

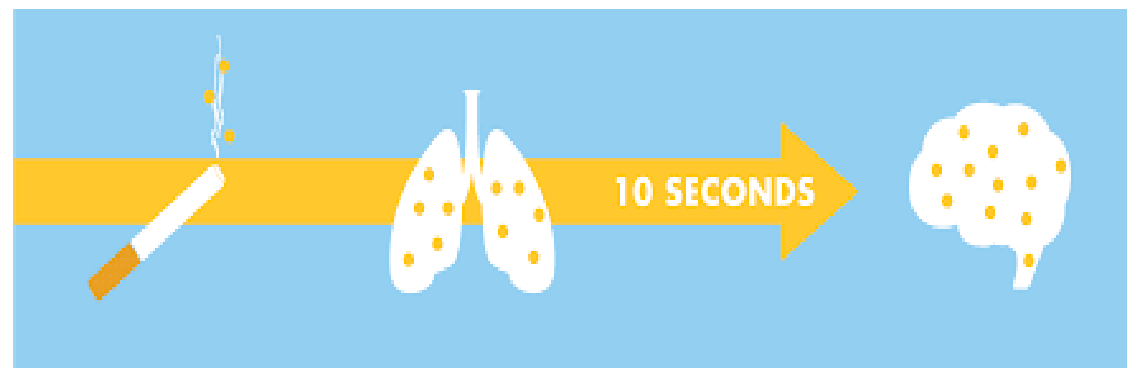
AL MUSTAQBAL UNIVERSITY COLLEGE
DEPARTMENT OF PHARMACY
4TH STAGE
TOXICOLOGY



Lab 5

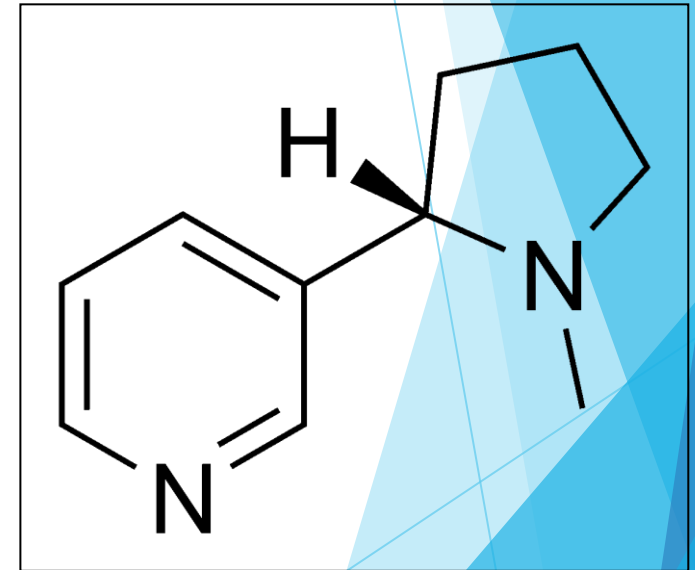
Nicotine Toxicity

Qassim A Zigam



Nicotine

- ❑ Nicotine is a bitter-tasting compound that naturally occurs in large amounts in the leaves of tobacco plants.
- ❑ Leaves of *Nicotiana tobacum* dried and (usually) smoked.



Nicotine Chemical Structure

Nicotine



Leaves of *Nicotiana glauca*



Dried leaves of *Nicotiana glauca*

Nicotine and tobacco

- ❑ Cigarette smoke contains **thousands** of different chemicals, or 'smoke constituents,' also referred to as '**smoke emissions**'
- ❑ The most commonly known smoke constituents are **tar, nicotine and carbon monoxide (CO)**.



Nicotine and tobacco

- ❑ In addition to these, more than **7,000 chemicals** have been identified in tobacco smoke to date
- ❑ **Tobacco and nicotine can be addictive** like alcohol, cocaine, and morphine.



• CHEMICAL COMPOUNDS IN CIGARETTE SMOKE •

A SUMMARY OF A SELECTION OF HAZARDOUS COMPOUNDS IN CIGARETTE SMOKE & THEIR EFFECTS

ESTIMATED NUMBER OF CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

7,357

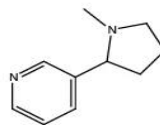
70

NUMBER OF THESE COMPOUNDS WITH CONFIRMED CARCINOGENIC ACTIVITY



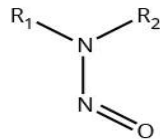
The compounds shown below are all found in cigarette smoke. The mass figures, given in μg , take into account both mainstream (inhaled) and sidestream smoke. 1 μg is equal to 1 millionth of a gram. Amounts of these compounds vary in different brands of cigarettes - these figures are approximate.

NICOTINE



- Approx. 919 μg per cigarette
- Addictive
- Increases heart rate
- Increases blood pressure
- Increases blood glucose
- Lethal dose: around 500-1000mg

N-NITROSAMINES



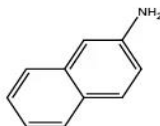
- Large class of compounds
- Several are tobacco-specific
- **Known human carcinogens**
- Most carcinogenic: NNK & NNN
- NNK: approx. 0.3 μg per cigarette
- NNN: approx. 2-50 μg per cigarette
- May cause reproductive damage

BENZENE



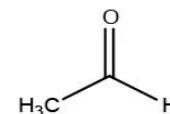
- Approx. 46-272 μg per cigarette
- **Known human carcinogen**
- Damages bone marrow
- Lowers red blood cell count
- May harm reproductive organs

AROMATIC AMINES



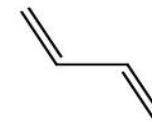
- Large class of compounds
- Includes 2-aminonaphthalene:
 - **Known human carcinogen**
 - Linked with bladder cancer
 - Approx. 0.04 μg per cigarette

ACETALDEHYDE



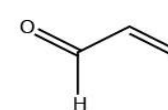
- Approx. 680-1571 μg per cigarette
- **Known animal carcinogen**
- **Probable human carcinogen**
- Irritant to skin & eyes
- Irritant to respiratory tract

1,3-BUTADIENE



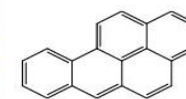
- Approx. 36-191 μg per cigarette
- **Known human carcinogen**
- **Suspected human teratogen**
- Irritant to eyes & skin
- Irritant to upper respiratory tract

ACROLEIN



- Approx. 69-306 μg per cigarette
- **Possible human carcinogen**
- **Known DNA mutagen**
- Irritant to skin & nasal passages
- May contribute to heart disease

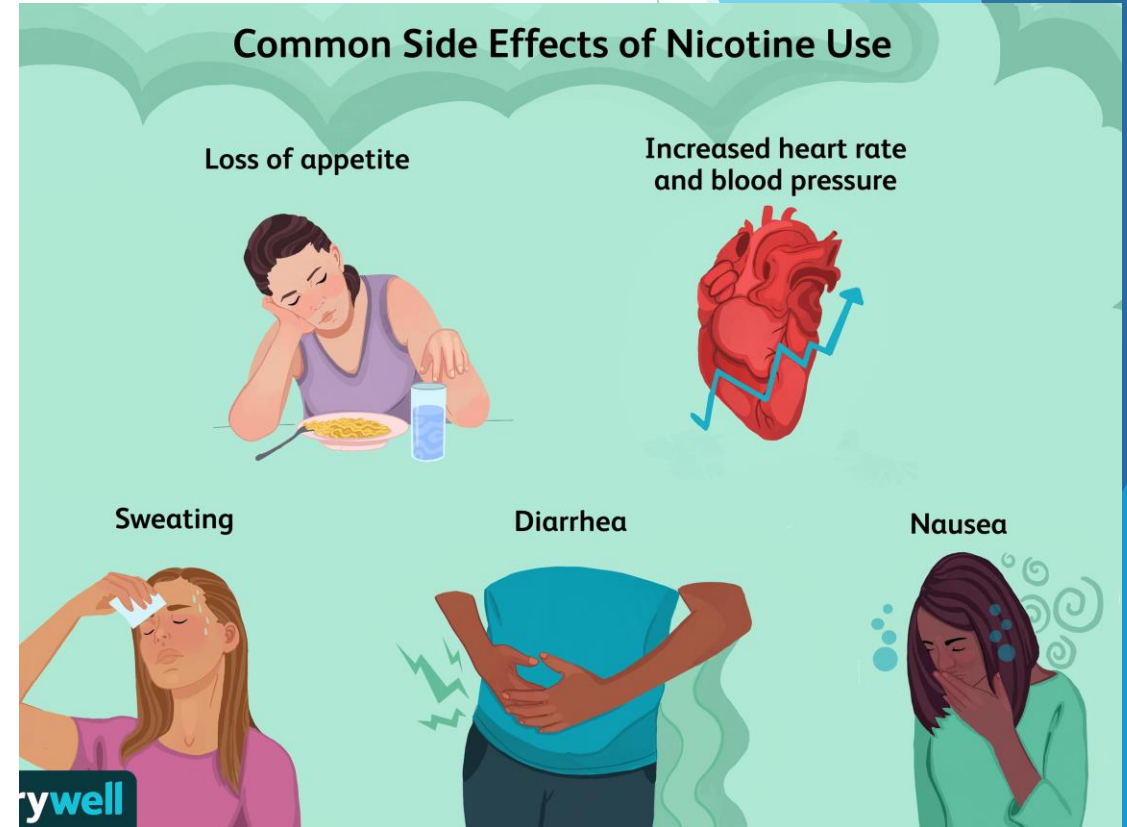
POLYAROMATICS



- Large class of compounds
- Includes benzo[a]pyrene:
 - **Known human carcinogen**
 - **Known DNA mutagen**
 - Affects reproductive capacity
 - Up to 0.14 μg per cigarette

Nicotine effects on the body

- ▶ Decreases the appetite
- ▶ Increases activity of the intestines
- ▶ Creates more saliva and phlegm
- ▶ Increases heart rate
- ▶ Increases blood pressure
- ▶ Sweating, nausea, and diarrhea
- ▶ Boosts mood and may even relieve minor depression
- ▶ Stimulates memory and alertness



Nicotine Pharmacokinetics

1. Absorption:

- Lungs, oral mucosa, skin, Intestinal tract increase in in more alkaline environment

2. Volume of distribution:

- Approximately 1 L/kg

3. Protein binding:

- 5-20%

4. Metabolism:

- 80-90% hepatic, rest in lung, kidney. principle (inactive) metabolite is cotinine

5. Half-life:

- Nicotine 1-4 h decrease with repeated exposure, cotinine 19-20h

4. Excretion:

- 2-35% excreted unchanged in the urine

Nicotine absorption



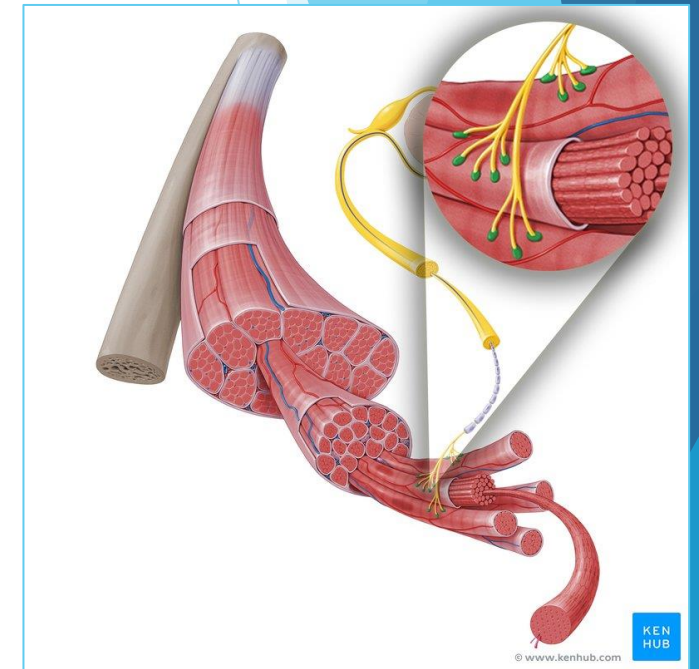
Lungs (nicotine enters the brain with in 7 seconds)

Skin (slower absorption, more constant blood levels)

Stomach, poor (acid- base interaction), better in intestine

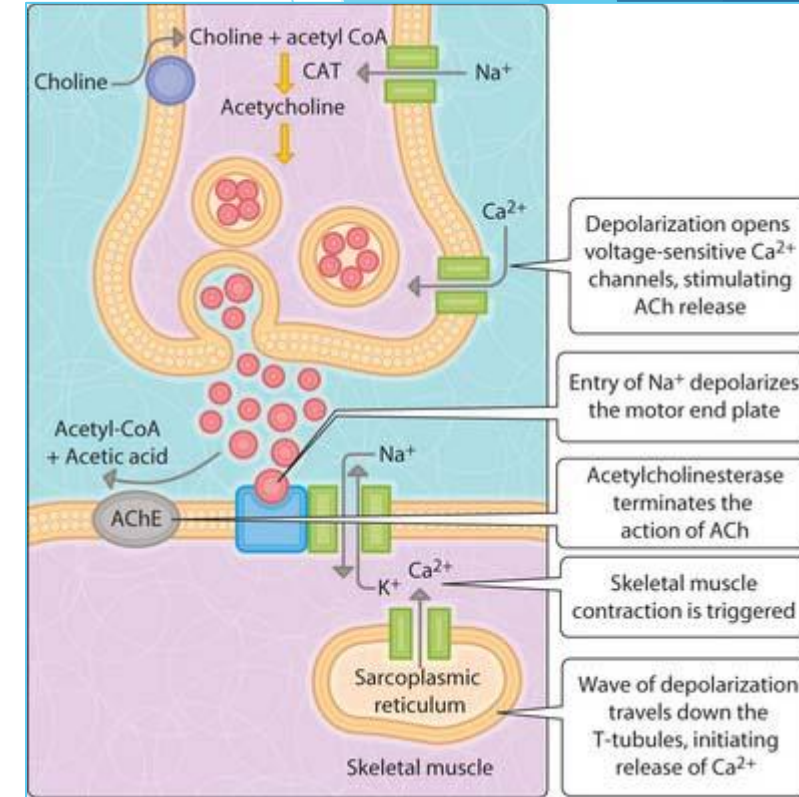
Nicotine Pharmacodynamics

- ▶ Many of the effects of nicotine result from its effects on the neuromuscular system which is made up of the brain and muscle.
- ▶ The neuromuscular system is consisting of the connections between the brain and muscle.
- ▶ The brain connects to the muscle fiber by a special neuron called the motor neuron. The place of contact between the motor neuron and the muscle is called the **NEUROMUSCULAR JUNCTION**.
- ▶ Normally, a signal from the brain stimulates a signal in the motor neuron. The signal travels down the motor neuron to the nerve terminals (the ends of the neuron).



Nicotine Pharmacodynamics

- ▶ A chemical called acetylcholine is then released from the motor neuron terminal and binds to proteins called receptors on the muscle fiber.
- ▶ Binding of acetylcholine to its receptor results in muscle contraction. Normally, following its release and action at its receptor, acetylcholine is broken down and can no longer exert its effects allowing the muscle to relax.
- ▶ Nicotine, however, is not broken down but is able to mimic the effects of acetylcholine at its receptor thus it is as if acetylcholine is always in the synapse and the muscle remains unable to relax.



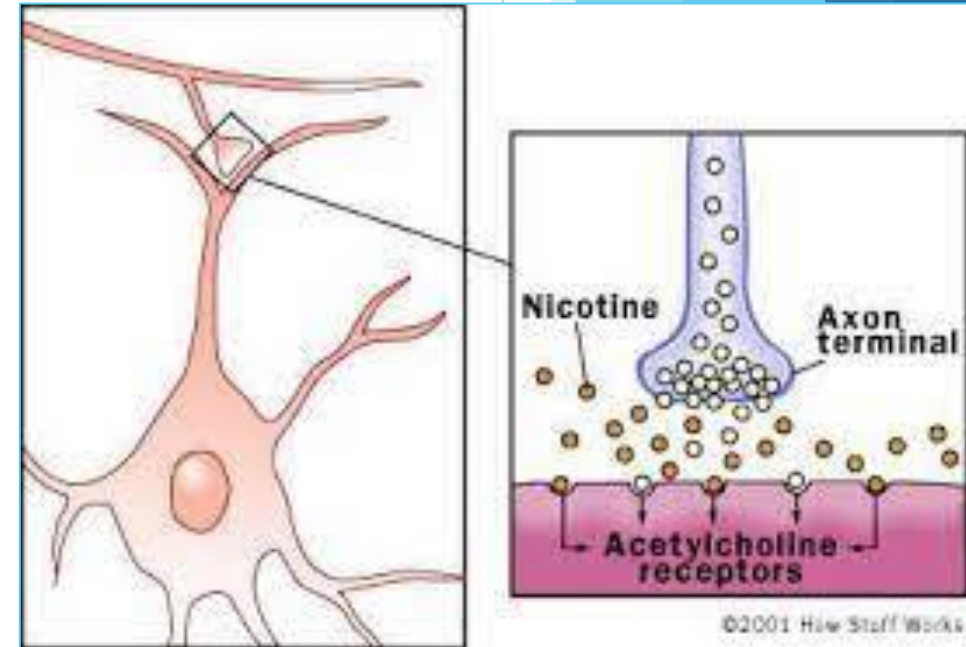
Nicotine Pharmacodynamics

Nicotine is a direct agonist for nicotinic ACh receptors (nAChRs)

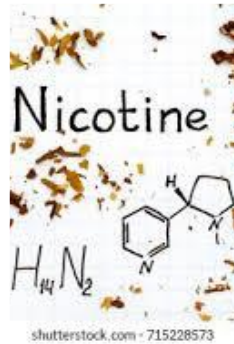
Low dose: Stimulate receptors

High dose: Block receptors

nAChRs found in brain, Muscles, Lymphoid tissue, Macrophages, Skin, Lung cells, Vascular tissue

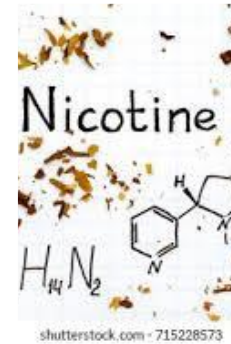


Nicotine Pharmacodynamics

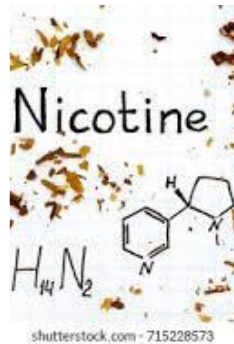


nAChRs are involved in a wide range of physiological and pathological processes

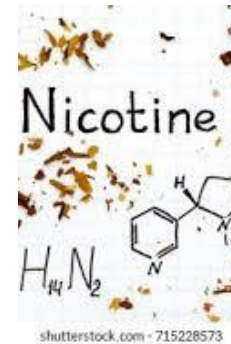
- Learning and memory
- Motor control and analgesia



nAChRs both postsynaptic and presynaptic, facilitating ACh, DA, 5-HT and Glutamate action



Nicotine also increases release of various neurohormones



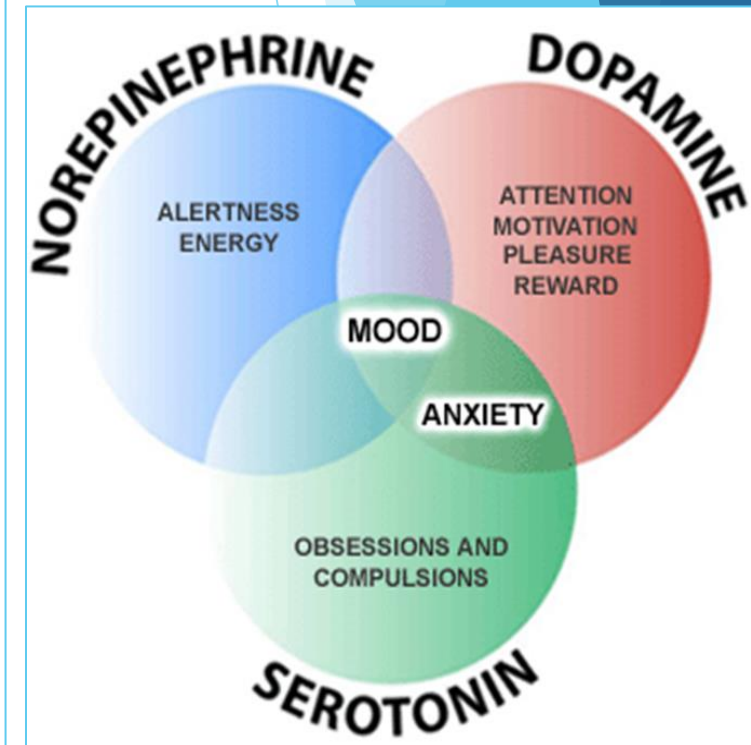
Has powerful effects on peripheral nervous system, heart, and other organs

Nicotine Pharmacodynamics



Nicotine initially causes a rapid release of adrenaline, the "fight-or-flight" hormone

NE, Ach, glutamate, serotonin, GABA, and dopamine are released by nicotine and associated with mood enhancement, appetite suppression and energy expenditure and anxiety reduction



Nicotine toxicity

Acute exposure to high dose nicotine produces a syndrome or set of specific symptoms called the nicotinic syndrome.

The neuromuscular system controls the muscle in many body organs via the acetylcholine receptor. Thus, nicotine produces effects in multiple body organs, but the response is different depending on the length of exposure.

Acute Effects of Nicotine

N/V, Salivation, diarrhea, dizziness, mental confusion, and weakness.

Fatal exposure (60 mg for adults, oral LD50=0.8mg/kg)

Decreased blood pressure, breathing difficulty, irregular pulse, convulsions, respiratory depression, and death

Death is usually due to paralysis of respiratory muscles and/or central respiratory failure

Chronic Effects of Nicotine

Chronic exposure to low dose nicotine also effects the neuromuscular system but leads to a different set of consequences.

Chronic administration leads to coronary artery disease and hypertension

Nicotine produces peptic ulcer disease, and esophageal reflux through its influences on the Gastrointestinal tract.

Nicotine enhances learning and memory

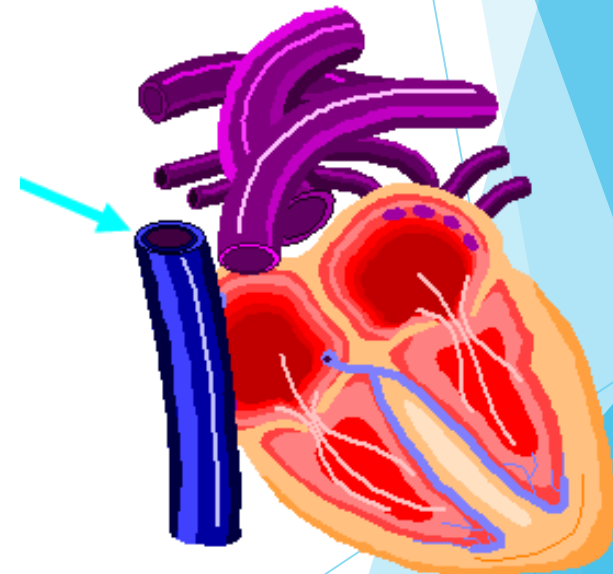
Nicotine's influences in the brain also produces its addictive properties

Cardiac effects of Nicotine toxicity

Nicotine produces

- Tachycardia
- Increase the blood pressure

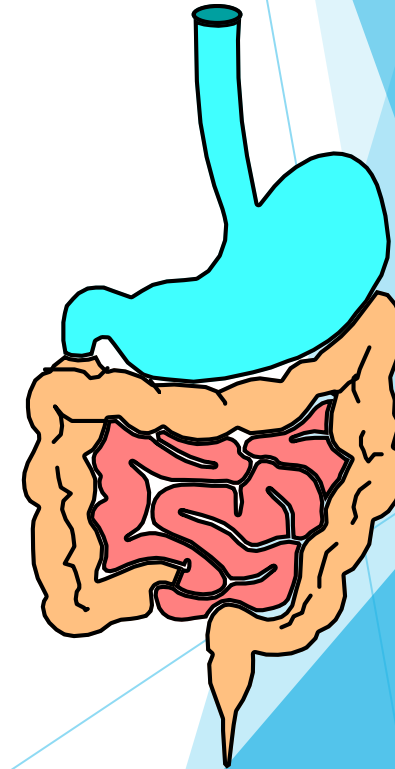
through its action in the sympathetic nervous system or the “Fight or Flight” system.



GIT effects of Nicotine toxicity

Acute action of nicotine in the enteric branch of the neuromuscular system

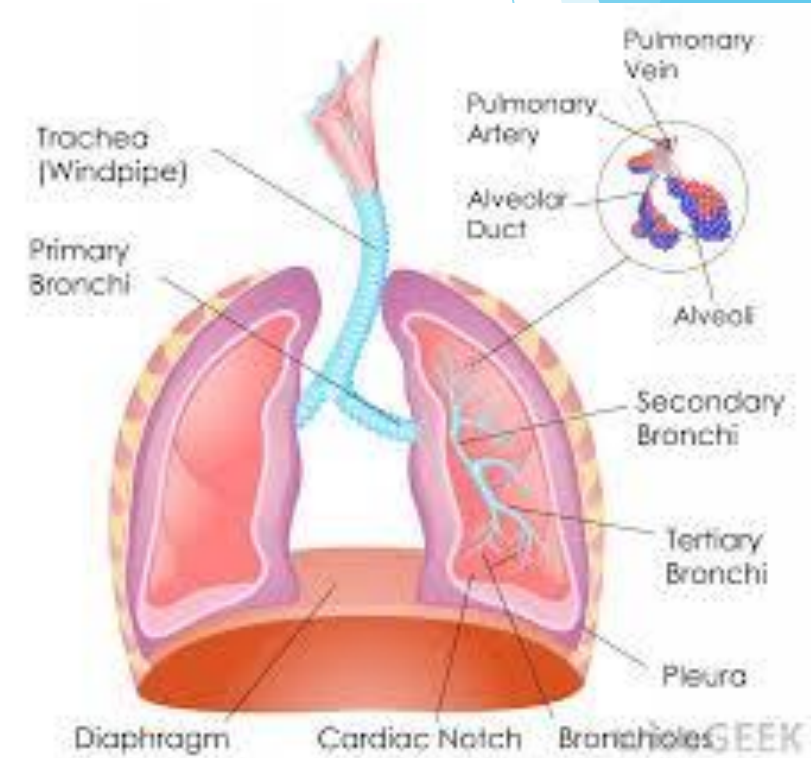
which controls muscle tone in the GI tract results in loss of appetite



Lung effects of Nicotine toxicity

Nicotine's action on skeletal muscles and the diaphragm

produce paralysis and asphyxiation



Nicotine Treatment options

- Nicotine lozenges
- Nicotine gum
- Nicotine patches
- Nicotine inhaler
- Nicotine nasal spray





**THANK YOU FOR
YOUR ATTENTION**