The nicotine stimulus: A new approach to disentangling its underlying neuropharmacological mechanisms

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Tobacco Use a World Health Problem

“No other consumer product is as dangerous, or kills as many people. Tobacco kills more than AIDS, legal drugs, illegal drugs, road accidents, murder, and suicide combined” (p. 36).
Tobacco Use in the United States

- 21% of adults smoke
- 367 billion cigarettes
- 440,000 deaths
- $167 billion
Quitting

70% motivated to quit

95% relapse without intervention

Intervention improves

ca. 70% failure--need to do better
Multi-faceted Etiology
Behavioral Process of Import
(Nicotine as Reinforcer or US)

Exteroceptive Stimuli

Nicotine US
Foundation for Cue-exposure Therapy

- Imagine situations
- Therapist describe
- Sham smoke

Niaura et al. (1999) *Addiction*

| Table 1. Urge changes during the treatment sessions for subjects in the cue exposure conditions |
|---|---|
| **Enter** | **Exit** |
| Session 1 | 4.0 (3.0) | 3.3 (2.3)* |
| Session 2 | 4.1 (3.3) | 2.3 (2.1)*** |
| Session 3 | 2.7 (2.5) | 2.3 (1.7) |
| Session 4 | 2.3 (2.3) | 1.7 (1.4) |
| Session 5 | 3.4 (3.1) | 2.6 (1.9) |

*p < 0.10; ***p < 0.001.*
Predominant Conceptualization
(Driven most theory and research)

Exteroceptive Stimulus

Nicotine US
Perceptible Interoceptive Effects

My Caffeine Level for Today:

High - Well Caffeinated & Easily Excitable

The Caffeine CLICK TEST

versus
Interoceptive Stimuli Guide Behavior

Doty (1961)

Perkins et al. (1994)

Stolerman et al. (1984)
Interoceptive Conditioning
(another contributing factor)

Nicotine Stimulus

Potential Reinforcers
In summary, the study provided inconclusive evidence for the ability of one drug to act as a CS for the presentation of another in human subjects.
Reflect on Learning History

1 year = 7300 cigarettes or >80,000 inhalations
20 years = 146,000 cigarettes or >1.6 million inhalations

Clements et al. (1996)
- average of 15.3 cigarettes per day
- mean age of 27 (range= 21 to 44)
- smoking at least 9 years
  not reported, but assume smoking since they were 18 years old
- cigarettes consumed estimated at just over 50,000
As Stated by Mark Twain

“As an example to others, and not that I care for moderation myself, it has always been my rule never to smoke when asleep and never to refrain when awake.”
Developing & Validating a Model
Exteroceptive Stimuli Control
Appetitive Behavior

Light Stimulus – Sucrose Solution

Farwell & Ayres (1979)
Appetitive Interoceptive Conditioning

Nicotine – Sucrose US

Interoceptive Stimulus
Discriminated Goal-tracking Task

Nicotine → 5 min → Conditioning Chamber (20 min)
(0.4 mg/kg base, SC)

* * * * * * * * (26% w/v sucrose)

intermixed with

Saline → 5 min → Conditioning Chamber (20 min)
(SC)
Evidence for conditioning

Nicotine $\rightarrow_{5 \text{ min}}$ Conditioning Chamber (20 min)
(0.4 mg/kg base, SC)

*(26\% w/v)*
Discrimination Quickly Acquired

Behavioral Validation: Good consistency!!!

- Susceptible to extinction
- Reacquired quickly
- Signal absence of US (CS-)
- US density affects CR
- CR varies with US quality
- Degrading CS-US relation
  \( \Delta \) acquisition
  \( \Delta \) expression
- CS salience
  \( \Delta \) acquisition and extinction
  \( \Delta \) generalization
- Not state-dependency
- Occasion Setter
  positive & negative
- Overshadowing
- Blocking
- Overexpectation

Bevins (2009) NE Symposium on Motivation
Extinction Protocol

Nicotine \[5 \text{ min}\] \rightarrow \text{Conditioning Chamber (20 min)}

no sucrose

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Goal Tracking

Wilkinson et al. (2006) *Behavioural Pharmacology*
Non-reinforcement Diminishes Interoceptive Conditioning

Wilkinson et al. (2006) *Behavioural Pharmacology*
Neuropharmacological Validation: Selectivity

- Central nACh receptors important
- Selectivity at some nAChR subtypes
  - DHβE antagonizes (α4β2), no effect of MLA (α7)
  - Varenicline (α4β2 partial agonist; α7 agonist)
  - Nornicotine (α7 & α6 agonist)
  - ABT-418 (α4β2 agonist)
- Role of ADHD drugs
  - SSRI & SNRI
  - NMDA not involved
  - No role for mGluR5 receptor
- Cannabinoid system important
  - CB1 substitution
- Perhaps an opioid component
- Dopamine role
  - Minimal role of D1, D2, D3
  - DA transporter (bupropion substitution)

Wooters et al. (2009) *Current Drug Abuse Reviews*
Train the Discrimination

Nicotine $\xrightarrow{5 \text{ min}}$ Conditioning Chamber (20 min)
(0.4 mg/kg base, SC)

* * * * * * * * *(26% w/v sucrose)

intermixed with

Saline $\xrightarrow{5 \text{ min}}$ Conditioning Chamber (20 min)
(SC)
Antagonism Protocol

MLA → 'x' min → nicotine → 5 min → 4 min
DHβE
mecamylamine
saline

Struthers et al. (2009) Pharmacol Biochem Behav
nAChR Antagonism: Mecamylamine

Struthers et al. (2009) Pharmacol Biochem Behav
nAChR Antagonism: MLA

α7* antagonist

Dose (mg/kg)

Dipper Entries per Second

MLA
Mecamylamine
Saline
Nic (0.4 mg/kg)

Struthers et al. (2009) Pharmacol Biochem Behav
nAChR Antagonism: DHβE

$\alpha_4\beta_2^*$ antagonist

Struthers et al. (2009) *Pharmacol Biochem Behav*
Substitution Protocol

saline → 'x' min → nicotine
ABT-418 → nornicotine
varenicline

Reichel et al. (2010) *Neuropharmacology*
ABT-418 is “nicotine-like”

Reichel et al. (2010) Neuropharmacology
Nornicotine is “nicotine-like”

Reichel et al. (2010) *Neuropharmacology*
Varenicline is “nicotine like”

Reichel et al. (2010) Neuropharmacology
What does it mean to be “nicotine-like”?

Bevins et al. (in press) *Behavioural Processes*
Substitute in Other Learning Situations

Reichel et al. (2010) *Neuropharmacology*

0.6 mg/kg ABT-418 = 0.4 mg/kg Nicotine

if they are really the same

Besheer et al. (2004) *Psychopharmacology*
Transfer of Extinction Learning

Interoceptive Conditioning w/ Nicotine

Extinguish w/ assigned solution

Test Nicotine

Reichel et al. (2010) *Neuropharmacology*
Transfer of Extinction Learning

Interoceptive Conditioning w/ Nicotine

Extinguish w/ assigned solution

Test Nicotine

Reichel et al. (2010) Neuropharmacology
Extinction with Assigned Solution

Nicotine → Conditioning Chamber (20 min) → no sucrose

ABT-418
Saline

Goal Tracking

Reichel et al. (2010) *Neuropharmacology*
Extinction with Assigned Drug

Reichel et al. (2010) *Neuropharmacology*
Transfer of Extinction Learning

Interoceptive Conditioning w/ Nicotine

Extinguish w/ assigned solution

Test Nicotine

Reichel et al. (2010) Neuropharmacology
No Transfer of Extinction

Reichel et al. (2010) *Neuropharmacology*
Extent of Generalization

- **stimulus substitution**
  - Blank to full

- **repeated extinction**
  - None to full

- **extinction transfer**
  - Blank to full
Transfer of Extinction Learning
~NORNICOTINE~
Extinction with Nornicotine

Reichel et al. (2010) *Neuropharmacology*
Transfer of Extinction with Nornicotine

Reichel et al. (2010) Neuropharmacology
Extent of Generalization

- **stimulus substitution**: none to full
- **repeated extinction**: none to full
- **extinction transfer**: none to full
Transfer of Extinction Learning

~VARENICLINE~

Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation
A Randomized Controlled Trial

Drug Treatment

- Varenicline (n=344)
- Bupropion SR (n=342)
- Placebo (n=341)

Abstinence Point Prevalence %

Week

Douglas E. Jorenby, PhD
J. Taylor Hays, MD
Nancy A. Rigotti, MD
Salomon Azoulay, MD
Eric J. Watsky, MD
Kathryn E. Williams, PhD
Clare B. Billing, MS
Jason Gong, MD
Karen R. Reeves, MD
for the Varenicline Phase 3 Study Group
Extinction with Varenicline

Reichel et al. (2010) *Neuropharmacology*
Transfer of Extinction with Varenicline

Reichel et al. (2010) *Neuropharmacology*
Extent of Generalization

- **stimulus substitution**
  - none
  - full

- **repeated extinction**
  - none
  - full

- **extinction transfer**
  - none
  - full
Transfer of Extinction Learning

~BUPROPION~
Extent of Generalization

Wilkinson et al. (2010) *Journal of Psychopharmacology*
Extinction with Bupropion

Charntikov et al. (in preparation)
Transfer of Extinction

Charntikov et al. (in preparation)
Extent of Generalization

- **stimulus substitution**
- **repeated extinction**
- **extinction transfer**

Levels:
- None
- Full
Deepen Extinction?

More extinction?

Charntikov et al. (in preparation)
Deepen Extinction with Bupropion

Nicotine CS Training

↓

Extinction with 20mg/kg Bup

(24, 12, 6, 3, 0 days)*

*saline on remainder of 24 days

↓

Transfer of Extinction Test

(0.4 mg/kg nicotine)

Charntikov et al. (in preparation)
Extinction with 20 mg/kg bupropion

Charntikov et al. (in preparation)
Transfer Test (or lack of...)
Reflections on Findings

-30+ years of drug discrimination research
  Similar outcome with 2-lever operant task

-What should be measured?
  mechanism or process
  which of import to addiction development of pharmacotherapies

-Questions and future directions
  deepening extinction
  other associative processes

Bevins et al. (in press) *Behavioural Processes*
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Bevins et al. (in press) Behavioural Processes
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Bevins et al. (in press) *Behavioural Processes*
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Questions & Comments

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