NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION

CHEMISTRY of NICOTINE

Nicotiana tabacum
Natural liquid alkaloid
Colorless, volatile base $pK_a = 8.0$

PHARMACOLOGY

Effects of the body on the drug
- Pharmacokinetics
  - Effects of the body on the drug
    - Absorption
    - Distribution
    - Metabolism
    - Excretion

NICOTINE ABSORPTION

Absorption is pH dependent
- In acidic media
  - Ionized $\Rightarrow$ poorly absorbed across membranes
- In alkaline media
  - Nonionized $\Rightarrow$ well absorbed across membranes
  - At physiologic pH (7.3–7.5), ~31% of nicotine is unionized

At physiologic pH, nicotine is readily absorbed.

NICOTINE ADDICTION


- Cigarettes and other forms of tobacco are addicting.
- Nicotine is the drug in tobacco that causes addiction.
- The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.


NICOTINE ABSORPTION: BUCCAL (ORAL) MUCOSA

The pH inside the mouth is 7.0.

Acidic media (limited absorption)
- Cigarettes

Alkaline media (significant absorption)
- Pipes, cigars, spit tobacco, oral nicotine products

Beverages can alter pH, affect absorption.
NICOTINE ABSORPTION: SKIN and GASTROINTESTINAL TRACT

- Nicotine is readily absorbed through intact skin.
- Nicotine is well absorbed in the small intestine but has low bioavailability (30%) due to first-pass hepatic metabolism.

NICOTINE ABSORPTION: LUNG

- Nicotine is “distilled” from burning tobacco and carried in tar droplets.
- Nicotine is rapidly absorbed across respiratory epithelium.
  - Lung pH = 7.4
  - Large alveolar surface area
  - Extensive capillary system in lung

NICOTINE DISTRIBUTION


NICOTINE METABOLISM


NICOTINE EXCRETION

- Half-life
  - Nicotine $t_{1/2} = 2$ hr
  - Cotinine $t_{1/2} = 19$ hr
- Excretion
  - Occurs through kidneys (pH dependent; ↑ with acidic pH)
  - Through breast milk

NICOTINE PHARMACODYNAMICS

Nicotine has predominantly stimulant effects.
NICOTINE PHARMACODYNAMICS (cont’d)

Central nervous system
- Pleasure
- Arousal, enhanced vigilance
- Improved task performance
- Anxiety relief

Cardiovascular system
- ↑ Heart rate
- ↑ Cardiac output
- ↑ Blood pressure
- Coronary vasoconstriction
- Cutaneous vasoconstriction

Other
- Appetite suppression
- Increased metabolic rate
- Skeletal muscle relaxation

NEUROCHEMICAL and RELATED EFFECTS of NICOTINE

- Dopamine ➔ Pleasure, reward
- Norepinephrine ➔ Arousal, appetite suppression
- Acetylcholine ➔ Arousal, cognitive enhancement
- Glutamate ➔ Learning, memory enhancement
- Serotonin ➔ Mood modulation, appetite suppression
- β-Endorphin ➔ Reduction of anxiety and tension
- GABA ➔ Reduction of anxiety and tension

WHAT IS ADDICTION?

“Compulsive drug use, without medical purpose, in the face of negative consequences”

Alan I. Leshner, Ph.D.
Former Director, National Institute on Drug Abuse
National Institutes of Health

BIOLOGY of NICOTINE ADDICTION: ROLE of DOPAMINE

Nicotine stimulates dopamine release
Pleasurable feelings
Repeat administration
Tolerance develops

Discontinuation leads to withdrawal symptoms.

Nicotine addiction is not just a bad habit.

CHRONIC ADMINISTRATION of NICOTINE: EFFECTS on the BRAIN

Human smokers have increased nicotine receptors in the prefrontal cortex.

Image courtesy of George Washington University / Dr. David C. Perry
**NICOTINE PHARMACODYNAMICS: WITHDRAWAL EFFECTS**

- Depression
- Insomnia
- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite/weight gain
- Decreased heart rate
- Cravings*

* Not considered a withdrawal symptom by DSM-IV criteria.

Most symptoms peak 24-48 hr after quitting and subside within 2-4 weeks.

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**NICOTINE ADDICTION CYCLE**

- Most symptoms peak 24-48 hr after quitting and subside within 2-4 weeks.

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**NICOTINE ADDICTION**

- Tobacco users maintain a minimum serum nicotine concentration in order to
  - Prevent withdrawal symptoms
  - Maintain pleasure/arousal
  - Modulate mood
- Users self-titrate nicotine intake by
  - Smoking/dipping more frequently
  - Smoking more intensely
  - Obstructing vents on low-nicotine brand cigarettes

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**ASSESSING NICOTINE DEPENDENCE**

Fagerström Test for Nicotine Dependence (FTND)

- Developed in 1978 (8 items); revised in 1991 (6 items)
- Most common research measure of nicotine dependence; sometimes used in clinical practice
- Responses coded such that higher scores indicate higher levels of dependence
- Scores range from 0 to 10; score of greater than 5 indicates substantial dependence

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**FACTORS CONTRIBUTING to TOBACCO USE**

- Tobacco advertising
- Conditioned stimuli
- Social interactions

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**TOBACCO DEPENDENCE: A 2-PART PROBLEM**

- Tobacco Dependence
  - Physiological
    - The addiction to nicotine
      - Treatment: Medications for cessation
  - Behavioral
    - The habit of using tobacco
      - Treatment: Behavior change program

Treatment should address the physiological and behavioral aspects of dependence.
### NICOTINE PHARMACOLOGY and ADDICTION: SUMMARY

- Tobacco products are effective delivery systems for the drug nicotine.
- Nicotine is a highly addictive drug that induces a constellation of pharmacologic effects.
- Nicotine activates the dopamine reward pathway in the brain, which reinforces continued tobacco use.
- Tobacco users who are dependent on nicotine self-regulate tobacco intake to maintain pleasurable effects and prevent withdrawal.

### NICOTINE PHARMACOLOGY and ADDICTION: SUMMARY (cont’d)

- Nicotine dependence is a form of chronic brain disease.
- Tobacco use is a complex disorder involving the interplay of the following:
  - Pharmacology of nicotine (pharmacokinetics and pharmacodynamics)
  - Environmental factors
  - Physiologic factors
- Treatment of tobacco use and dependence requires a multifaceted treatment approach.