Neurobiology of Nicotine Dependence and Pharmacotherapy for Nicotine Dependence

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Outline

• Neurobiology of addiction
• Pharmacology of nicotine
• Pharmacological strategies for nicotine dependence:
  1. Nicotine Replacement Therapy
  2. Other pharmacological interventions
• Future directions
Substance Use Disorders

• SUD in general and nicotine dependence in particular account for significant mortality, morbidity and socio-economic burdens.
Nicotine addiction

• While positive reward from nicotine initiates smoking; it is mainly the relief from withdrawal symptoms and the negative effects associated with withdrawal that contribute to the persistence of smoking and relapse.

(Perkins et al 2001)
Nicotine: Pyrrolidine-Pyrididine ring
In nature few chemicals are addictive

~ 30,000,000 known chemicals

~ 100 only are addictive:

- Nicotine
- Alcohol
- Psychostimulants (cocaine, amphetamines)
- Opiates
- Cannabinoids
- Barbiturates
- Benzodiazepines
What makes chemicals addictive?

They are rewarding, reinforcing, pleasurable.

They activate the reward circuitry in the brain.

Degree of activation correlates with addictiveness.
Circuits involved in Abuse and Addiction
Basic reward circuitry of the brain is a discrete mono synaptic circuit

- Ventral tegmental area (VTA) → Nucleus Accumbens (NAcc) via MFB

- Dopaminergic cells in VTA are activated by certain compounds and subsequently stimulate the dopaminergic reward cells in the NAcc which in turn activates secondary pathways....
Dopamine: The crucial reward neurotransmitter

Virtually all addictive drugs are DA modulators

Microinjections of DA agonists: Pleasure

Effects of DA Antagonists: dysphoria (anti psychotics)
Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Release

Di Chiara and Imperato, PNAS, 1988
## Risk of Addiction

| (%)
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Tobacco</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cannabis</td>
</tr>
</tbody>
</table>

Vulnerability Factors for Addiction

- High reactivity to stress
- High novelty-seeking/High impulsivity
- Reward “deficiency” (Dopamine)

The above sometimes manifesting clinically as:
- Conduct disorder (especially in adolescence)
- Depression
- Attention Deficit/Hyperactivity Disorder
Individual Differences in Response to Drugs: DA Receptors influence drug liking

As a group, subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant. (Adapted from Volkow et al., Am. J. Psychiatry, 1999)
Addiction is a disease that starts in adolescence.

*National Epidemiologic Survey on Alcohol and Related Conditions.*
Progression of Addiction

• Recreational occasional use $\rightarrow$ Recreational steady use $\rightarrow$ Habit-driven use (shift from ventral striatum to dorsal striatum)

• Habit-driven use $\rightarrow$ Compulsive use (addicted disease state)

(Haber et al, 2000)
Challenge in Addiction is Relapse: Triggers of Relapse:

• **Re-exposure** to DRUG: cross-triggering between similar drug classes

• Exposure to **STRESS**: even Mild stress

• Exposure to environmental **CUES**: Sights, sounds, smells associated with drug “People, places, things”
Craving

- Long-term potentiation and long-term depression in the following areas:
  1. Nucleus accumbens
  2. Amygdala
  3. Hippocampus

- BDNF is likely responsible for the long term changes

- Responsible for **“incubation of craving phenomenon”**
Nicotine
Jean Nicot (1530 – 1600)
Nicotine

• Nicotine is a natural alkaloid found in tobacco and some plants

• Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring

• (S)-nicotine is the active isomer binds nicotinic acetyl-choline receptors (nAChRs)
Natural nicotine which is in the diprotonated form is poorly absorbed by biological membranes.
Nicotine in tobacco

• The absorption of nicotine depends on pH.

• Below pH 6: smoke contains only 1% unprotonated (free) nicotine.

• Unprotonated nicotine is absorbed through biological membranes

• Smoke from cigarettes has an acidic pH and buffered in the alveoli to higher pH before it can be absorbed

• Alkaline smoke is harsh and difficult to inhale.
Nicotine

• Inhaled nicotine avoids first-pass metabolism.

• Nicotine reaches the brain in approximately 15-20 seconds after inhalation
Nicotine

- Nicotine is extensively metabolized in the liver (Metabolized to cotinine: detectable in urine).

- CYP 2A6 is primarily responsible the oxidation of nicotine.

- Smoking accelerates the metabolism of many drugs, particularly those metabolized by CYP1A2.
Nicotine Receptor: ligand-gated ion channels
Nicotine receptors

- Acetylcholine (endogenous agonist) and nicotine (exogenous agonist) both stabilize the “open conformation”
- Open nAChR conduct (cations) that causes depolarization of the membrane
- The receptor-channel complex consists of 5 subunits: variable subunit combinations
a One subunit of nAChR

b Cross-section of five assembled subunits (2x α + 3x β) of nAChR

Structure of a neuronal nicotinic acetylcholine receptor (nAChR)

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press
• 3 classes of nAChRs: 1 muscle and 2 neuronal
• Neuronal alpha-beta combination receptors involved in smoking
[alpha4 beta2] nicotine receptors implicated in nicotine addiction

• Genetic studies in mice indicate a primary role for the alpha4 beta2 receptors in mediating nicotine dependence.

• In alpha beta subunit knockout mice: nicotine is less able to release dopamine in the brain and these animals do not self-administer nicotine.
Physiologic effects of nicotine

- High potency drug (1-2 mg delivered/cigarette)
- Short half-life (~100 minutes)
- Releases: DA, GH, epinephrine, cortisol
- In particular the adrenals release large amounts of epinephrine/NE which causes most of the CV effects (Tachycardia/HTN/Elevated glucose)
Pharmacotherapy for Nicotine

• ~85% of people who have successfully quit smoking did so without medication

• Use of appropriate medications doubles the success rate in smoking cessation

Even with treatment very high relapse rates within one year up to 70%
Nicotine polacrilex (gum)

- Reduces withdrawal/convenient
- OTC: 2-4 mg/pc
- Unpleasant taste, must keep saliva in mouth
- May need up to 1 pc/hr
- Must avoid acidic beverages, foods
- Pregnancy C
Nicotine Transdermal (patch)

- Improves quit rates/withdrawal (7, 14, 21 mg/d patches)
- Achieves steady-state levels
- OTC: once daily, start after Quit Date
- Skin irritation, nausea, bad dreams

**Smoking + Patch maybe dangerous**

- Pregnancy C
Patch dosing

**TABLE 52.1** Nicotine Patch Dose Based on Baseline (while Smoking) Blood Cotinine Concentration

<table>
<thead>
<tr>
<th>Cotinine in ng/mL</th>
<th>Nicotine patch dose</th>
</tr>
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<tbody>
<tr>
<td>&lt;200</td>
<td>14–21 mg/day</td>
</tr>
<tr>
<td>200–300</td>
<td>21–42 mg/day</td>
</tr>
<tr>
<td>&gt;300</td>
<td>≥42 mg/day</td>
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</table>

**TABLE 52.2** Recommended Initial Dosing of Nicotine Patch Therapy Based on Number of Cigarettes Smoked Daily

<table>
<thead>
<tr>
<th>Cigarettes per Day</th>
<th>Patch dose (mg/d)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>7–14</td>
</tr>
<tr>
<td>10–20</td>
<td>14–21</td>
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<tr>
<td>21–40</td>
<td>21–42</td>
</tr>
<tr>
<td>&gt;40</td>
<td>42</td>
</tr>
</tbody>
</table>

*Nicotine patches are available in the following doses: 7, 14, and 21 mg.

*Principles and practice of Addiction Medicine*
Nicotine spray

• Improves quit rates/easy to use
• Rapid rise in nicotine levels
• Addictive potential
• Irritates nasal mucosa

• Pregnancy C
Nicotine inhaler

• Moderately rapid rise in nicotine levels
• Looks and feels like a cigarette holder

Kinetics similar to gum

Spray/inhaler absorbed through oral/nasal mucosa NOT lungs/alveoli

• Pregnancy C
Newer NRTs

- Lozenges: 2 or 4 mg/pc (similar in concept to gum)

- Electronic cigarettes: inhalers that more closely simulate the “real” smoking experience
Fig. 1. Plasma nicotine levels after a smoker has smoked a cigarette, received nicotine nasal spray, begun chewing gum, or applied a nicotine patch. The amount of nicotine in each product is given in parentheses. The pattern produced by the use of the nicotine inhaler (not shown) is similar to that of nicotine gum. ◊, cigarette (1-2 mg); △, nasal spray (1 mg); ◇, gum (4 mg); ⊗, patch (21 mg). Reproduced with permission. Copyright © 2003 Massachusetts Medical Society.
Bupoprion
Depression and Smoking

- Smokers are more likely to have a history of MDD.
- During the course of an attempt to stop, many smokers develop a depression
- The development of MDD during an attempt to stop smoking is associated with relapse
- This association has raised the question of the role antidepressants might play in treating tobacco dependence
Bupropion

- Related to amphetamine like stimulants
- Increases DA and NE in the CNS (reduces withdrawal symptoms)
- Antagonist at nicotinic receptors (blocks the reinforcing effects of smoking)
Bupropion

- Improves quit rates and reduces withdrawal symptoms and carvings.

- Reduces depressive symptoms and weight gain

- Contraindications: Hx of seizures, Hx of eating disorders

- Seizures rare in healthy individuals; risk at higher doses (>450 mg/day)

- Pregnancy B
Bupropion

- Set a Quit Date and start 1-2 weeks before Quit Date
- Initial dose: 150 mg daily
- Maintenance dose: 150 mg BID
- Continue treatment at least 7 weeks
Varenicline

- Approved in 2006
- Partial agonist at nAChR: very high affinity for $\alpha_4\beta_2$ (3x nicotine)
- Related to plant derived chemical cytisine
- Reduces craving / withdrawal symptoms
- Trade names: Chantix / Champix
Cytisine
Varenicline

- 1 mg BID: start 1 wk before quit date for 12 weeks
- Minimal hepatic metabolism (T½: 17 ± 3 hours)

Common adverse effects: Nausea, HA, and insomnia

**2009: Black Box Warning:** Risk of psychiatric symptoms, including depression and suicidal ideation.

**Figure 3** Highly simplified scheme showing effects of (A) nicotine from cigarettes (B) nicotine withdrawal and (C) varenicline on nicotinic receptors and dopamine release.
Second line agents

• Nortriptyline (TCA): anti depressant

• Cloninde (oral or patch): central alpha agonist: reduces sympathetic outflow
Review of Literature

• Recent large review of NRTs (Carpenter et al 2013):
  
  • All forms of NRT can help people who make a quit attempt increase their chances of successfully stopping smoking.
  
  • NRTs increase the rate of quitting by 50%-70%
  
  • A combination of NRT and bupropion was more effective than bupropion alone (RR 1.24)
  
  • There is no evidence that NRT increases the risk of heart attacks
Effective combinations

• Nicotine patch + nicotine gum
• Nicotine patch + nicotine nasal spray
• Bupropion plus + gum
• Bupropion plus + patch
• Bupropion plus + nasal spray
# Cochrane Review

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of studies (subjects)</th>
<th>Relative risk (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (2mg/day) versus placebo</td>
<td>15</td>
<td>2.27 (2.02-2.55)</td>
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<tr>
<td>Varenicline (2mg/day) versus bupropion</td>
<td>3</td>
<td>1.52 (1.22-1.88)</td>
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<tr>
<td>Varenicline (2mg/day) versus NRT</td>
<td>2</td>
<td>1.13 (0.94-1.35)</td>
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<tr>
<td>NRT (any form) versus control</td>
<td>NA</td>
<td>1.58 (1.50-1.66)</td>
</tr>
<tr>
<td>Nicotine gum versus control</td>
<td>53</td>
<td>1.43 (1.33-1.53)</td>
</tr>
<tr>
<td>Nicotine patch versus control</td>
<td>41</td>
<td>1.66 (1.53-1.81)</td>
</tr>
<tr>
<td>Nicotine inhaler versus control</td>
<td>4</td>
<td>1.90 (1.36-2.67)</td>
</tr>
<tr>
<td>Oral tablet/lozenges versus control</td>
<td>6</td>
<td>2.00 (1.63-2.45)</td>
</tr>
<tr>
<td>Nicotine nasal spray versus control</td>
<td>4</td>
<td>2.02 (1.49-3.73)</td>
</tr>
<tr>
<td>Bupropion SR versus placebo</td>
<td>36</td>
<td>1.69 (1.53-1.85)</td>
</tr>
<tr>
<td>Nortriptyline versus placebo</td>
<td>6 (975)</td>
<td>2.03 (1.48-2.78)</td>
</tr>
<tr>
<td>Clonidine versus placebo</td>
<td>6</td>
<td>1.63 (1.22-2.18)</td>
</tr>
</tbody>
</table>
Effectiveness

• Compared to placebo:

Varenicline: 2.27 (95% CI 2.02-2.55)
Bupropion: 1.69 (95% CI 1.53-1.85)
Any NRT: 1.60 (95% CI 1.53-1.68)

(Aubin et al 2013)
Future directions: Neuromodulation

• **Transcranial Magnetic Stimulation** (NON invasive) has been shown to reduce cravings, responsiveness to cues, and consumption of addictive substances in a number of studies including cocaine, alcohol, opiates, and in several nicotine studies (Li et al, 2013)

• Intracerebral microdialysis in animals has shown that TMS can stimulate DA release in the hippocampus and NA.

• DLPFC stimulation has also been shown to reduce impulsivity, a major problem in addictions

• **Deep Brain Stimulation (invasive)**: refractory cases for alcohol and heroin addiction
Optogenetics: showing promise in animal addiction models
THANK YOU