Delineating the neurochemical effects of tobacco smoking from alcohol drinking

Julie K. Staley, Ph.D.
Department of Psychiatry
Yale University School of Medicine
Alcohol & Tobacco Smoking

• Alcohol drinkers smoke more than nondrinkers & tobacco smokers drink more than nonsmokers

• Alcoholic smokers have an earlier age of onset of alcohol dependence and more alcohol related problems

• Smokers feel less intoxicated upon alcohol challenge suggesting that smoking enhances tolerance to alcohol

[Bien et al., 1990; Difranza & Guerrera, 1990; Abrams et al., 1992; Johnson and Jennison, 1992; Gulliver et al., 1995; Deappen et al., 2000]
Tobacco is Like Love

Tobias Humb

Musicall Humors 1605

Tobacco, Tobacco, sing sweetly for tobacco, tobacco is like love, O love it For you see I will prove it.

Love maketh leane the fatte mens tumor, so doth tobacco,

Love still dries uppe the wanton humor, so doth tobacco,

Love makes men sayle from shore to shore, so doth tobacco,

Tis fond love often make men poor, so doth tobacco,

Love makes men scorn al Coward feares, so doth tobacco,

Love often sets men by the eares, so doth tobacco,

Tobaccoe, Tobaccoe, sing sweetly for tobaccoe, Tobaccoe is like Love, O love it, For you see I have provde it.

Anonymous
Components of Tobacco Smoke

- Nicotine
- Cembranoids
- Cyanide
- Thiocyanate
- MAO-A Inhibitor
- MAO-B Inhibitor
- Hydrazine
- Norharman
- Harman
- Phenylpyridine
Like Alcohol, Tobacco Smoke Facilitates DA Neurotransmission

Via its actions on the cholinergic nicotinic receptor, nicotine indirectly

↓ DA reuptake (brain*cells®)

↑ DA release (brain#)

An unknown component of tobacco smoke

↓ MAO-B activity&

NET EFFECT  ↑ DA neurotransmission

*Izenwasser et al., 1991,®Yamashita et al., 1995,#Westfall et al., 1974; Marien et al., 1983;Rapier et al., 1988;Nisell et al., 1994;Pontieri et al., 1996;&Essman, 1977;Yu and Boulton, 1987
Striatal DA Synapse in Smokers and Alcohol Drinkers

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Alcohol Drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO-B#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVA/DA*#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₁ Receptor*/^</td>
<td>(-)/↓</td>
<td>?</td>
</tr>
<tr>
<td>D₂ Receptor*</td>
<td>(-)</td>
<td>?</td>
</tr>
<tr>
<td>D₃ Receptor* &amp;</td>
<td>(-)</td>
<td>?</td>
</tr>
<tr>
<td>DA Transporter**</td>
<td>(-)</td>
<td>(-)/↓↑</td>
</tr>
</tbody>
</table>

# Fowler et al., 1996; * Court et al., 1998; ^ Bliecher et al., 1999; # Fulton et al., 1995; Heinz et al., 1996; * Tiihonen et al., 1995; 1998; Volkow et al., 1996; Heinz et al., 1998; Laine et al., 1999; & Hietala et al., 1994
Higher Striatal $^{123}$Iβ-CIT Uptake in Women vs Men (p = 0.025)
No Change in Smokers vs Nonsmokers

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmokers</td>
<td>Smokers</td>
<td>Nonsmokers</td>
</tr>
<tr>
<td>V3' $^{[\text{Striatum-CB}]}/\text{CB}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmokers</td>
<td>Smokers</td>
<td>Nonsmokers</td>
</tr>
<tr>
<td>V3' $^{[\text{Striatum-CB}]}/\text{CB}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmokers</td>
<td>Smokers</td>
<td>Nonsmokers</td>
</tr>
<tr>
<td>V3' $^{[\text{Striatum-CB}]}/\text{CB}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Striatal $[^{123}\text{I}]\beta$-CIT Uptake in Healthy & Alcohol Dependent Smokers & Nonsmokers

HNS ($n=2$)  HS ($n=5$)  ANS ($n=2$)  AS ($n=5$)
Like Alcohol, Tobacco Smoke Facilitates Serotonin Neurotransmission

Via its actions on the cholinergic nicotinic receptor, nicotine indirectly

5-HT reuptake (platelet#; brain@)

5-HT release (platelet*; brain^)

An unknown component of tobacco smoke

MAO-A activity&

NET EFFECT ↑ 5-HT neurotransmission

*Schievelbein et al., 1967; *Rausch et al., 1989; @King et al., 1991; ^Ribeiro et al., 1993; &Essman, 1977; Yu and Boulton, 1987
## Status of 5-HT Synapse in Smokers & Alcohol Drinkers

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Alcohol Drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO-A (^1)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>5-HT (Platelet*; Urine#)</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>5-HIAA (Urine)#</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>5-HT(_{1A}) Receptor (Brain(^\wedge))</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>5-HT(_{2A}) Receptor (Platelet@; Brain(^\wedge))</td>
<td>↓/(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>5-HT Transporter</td>
<td>?</td>
<td>↓/(-)</td>
</tr>
</tbody>
</table>

\(^1\)Fowler et al., 1996; *Marasini et al., 1986; Racke et al., 1992; #Sparrow et al., 1992; ^Benwell et al., 1990; @Markowitz et al., 1999
Higher Diencephalon $[^{123}I]\beta$-CIT Uptake in Women vs Men ($p = 0.008$). No Change in Smokers vs Nonsmokers.
Higher Brainstem [$^{123}$I]β-CIT Uptake in Women vs Men (p = 0.013) & Men Smokers vs Nonsmokers (p = 0.046)

* * p < 0.05
Diencephalon $[^{123}I] \beta$-CIT Uptake in Healthy & Alcoholic Smokers & Nonsmokers
Brainstem $[^{123}\text{I}]\beta$-CIT Uptake in Healthy & Alcoholic Smokers & Nonsmokers

![Graph showing brainstem $[^{123}\text{I}]\beta$-CIT uptake in different groups: HNS (n = 2), HS (n = 5), ANS (n = 2), AS (n = 5).]
GABA & Ethanol Bind to Distinct but Allosterically Regulated Sites on the GABA\textsubscript{A} Receptor
**Tobacco Smoke & GABA**

- **Nicotine**
  - Low doses nicotine enhance GABAergic transmission; higher doses no effect [Zhu & Chiappinelli, 1999]
  - Chronic nicotine treatment in mice increase \[^{125}\text{I}]omazenil binding sites [Magata et al., 2000]

- **Beta carbolines**
  - Competitive antagonists at benzodiazepine receptor [Totsuka et al., 1999]
  - Elevated levels of beta carbolines in plasma from healthy and alcoholic smokers [Breyer-Pfaff et al., 1996]
### Status of GABA Synapse in Smokers and Alcohol Drinkers

<table>
<thead>
<tr>
<th></th>
<th>Smoker</th>
<th>Alcohol Drinker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GABA Plasma/CSF</strong></td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td><strong>GABA Brain</strong></td>
<td>(-)/↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>GABA_A Receptor (Agonist)</strong></td>
<td>?</td>
<td>↑</td>
</tr>
<tr>
<td><strong>GABA_A Receptor (BZ Agonist)</strong></td>
<td>?</td>
<td>(-)/↓↑</td>
</tr>
<tr>
<td><strong>GABA_A Receptor (BZ Antagonist)</strong></td>
<td>?</td>
<td>(-)/↓</td>
</tr>
</tbody>
</table>

Tran et al., 1981; Coffman & Petty, 1985; Kril et al, 1988; Freund & Ballinger, 1988; Dodd et al., 1992; Korpi et al., 1992; Petty et al., 1993; Adinoff et al., 1995; Lewohl et al., 1997
Negative Correlation between $[^{123}\text{I}]$Iomazenil Uptake in Alcohol Dependent Subjects Abstinent for $< 7$ Days and FTND Score for Nicotine Dependence

Corrected p values $< 0.006$ @ cluster level
BDZ-GABA-A Receptor Expression in Healthy & Alcoholic Smokers & Nonsmokers

### Anterior Cingulate

- Smokers
- NS
- AS < 7d
- ANS < 7d
- AS 4 wks
- ANS 4 wks

### Frontal Cortex

- Smoker
- NS
- AS < 7d
- ANS < 7d
- AS 4 wks
- ANS 4 wks

### Hippocampus-Amygdala

- Smokers
- NS
- AS < 7d
- ANS < 7d
- AS 4 wks
- ANS 4 wks

### Occipital Cortex

- Smokers
- NS
- AS < 7d
- ANS < 7d
- AS 4 wks
- ANS 4 wks
[\textsuperscript{123}I] Iomazenil SPECT Images of GABA-A Receptors

Control
Alcoholic Nonsmoker
5 Days Abstinent
Alcoholic Nonsmoker
25 Days Abstinent
Alcoholic Nonsmoker
157 Days Abstinent
Tobacco Smoke & nAChR

Increased nicotinic agonist binding in
- Peripheral blood cells from tobacco smokers
- Postmortem human brain Benwell et al., 1988; Breese et al; 1997; Court et al., 1998; Perry et al., 1999

Animal studies demonstrate that the upregulation is due to repeated exposure to nicotine
Alcohol & nAChR

- Low doses of nicotine, decrease or have not effect on ethanol consumption [Gauvin et al., 1993; Katner et al., 1997; Dyr, 1999]

- Nicotine enhances alcohol consumption [Pothoff et al., 1983; Signs et al., 1986; Blomqvist et al., 1996; Gauvin et al., 1993; Le et al., 2000], especially alcohol preferring rats [Gordon et al., 1993]

- Nicotine attenuates ethanol-induced motor impairment [Dar, 1994]
Role of nAChR in Dual Alcohol/Tobacco Smoking: Hypothesis

Tobacco smoking enhances nAChR desensitization. Ethanol may facilitate re-sensitization of β₂-nAChR receptors (and not acute activation or prolonged desensitization) and promote tobacco smoking in alcohol drinkers.
Test-Retest Reliability of $[^{123}\text{I}]5$-IA
### Summary of Test-Retest Reliability for Various Brain Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>kBq/cc</th>
<th>%ID/ce</th>
<th>Vₜ'</th>
<th>Vₜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC</td>
<td>15.2 ± 13.0</td>
<td>13.5 ± 12.6</td>
<td><strong>5.4</strong> ± <strong>6.6</strong></td>
<td>13.4 ± 12.2</td>
</tr>
<tr>
<td>AC</td>
<td>15.3 ± 12.3</td>
<td>12.6 ± 11.5</td>
<td><strong>5.2</strong> ± <strong>5.3</strong></td>
<td>13.0 ± 11.8</td>
</tr>
<tr>
<td>TC</td>
<td>15.3 ± 12.4</td>
<td>12.3 ± 10.6</td>
<td><strong>5.6</strong> ± <strong>5.8</strong></td>
<td>12.1 ± 13.2</td>
</tr>
<tr>
<td>OC</td>
<td>17.4 ± 13.4</td>
<td>14.2 ± 12.3</td>
<td><strong>5.0</strong> ± <strong>5.8</strong></td>
<td>12.0 ± 12.7</td>
</tr>
<tr>
<td>Cd</td>
<td>16.5 ± 13.7</td>
<td>12.0 ± 11.5</td>
<td><strong>4.8</strong> ± <strong>6.4</strong></td>
<td>11.3 ± 14.3</td>
</tr>
<tr>
<td>Pt</td>
<td>13.1 ± 10.3</td>
<td>11.3 ± 9.4</td>
<td><strong>7.2</strong> ± <strong>6.9</strong></td>
<td>12.8 ± 14.0</td>
</tr>
<tr>
<td>Thal</td>
<td>12.3 ± 10.1</td>
<td>11.2 ± 9.7</td>
<td><strong>6.5</strong> ± <strong>4.8</strong></td>
<td>13.3 ± 12.5</td>
</tr>
<tr>
<td>HA</td>
<td>13.7 ± 9.9</td>
<td>11.2 ± 8.4</td>
<td><strong>5.4</strong> ± <strong>5.7</strong></td>
<td>12.1 ± 11.7</td>
</tr>
<tr>
<td>CB</td>
<td>16.3 ± 13.6</td>
<td>12.8 ± 12.1</td>
<td><strong>5.9</strong> ± <strong>5.4</strong></td>
<td>13.8 ± 13.5</td>
</tr>
</tbody>
</table>

The mean ± S.D. % Test-Retest Reliability is shown (n = 10).
Displacement of $[^{123}\text{I}]5$-IA-85830 by Nicotine in Nonhuman Primate Brain

- **Thalamus**
- **Hipp/Amyg**
- **Ant Cing**
- **Cerebellum**

**Graphs:**
- **Nicotine 0.06 mg/kg i.v.**
- **Cotinine 0.06 mg/kg i.v.**
- **Transdermal Nicotine Patch 14 mg**
\[ ^{123}\text{I} \]5IA SPECT Imaging of Nonhuman Primates Administered Oral Nicotine

**Salem**

- [\(^{123}\text{I} \]5IA Uptake) $V_T$
- Cotinine Dip Level

**Winston**

- [\(^{123}\text{I} \]5IA Uptake) $V_T$
- Cotinine Dip Level

---

**Graphs**:

- Measurements over time (in weeks/day) for B1, B2, 6wk/1d, 8wk/7d.
- Cotinine dip levels during withdrawal.

---

**Legend**:

- thalamus
- CC
- FC
- OC
- BG
Urinary Cotinine in Human Tobacco Smokers Over the First Week of Abstinence

[Krishnan-Sarin & Colleagues, unpublished data]
$[^{123}\text{I}]5\text{-IA-85830 Imaging of nAChR in Healthy & Alcohol Dependent Smokers & Nonsmokers$
SUMMARY

Critical need to control for possible regulatory effects of tobacco smoke in brain imaging studies of alcoholics

- Alcohol Abstinence*Smoking
- Alcohol Drinking* Smoking Cessation
- Alcohol Abstinence*Smoking Cessation
- All of above*Genotype
- All of above*Personality Traits
- All of above*Sex

- Chronic effects of tobacco smoking on blood flow
Acknowledgments

Imaging Group
John Krystal, MD
Ronald Baldwin, PhD
Gilles Tamagnan, PhD
Suzanne Giddings
Louis Amici
Nina Sheung
Erin Frohlich
Meredith Terlecki
Shawna Ellis
Noah McGuire Schwartz
Quinn Ramsby
Kristina Estok
Kelly Cosgrove, PhD
Lavinia Bizeta, MD
Effie Mitsis, PhD
David Alagille, PhD
Eric Brenner, PhD
Haibin Tian, PhD
Rebecca Vogel
Carol Magnussen
Mohammed Al Tikriti, PhD

Collaborators
Stephanie O'Malley, PhD
Suchitra Krishnan-Sarin, PhD
Ismene Petrakis, MD
Edward Perry, MD
Christopher Van Dyck, MD
Louis Trevisan, MD
Robert Innis, MD, PhD
Paul K. Maciejewski, Ph.D.
Ralitza Gueorguieva, PhD
Joel Dublin, PhD

NeuroSPECT/IND
John Seibyl, MD
Michele Early
Andrea Perez
Eileen Smith
Michele Early
Gary Wisenski
Support

• NIAAA
  K01 AA00288
  RO1 AA11321
• ABMRF
• Patterson Trust
• VA MIRECC
• VA Alcohol Research Center
• The Donaghue Women's Health Investigator Program at Yale