Nicotine addiction = chronic disease

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Dealing with frustration

• Patient’s internal conflict → ambivalence

• Our responsibility is to help patients resolve ambivalence
  – Motivational interviewing which enhances motivation to change through reflective listening without confrontation or judging
  – Ellicit trust by demonstrating
    • Empathy - develop a sense of “shared experience”
    • Joining – develop shared goals
Dealing with Frustration

• Validation – confirm that the patient’s experience/frustration with quitting has a “biologic/physiologic basis”, but don’t undermine “self-efficacy” by over emphasizing “how difficult quitting can be”

• Hope-hopelessness is a common barrier to behavior change in addiction.
Dealing with frustration

• Hope – Work to reinvigorate hope by maintaining a positive non judgmental attitude, emphasizing creative solutions to common problems.
“Not a Bad Person with a Bad Habit, but a Good Person with a Difficult Disease”

--Tom Gauvin, NDC Counselor
References

1. “Neurobiology of Nicotine Addiction: Implications for smoking cessation Treatment” Neal L Benowitz, MD
   – American Journal of Medicine (supplement) vol. 121 (4A) S3-S10
   April, 2008
References

Association for the Treatment of Tobacco Use and Dependence

An organization of providers dedicated to the promotion of and increased access to evidence-based tobacco treatment for the tobacco user.

www.attud.org