Tobacco Addiction: Neurobiology and Its Clinical Implications

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Acknowledgements

Dr. Anthenelli’s research is supported by:

- VA Merit Review NEUA-003-08S

- National Institute on Alcohol Abuse and Alcoholism (NIAAA) RO1 AA019720

- National Institute on Drug Abuse (NIDA) / VA Cooperative Study #1031

- NIAAA’s Integrative Neuroscience Initiative on Alcoholism (INIA) Stress Consortium
Faculty Disclosure

- **Sources of Funding for Research:** Pfizer, Inc.; Alkermes

- **Current Consulting Agreements:** Pfizer, Inc.; Arena Pharmaceuticals

- **Advisory Board / Steering Committees:** Pfizer, Inc.; Arena Pharmaceuticals

- The opinions expressed in this talk are Dr. Anthenelli’s own and do not necessarily reflect the views of the University of California and the Department of Veterans Affairs
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- This conference has received financial support from Pfizer, Inc. in the form of an educational grant.

- Potential for conflict of interest: Dr. Anthenelli’s employer, the University of California, has been compensated by this sponsor for his UC-contracted work as a consultant and researcher.
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- Dr. Anthenelli has disclosed potential areas for conflict of interest for the audience’s consideration.
Objectives

- Provide cursory overview of some of the brain mechanisms involved in tobacco addiction

- Discuss how these neuroadaptive changes might underlie:
  - Learning, wanting, and needing to smoke (i.e., nicotine tolerance and withdrawal)
  - Protracted abstinence and negative affect
  - Smoking cessation-related neuropsychiatric adverse events
Scope of the Problem

- Smoking is a Global Epidemic
  - 1.25 billion smokers worldwide (W.H.O. 2002)
  - 35% of men / 22% of women in developed countries
  - 50% of men / 9% of women in developing countries

- Smoking is the No. 1 Cause of Death Worldwide
  - 4.9 million tobacco-attributable deaths in 2000
  - 10 million projected annual deaths by 2020
Quitting Smoking is Challenging

- Not a question of desire
  - 70% smokers (USA / Europe) say they want to quit
  - 30% - 50% make an attempt each year, generally unaided
  - Less than 5% of unaided attempts are successful

- Obstacles to quitting smoking
  - Nicotine/tobacco is highly addictive
  - Relatively few medications (i.e., nicotine replacement therapy, sustained-release bupropion, varenclline) currently approved

Despite current existing therapeutic aids to smoking cessation, patient needs are still unmet
Tobacco’s Addiction Potential

- Lifetime prevalence of DEPENDENCE
  - overall: 26% in men and 23% in women\(^a\)
  - among one-time users: 33% in men and 31% in women\(^a\)
  - among daily users: as high as 90%

Among last year users of alcohol, tobacco, cannabis and cocaine, TOBACCO USERS WERE MORE LIKELY TO BE NICOTINE DEPENDENT (28%) than alcohol (5.2%), cannabis (8.2%) or cocaine (11.6%) users\(^b\)

\(^a\)National Comorbidity Study (DSM-III-R)
\(^b\)National Household Survey on Drug Abuse; Kandel D et al. Drug Alcohol Depend 1997
Nicotine and Other Drugs of Abuse Hijack the Brain’s Reward Circuit
Brain Reward Center Connectivity

Structure of Nicotinic ACh Receptors

Acetylcholine binds at the pore of the receptor, leading to ion flow. There are two types of nicotinic receptors: muscle type and neuronal type. Each type has different subunits.

Muscle type nicotinic receptor: 
- α1
- γ
- δ
- β

Neuronal type nicotinic receptors: 
- αx
- βy
- αx
- βy
- αx

Picciotto, Marina; Emerging Neuronal Nicotinic Receptor Targets; SRNT 9th Annual Meeting, Feb. 2003, New Orleans, LA
Nicotinic ACh Receptors (nAChRs) Come in a Variety of Flavors

- Number and types of subunits affect role and function
- Are located in specific brain regions (e.g., α4β2 predominate in brain)
- Are located both on nerve cell bodies (soma) and on nerve terminals
- This specificity and selectivity allows nicotine to affect brain reward, mood, cognition, etc.
Nicotine Modulates Activity of Dopamine in the Brain Reward Center

McGehee, Daniel Ph.D; *Synaptic Mechanisms Underlying Nicotine-Induced Excitation of Brain Reward Areas*; SRNT 9th Annual Meeting, Feb. 2003, New Orleans, LA
Nicotine’s Direct Stimulatory Effects on Dopamine Release via NACRHs

Learning to Smoke: Nicotine Enhances Long-Term Potentiation Undergirding Memory Formation

Wanting to Smoke: Nicotine Modulates Activity of Dopamine in the Brain Reward Center

Too Much of a Bad Thing: How Nicotine Receptors Adapt to Too Much Nicotine

- Resting state = closed
- Active state = open
- Desensitized state = closed for minutes to hours
- Inactivated state = remain closed until degraded within cell
- Desensitized receptors turn over more slowly → Upregulation (increase in # of nAChRs with chronic smoking)
Nicotine, at the Concentration Experienced by Smokers, Activates and Desensitizes nAChRs

Dani, JA, De Biasi, M; Pharmacology, Biochemistry, and Behavior 70 (2001) 439-446
Needing to Smoke: Chronic Nicotine Use Up-Regulates nAChRs

^3H-nicotine

Nicotine Withdrawal

- nAChR activity returns when nicotine absent (e.g., person quits smoking)
- increased receptor number and activity contribute to nicotine withdrawal dysphoria
- smoker relapses to “feel normal” again

Clinical Relevance of Activating, Desensitizing and Upregulating nAChRs in Dopamine Brain Reward Circuit

- Activation reinforces the smoking behavior in a type of learned process
- Desensitization contributes to TOLERANCE to nicotine
- Upregulation contributes to WITHDRAWAL from nicotine
- Long-term synaptic changes contribute to conditioned cues and cravings
Why Do Smokers Have a Hard Time Quitting Smoking?

**They’ve Learned to Smoke:** Nicotine enhances long-term potentiation undergirding memory formation

**They Want to Smoke:** Nicotine modulates activity of dopamine in the brain reward center

**They Need to Smoke:** Chronic nicotine use up-regulates nAChRs
- nAChR activity returns when nicotine absent (e.g., person quits smoking)
- Increased receptor number and activity contribute to nicotine withdrawal dysphoria; smoker relapses to “feel normal” again
Tobacco Smoke Also Inhibits Monoamine Oxidase (MAO) Activity

- Mitochondrial, flavin-containing enzyme
- Ubiquitously distributed in brain and other tissues
- Exists in two distinct forms, types A & B
- Catabolizes monoamine neurotransmitters (i.e., dopamine, norepinephrine, serotonin) and other substances (tyramine)
Monoamine Metabolism

Cigarette Smoking Lowers Both MAO-A & B Activity Levels

Platelet MAO-B Activity, Plasma Dihydroxyphenylglycol (DHPG), Plasma Dihydroxyphenylacetic Acid (DOPAC), Plasma Dihydroxyphenylalanine (L-DOPA), and Plasma Norepinephrine (mean ± SD) in Heavy Smokers and Nonsmokers

<table>
<thead>
<tr>
<th></th>
<th>Heavy Smokers (n = 88)</th>
<th>Nonsmokers (n = 54)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet MAO-B activity (nmol/hour/10^9 platelets)</td>
<td>15.39 ± 7.82</td>
<td>32.83 ± 12.35</td>
<td>0.0001</td>
</tr>
<tr>
<td>DHPG (pmol/mL)</td>
<td>6.05 ± 1.66</td>
<td>7.48 ± 1.74</td>
<td>0.0001</td>
</tr>
<tr>
<td>DOPAC (pmol/mL)</td>
<td>13.32 ± 8.76</td>
<td>20.98 ± 7.45</td>
<td>0.0001</td>
</tr>
<tr>
<td>L-DOPA (pmol/mL)</td>
<td>7.72 ± 3.46</td>
<td>9.25 ± 3.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Norepinephrine (pmol/mL)</td>
<td>1.53 ± 0.92</td>
<td>1.38 ± 1.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

Smoking Effects on MAO-B Activity

Fowler, JS et al.; Proc. Natl. Acad. Sci. USA 2003 100, 11600-11605
Cigarette Smoke’s Effect on MAO

- Smoke contains nicotine and thousands of other components
- Nicotine probably not the culprit
- Thiocyanate – little effect on MAO
- Role of tetrahydroisoquinoline (TIQ) adducts?
Consequences of Smoking-Induced MAO Inhibition

- Potentiates dopaminergic neurotransmission → smoking more reinforcing
- Smoking cessation → ↑ MAO activity
- Tobacco withdrawal associated with catecholamine depletion state, thus, return of MAO activity might contribute to subacute / protracted withdrawal
Smoking & Neuropsychiatric Events: Independent Association With Suicide

- Regardless of the use of smoking cessation aids, and after controlling for potential confounders (e.g., demographics, heavier drinking, less education), cigarette smoking is reliably associated with suicide.

- Association appears dose dependent:
  Smokers of > 20 cigarettes/day more than twice as likely than non-smokers to commit suicide.

Neuropsychiatric Events: Plausible Explanations for the Relationship Between Smoking and Suicide

- Smokers have pre-existing conditions that increase their risk for suicide
  - Psychiatric comorbidity hypothesis
- Smoking causes painful and debilitating conditions that might lead to suicide
  - Medical comorbidity hypothesis
- Smoking changes multiple aspects of brain function
  - Brain dysregulation hypothesis

Adapted from Hughes JR Drug and Alcohol Dependence 2008; 98: 169-178
Compelling Evidence For the Brain Dysregulation Hypothesis: 4 Examples

1. Smoking Decreases Brain Serotonin Levels
2. Smoking Inhibits Monoamine Oxidase (MAO) Activity
3. Smoking Upregulates nAChRs
4. Smoking Reduces Glutamate (mGluR5) Receptor Binding

Blunted Prolactin Response to Serotonergic Stimulation In Smokers vs Non-Smokers

Fig. 1. Prolactin responses to d,l-fenfluamine in smokers (n = 76; filled circles) and nonsmokers (n = 34; open circles). Points on the curves represent mean values. Bars represent SEM. Effects in smokers significantly attenuated at time point +270 min (p < .05) after drug administration.
Smoking Reduces Glutamate (mGluR5) Receptor Binding

Figure 3 pg 741 from Akkus F et al. PNAS 2013
Summary & Conclusions

1) Nicotine commandeers nAChRs in the brain reward center, thus, reinforcing the smoking behavior through both positive and negative reinforcement mechanisms.

2) Chronic smoking produces profound, widespread neuroadaptive changes affecting brain circuits regulating reward, cognition and mood states.

3) The smoking-related brain dysregulation hypothesis probably explains aspects of protracted abstinence and negative affect and possibly explains some smoking cessation-related neuropsychiatric adverse events.