NICOTINE DELIVERY-ISSUES AND TECHNOLOGY

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1. “To what degree is habit maintenance reinforced by the nicotine content and delivery itself and/or by factors other than nicotine?”

2. “What predictors of quitting and relapse exist, how strong are they and how might these interact with the existence of potential reduced risk tobacco products?”
1. PHARMACOLOGY AND PHARMACOKINETICS OF NICOTINE

2. SENSORY/HABIT FACTORS IN TOBACCO ADDICTION

3. IMPLICATIONS FOR SMOKING CESSION AND REDUCED RISK PRODUCTS
NICOTINE

\[
\text{CH}_3\text{-C-O-CH}_2\text{-CH}_2\text{-N(CH}_3\text{)_3}^+\text{CH}_3
\]

ACETYLCHOLINE
A₁ Excitation by transmitter due to opening an ion channel

Receptor

Na⁺

K⁺

Closed

A₂

Na⁺

ACh

Open

K⁺
PET Image of Human Brain with 2-[^18F]Fluoro-A-85380
PHARMACOKINETICS OF INHALED NICOTINE
Measurement of arterial blood nicotine concentrations every 5 s during cigarette smoking vs. IV nicotine administration

Sample:
13 smokers (10 males, 3 females)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr.)</td>
<td>38 (7.9)</td>
</tr>
<tr>
<td>Cigs/day</td>
<td>28 (11)</td>
</tr>
<tr>
<td>FTND score</td>
<td>7.0 (1.6)</td>
</tr>
<tr>
<td>FTC nicotine</td>
<td>0.7 (.34)</td>
</tr>
<tr>
<td>Puff vol. (ml)</td>
<td>48 (28)</td>
</tr>
<tr>
<td>Dose/puff (mg)</td>
<td>.12 (.04)</td>
</tr>
<tr>
<td># puffs</td>
<td>6.2 (1.9)</td>
</tr>
<tr>
<td>Interpuff interval (s)</td>
<td>66 (31)</td>
</tr>
</tbody>
</table>
TEMPORAL PATTERN OF ARTERIAL NICOTINE CONCENTRATION:
PREDICTED VS. MEASURED

ARterial nicotine concentration (ng/ml) vs. time (sec)

- Predicted
- Measured
Short-term distribution of nicotine in the rat lung

(courtesy of Peter P. Rowell, Ph.D.)
<table>
<thead>
<tr>
<th>GROUP</th>
<th>CIGARETTE</th>
<th>I.V. CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DENIC (or no smoking)</td>
<td>Continuous Nicotine</td>
</tr>
<tr>
<td>2</td>
<td>DENIC (or no smoking)</td>
<td>Pulsed Nicotine</td>
</tr>
<tr>
<td>3</td>
<td>DENIC (or no smoking)</td>
<td>Saline</td>
</tr>
<tr>
<td>4</td>
<td>USUAL BRAND (or no smoking)</td>
<td>Saline</td>
</tr>
</tbody>
</table>
CRAVING REDUCTION

RATING (1-7)

NO SMOKE

DENIC

IV SALINE
IV CONTINUOUS INFUSION
IV PULSED INJECTION
IV SALINE
IV CONTINUOUS INFUSION
USUAL BRAND + IV SALINE
EFFECTS ON AD LIB SMOKING BEHAVIOR OF CONTROLLED PRESENTATIONS OF SMOKE COMPONENTS VS. IV NICOTINE

EXPERIMENTAL CONDITIONS

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CONTROLLED SMOKE</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>USUAL BRAND</td>
<td>SALINE</td>
</tr>
<tr>
<td>B</td>
<td>DENICOTINIZED</td>
<td>SALINE</td>
</tr>
<tr>
<td>C</td>
<td>DENICOTINIZED</td>
<td>NICOTINE (pulsed)</td>
</tr>
<tr>
<td>D</td>
<td>NO SMOKE</td>
<td>NICOTINE (pulsed)</td>
</tr>
<tr>
<td>E</td>
<td>NO SMOKE</td>
<td>NICOTINE (slow infusion)</td>
</tr>
<tr>
<td>F</td>
<td>NO SMOKE</td>
<td>SALINE</td>
</tr>
</tbody>
</table>
Apparatus for delivering smoke doses and for assessing *ad lib* smoking

**Controlled Puff Apparatus**

**CReSS Smoking Topography Monitor (*ad lib* smoking)**
AD LIB SMOKING

Cumulative Puff Volume (cc)

Controlled Smoke
- Usual Brand
- Denic CIG + IV NIC
- Denic CIG

No Controlled Smoke
- IV NIC Pulsed
- IV NIC Infusion
- Saline
RATING SCALE (1-7)

UB DENIC+PULSED IV DENIC PULSED IV CONT IV SALINE

CRAVING

NEGATIVE AFFECT

AROUSAL

EXPERIMENTAL CONDITION

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60

0    30   60
SMOKE/IV NICOTINE PREFERENCE TEST
APPARATUS
PREFERENCE TEST RESULTS

NUMBER OF TIMES CHOSEN

DENIC PUFFS

SHAM PUFFS

NICOTINE INFUSIONS

SALINE INFUSIONS

A (DEN+NIC)  B (DEN+SAL)  C (SHM+NIC)  D (SHM+SAL)

Mean Number of Times Chosen

DENIC

PUFFS

SHAM

PUFFS

NICOTINE

INFUSIONS

SALINE

INFUSIONS
PHARMACOLOGIC AND HABIT/SENSORY COMPONENTS OF CIGARETTE SMOKING

SITUATIONAL CUES
- Withdrawal state
- Social Influences
- Tasks demands

HABIT COMPONENTS
Sensory
Taste
Aroma
Airway sensations

Motor
Manipulation
Puffing
Inhalation

CNS NICOTINE EFFECTS:
Direct action at nicotinic receptors
Neurotransmitter Release:
- Dopamine
- Acetylcholine
- Norepinephrine
- Glutamate

Reinforcement of habit components
Cue-Induced Responses (Across smoking conditions)
Ventral Striatum/Ventral ACC

Stimulus, $p = .074$

Stimulus, $p = .037$
Cue-induced effects (Across smoking conditions)
Superior Frontal Gyrus

Stimulus, $p = .009$
Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues.

McCleron FJ, Hiott FB, Huettel SA, Rose JE

Neuropsychopharmacology, in press, 2005
Citric acid aerosol as a potential smoking cessation aid
JE Rose and CS Hickman
Chest, Vol 92, 1005-1008

Development of a citric acid aerosol as a smoking cessation aid
Levin ED, Rose JE, Behm F.

Clinical evaluation of a citric acid inhaler for smoking cessation
Behm FM, Schur C, Levin ED, Tashkin DP, Rose JE
HAND-HELD AEROSOL DELIVERY SYSTEM

- 40 cc Plastic Reservoir
- Actuator
- Press to actuate
- Canister
- Air Inlet
- Flavor Cartridge
- Mouthpiece
Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized, placebo-controlled trial using a citric acid inhaler

EC Westman, FM Behm and JE Rose

Chest, Vol 107, 1358-1364, 1995
Continuous Smoking Abstinence
Citric Acid Inhaler and Nicotine Patch vs. Lactose Inhaler and Nicotine Patch

Days After Quit Date

Abstinence

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

Nicotine Patch x 6 weeks
Cigarette Substitute x 10 weeks
Citric Acid
Lactose
USE OF LOW NICOTINE CONTENT TOBACCO CIGARETTES IN SMOKING CESSION TREATMENT
Research Design

<table>
<thead>
<tr>
<th>Phase</th>
<th>Baseline 2 weeks</th>
<th>Treatment 4 weeks</th>
<th>Follow-up 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette</td>
<td>Usual Brand</td>
<td>.05 mg (Quest®)</td>
<td>Quit</td>
</tr>
<tr>
<td>Patch</td>
<td>21 mg/day Nicoderm®</td>
<td>14 mg/day</td>
<td>7 mg/day</td>
</tr>
<tr>
<td>fMRI</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Office Visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Event-related fMRI results
Ventral Striatum: Stimulus x Scan x Group*, $p = .041$
Event-related fMRI results
Thalamus: Stimulus x Scan x Group*, $p = .031$

![fMRI Graphs](Graphs)
CONCLUSIONS

1. Nicotine plays a major role in tobacco addiction; nicotine absorption from cigarette smoking is fast, but not substantially more rapid than IV administration or nasal spray administration. 5-10 min bolus may be as effective as 5-10 s bolus.

2. Rapid nicotine administration (e.g. 5 min) appears to relieve craving for cigarettes more effectively than slow (e.g. 40 min) nicotine administration.
3. Sensory cues, both exteroceptive and interoceptive, also play a major role in tobacco addiction.

4. Therapeutic strategies that entail substituting for these cues, or, alternatively, attenuating their potency (e.g. extinction therapy), may be promising avenues for new smoking cessation treatments.