Metabolism and Pharmacology of Ethanol

Prof. David W. Craig
Dept. of Chemistry
Hobart and William Smith Colleges

Behavioral Manifestations of Alcohol Ingestion

- With 1 to 2 drinks (.01-.05 g/dL BAC) -- euphoria and perceived reduction in anxiety
- With 3 to 5 drinks (.06-.10 g/dL BAC) -- judgement and motor coordination impaired, sometimes increased aggression
- With 10 to 13 drinks (.20-.25 g/dL BAC) -- sedation
- With 0.30 g/dL BAC -- memory impairment and loss of consciousness
- With 0.40 to .50 g/dL BAC -- depressed respiration , coma, death

*BACs for inexperienced user

What Factors Determine a Person's Blood Alcohol Concentration (BAC in g/dL)?

- Number of Drinks Consumed
- Body Size and Build
- Sex
- Time
- Past Drinking Experiences
- Is Stomach Empty or Full?

Ethyl alcohol CH_3-CH_2-OH

Dose – Number of drinks consumed

- 12 oz Beer 3.6-4.0% alcohol contains 13-17g alcohol
- 4 oz Wine 12-14% alcohol contains 14-17g alcohol
- 1-1.5 oz 80 proof Whiskey contains 12-18g alcohol

But

Long Island Iced Tea: 1oz vodka(40%), 1oz tequila (40%), 1oz rum(40%), 1oz gin(40%), 1oz triple sec (40%) , 1.5oz sweet and sour mix, splash cola.

59g alcohol
~4 drinks

Four Loko: 23.5oz 12% alcohol

85g alcohol
~5.5 drinks

Ethyl alcohol CH_3-CH_2-OH

Body size, build, and sex determines the volume accessible to ethanol

Chemical Solubility

- Completely soluble in water
- Somewhat soluble in fat
- 30x more soluble in water that in fat

- Proportion water in the body: Men .58, Women .49

Time – How rapidly can ethanol be absorbed?

- Rate of absorption is dependent on:
  - concentration gradient between gut and blood
  - surface area of contact
  - degree of vascularization
- Effect of Food on Absorption
  - food dilutes alcohol in the digestive system
  - fatty foods are slow to digest and slow to move from the stomach to the small intestine

Time – How rapidly can ethanol removed?

- Ethanol clearance is zero order … the rate of clearance is independent of the ethanol concentration
- Average ethanol clearance rates
  - For moderate drinkers - .017 g/dL/hr
  - Drinkers consuming >60 drinks/month - .020 g/dL/hr
  - 80% of adult population > .012 g/dL/hr

Estimation of BAC

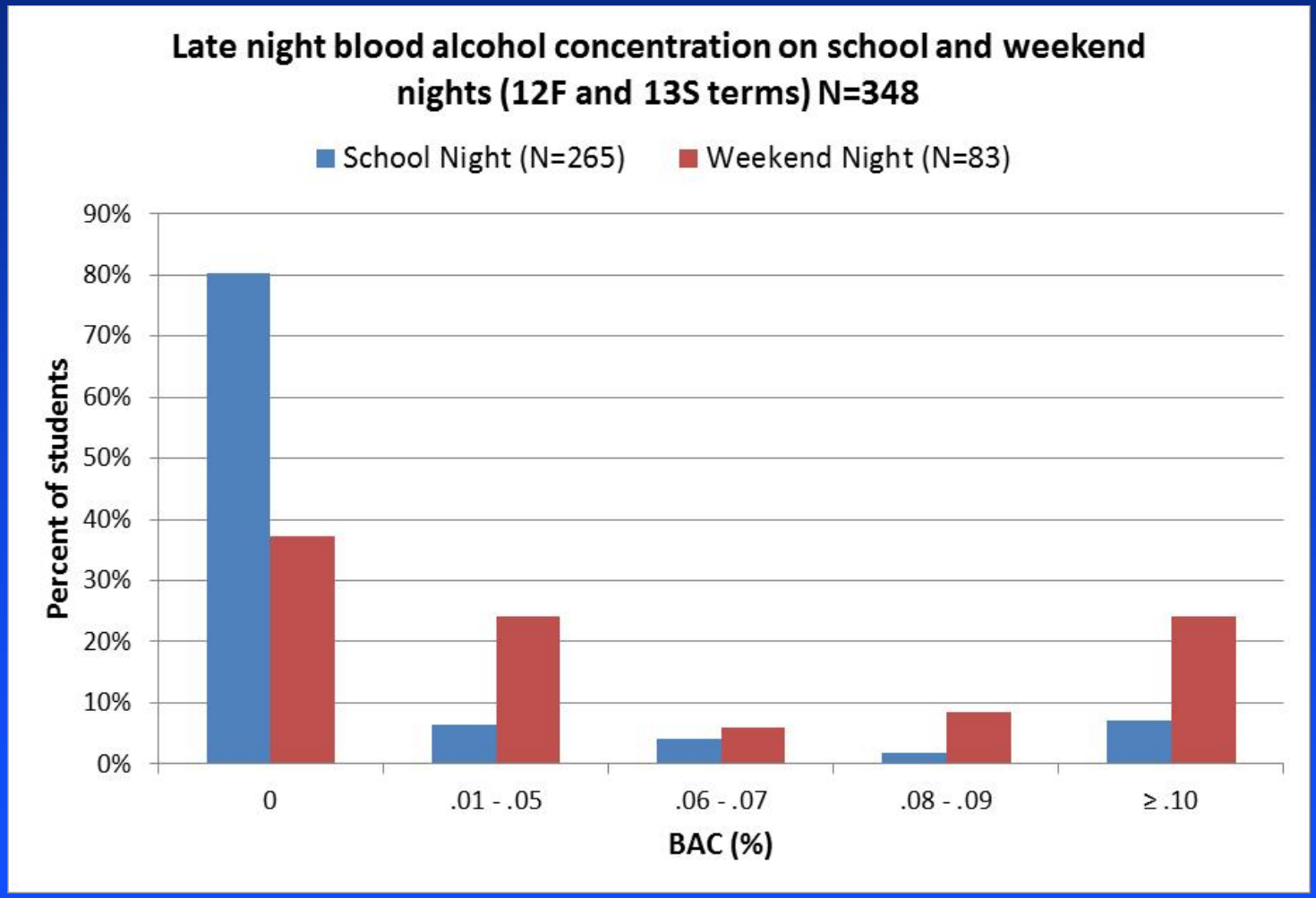
Calculation of BAC for moderate drinkers -- The American Happy Hour Experience

		male1	male2
	Weight lb	220	180
	Frac H2O	0.58	0.58
Drinks	Time (hr)	BAC	BAC
1	0.25	0.0165	0.0208
2	0.5	0.0329	0.0416
3	0.75	0.0494	0.0624

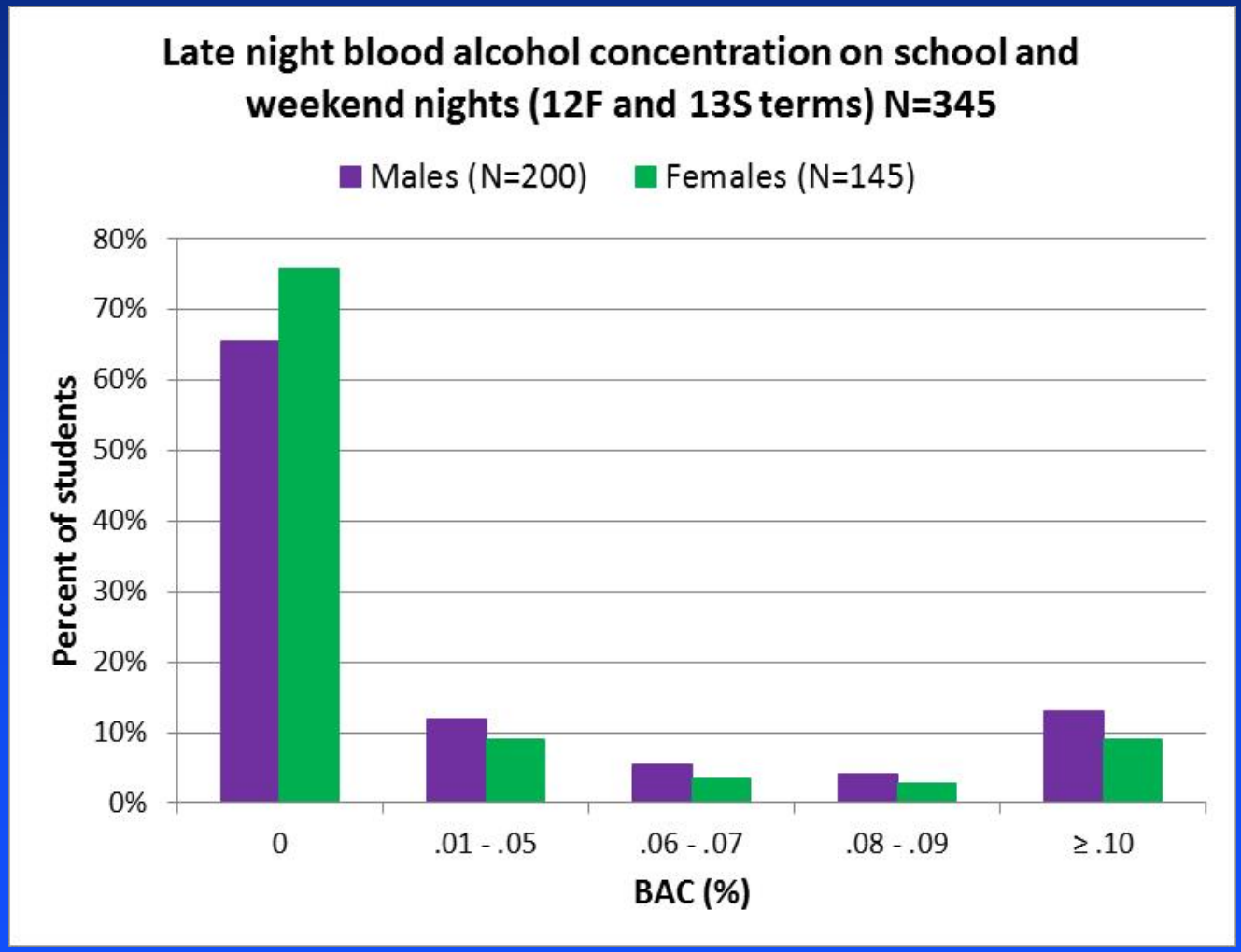
$$peakBAC(g/dL) = \frac{Drinks \times 13g/drink \times .806 \times 100(mL/dL)}{BodyWeight(kg) \times FractionWater(mL/g) \times 1000g/kg} - MR(g/dL/hr) \times T(hr)$$

Ref: National Highway traffic Safety Administration

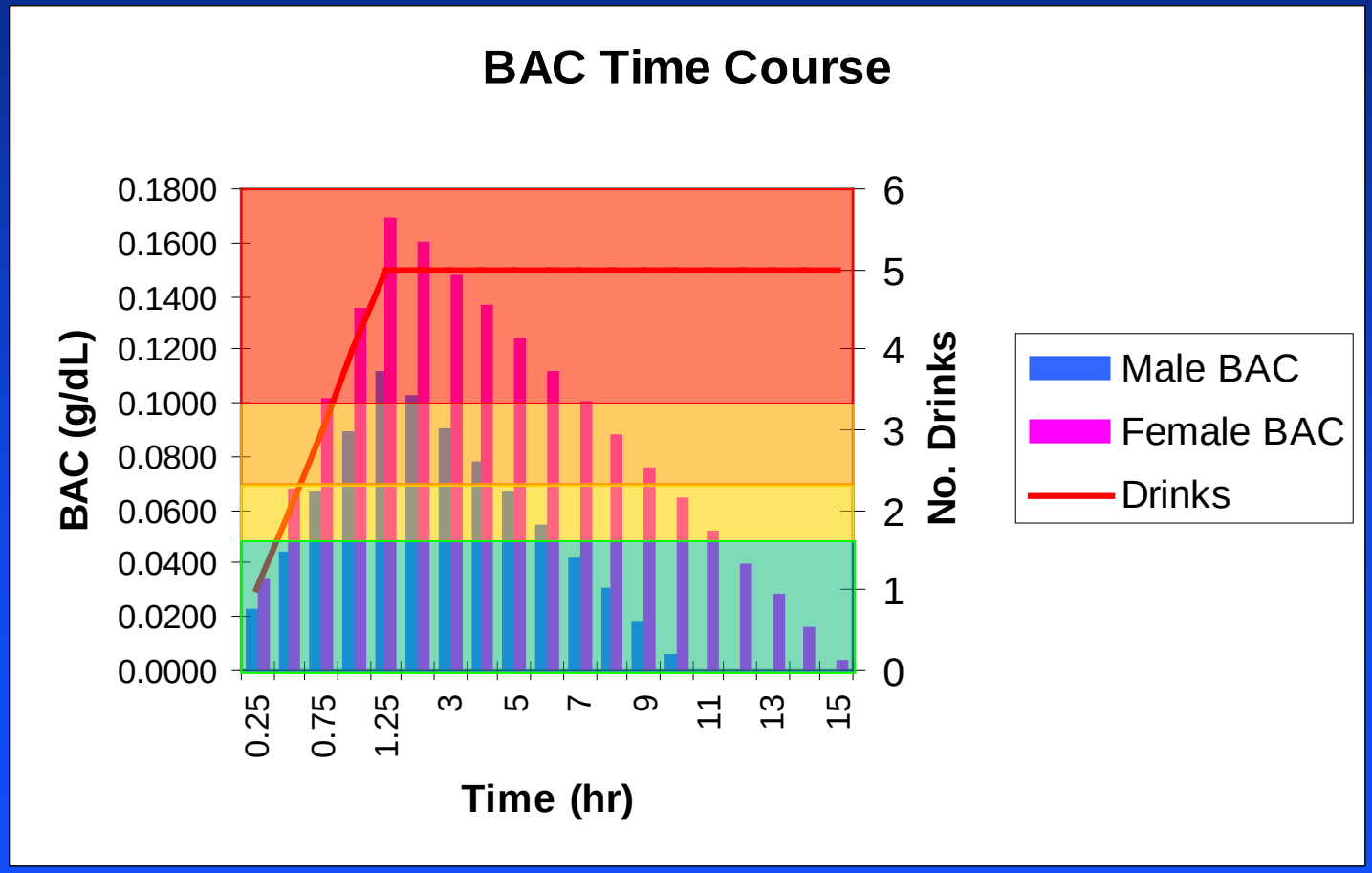
BAC distribution of HWS students returning home late at night



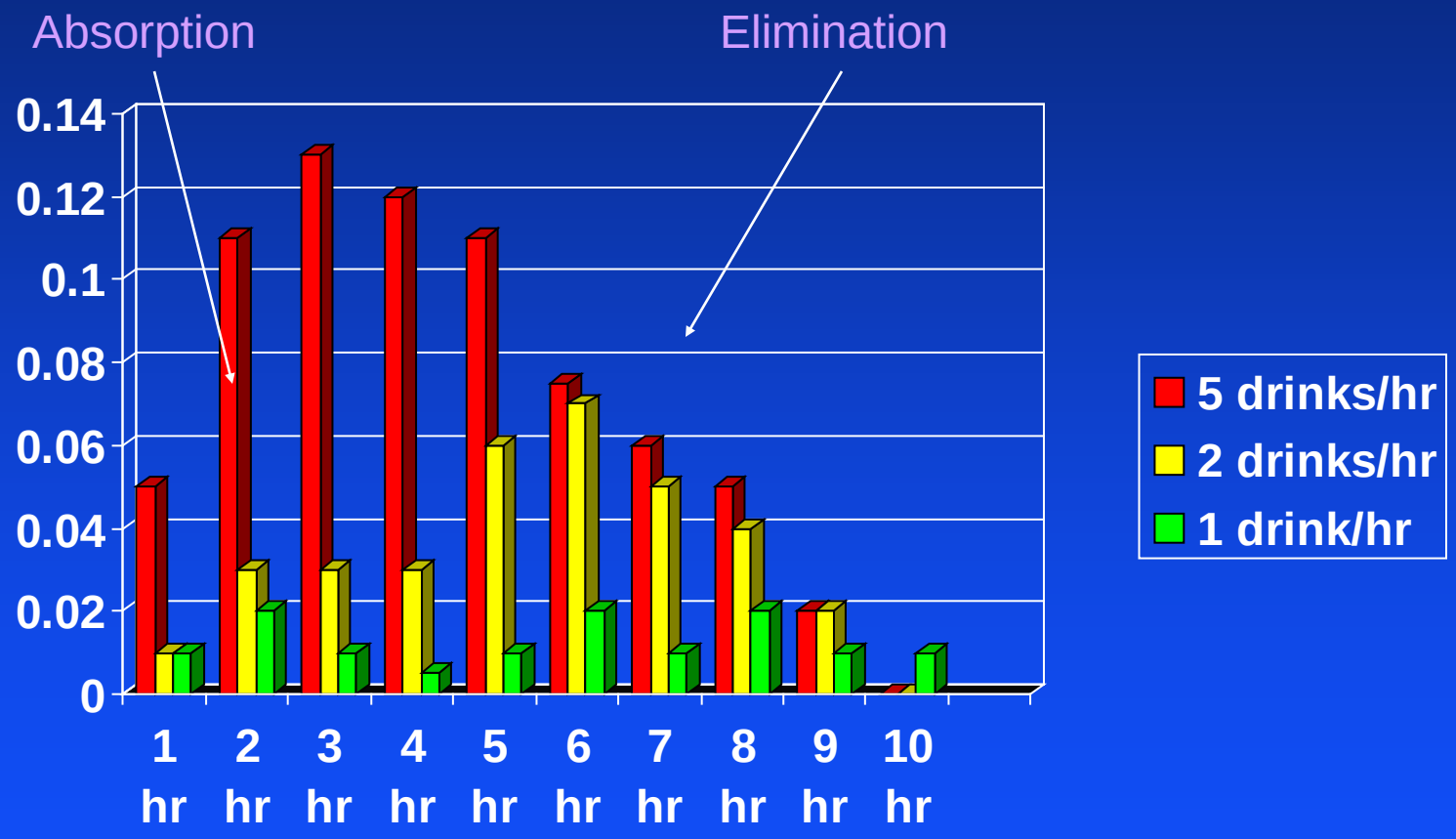
BAC distribution of HWS students returning home late at night



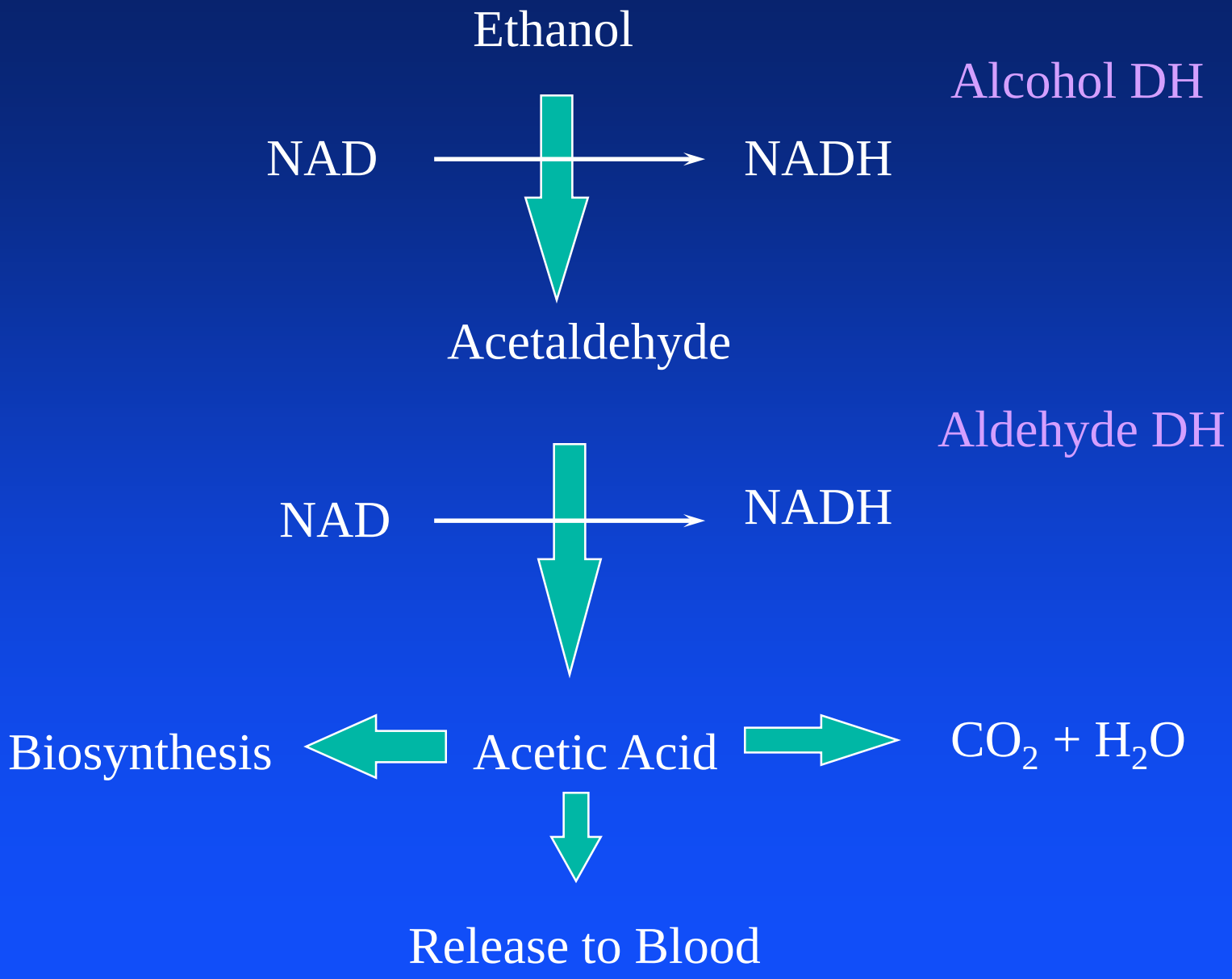
What if we were to continue for five drinks?



Effect of Rate of Ingestion of 10 Drinks on BAC (following a light meal)



Major Pathway for Alcohol Metabolism



Differences Between Men and Women

- Women are smaller than men
- Women have lower total body water content (49%) than men (58%) of comparable size
- Gastric ADH lower in women
  - virtually nonexistent in alcoholic women
  - declines in men over 50
- Fluctuations in gonadal hormone levels during the menstrual cycle may affect the rate of alcohol metabolism

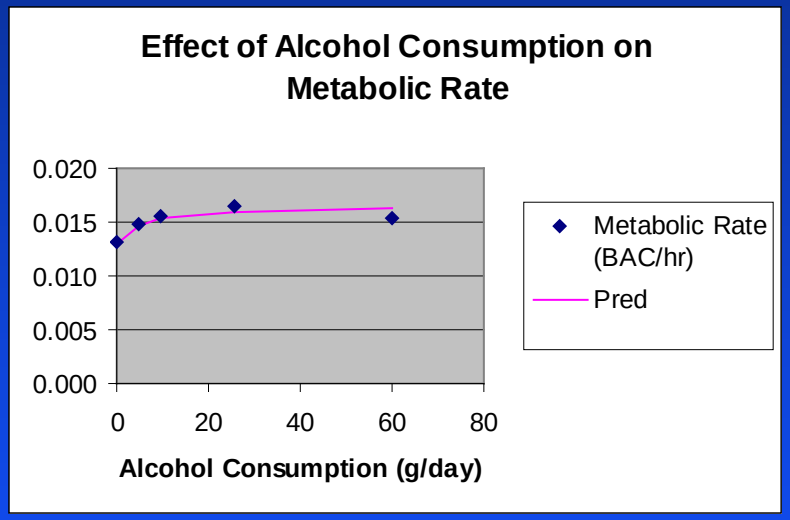
SOURCE: Alcohol Alert #10, NIAAA (1990)

Metabolic Differences Between Racial Groups

- Isoenzymes in Alcohol DH (ADH)
  - Beta1 in Caucasian has Km 0.00023 g/dL
  - Beta2 in Asian has Km 0.0043 g/dL
  - Beta3 in 15% African Amer. has Km .165 g/dL
- 50% Chinese and Japanese Asians have inactive mitochondrial Aldehyde DH (ALDH) resulting in facial flushing, palpitations, dizziness, and nausea

Effect of Chronic Use

- Metabolic Tolerance



- But….This is not the whole story….more to come

Alcohol on the Brain

Behavioral Manifestations of Alcohol Ingestion

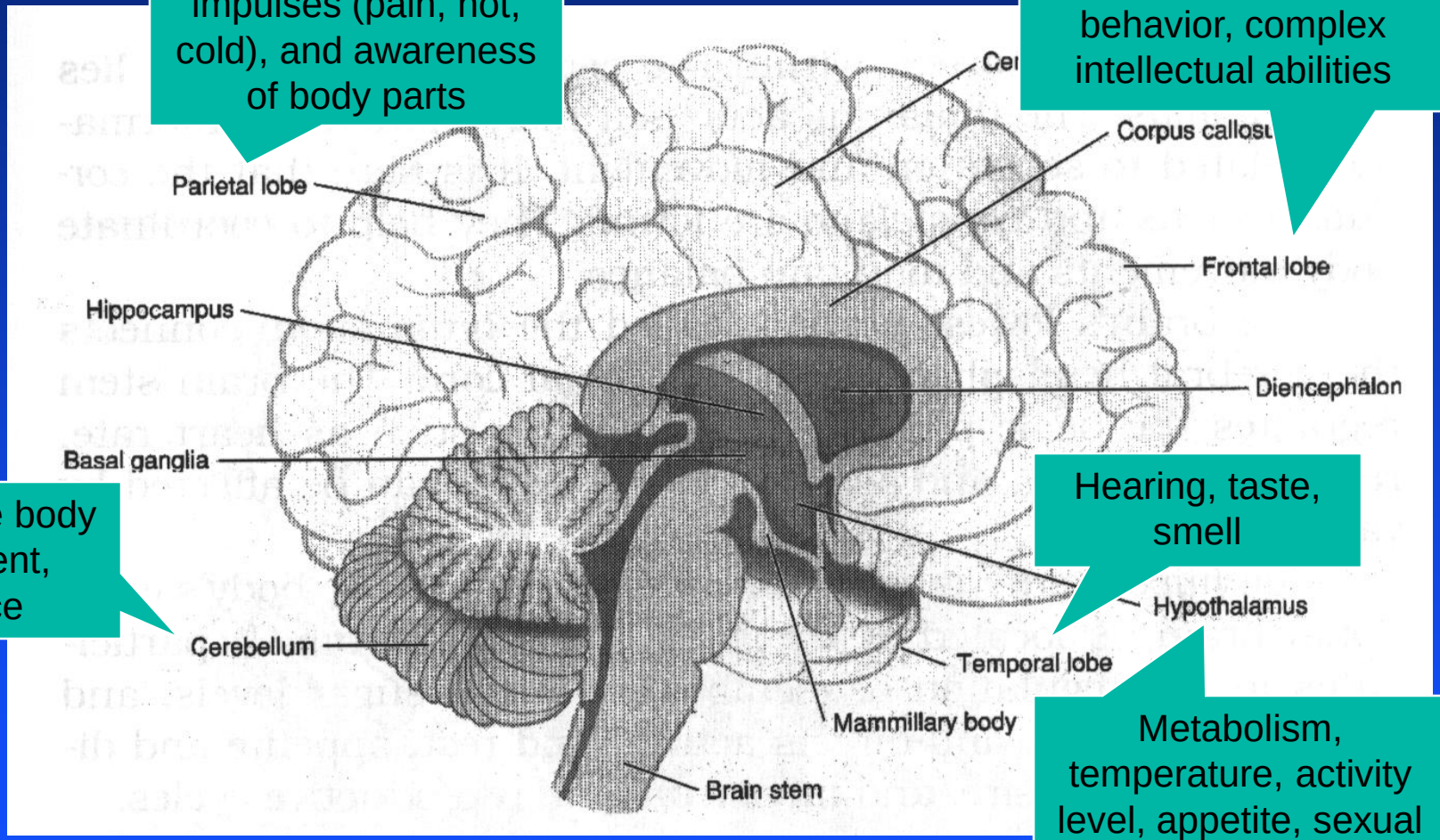
- With 1 to 2 drinks (.01-.05 g/dL BAC) -- euphoria and perceived reduction in anxiety
- With 3 to 5 drinks (.06-.10 g/dL BAC) -- judgement and motor coordination impaired, sometimes increased aggression
- With 10 to 13 drinks (.20-.25 g/dL BAC) -- sedation
- With 0.30 g/dL BAC -- memory impairment and loss of consciousness
- With 0.40 to .50 g/dL BAC -- depressed respiration , coma, death

*BACs for inexperienced user

The Brain's Division of Labor

Receives sensory impulses (pain, hot, cold), and awareness of body parts

Voluntary muscle movement, motor area for speech, emotional behavior, complex intellectual abilities

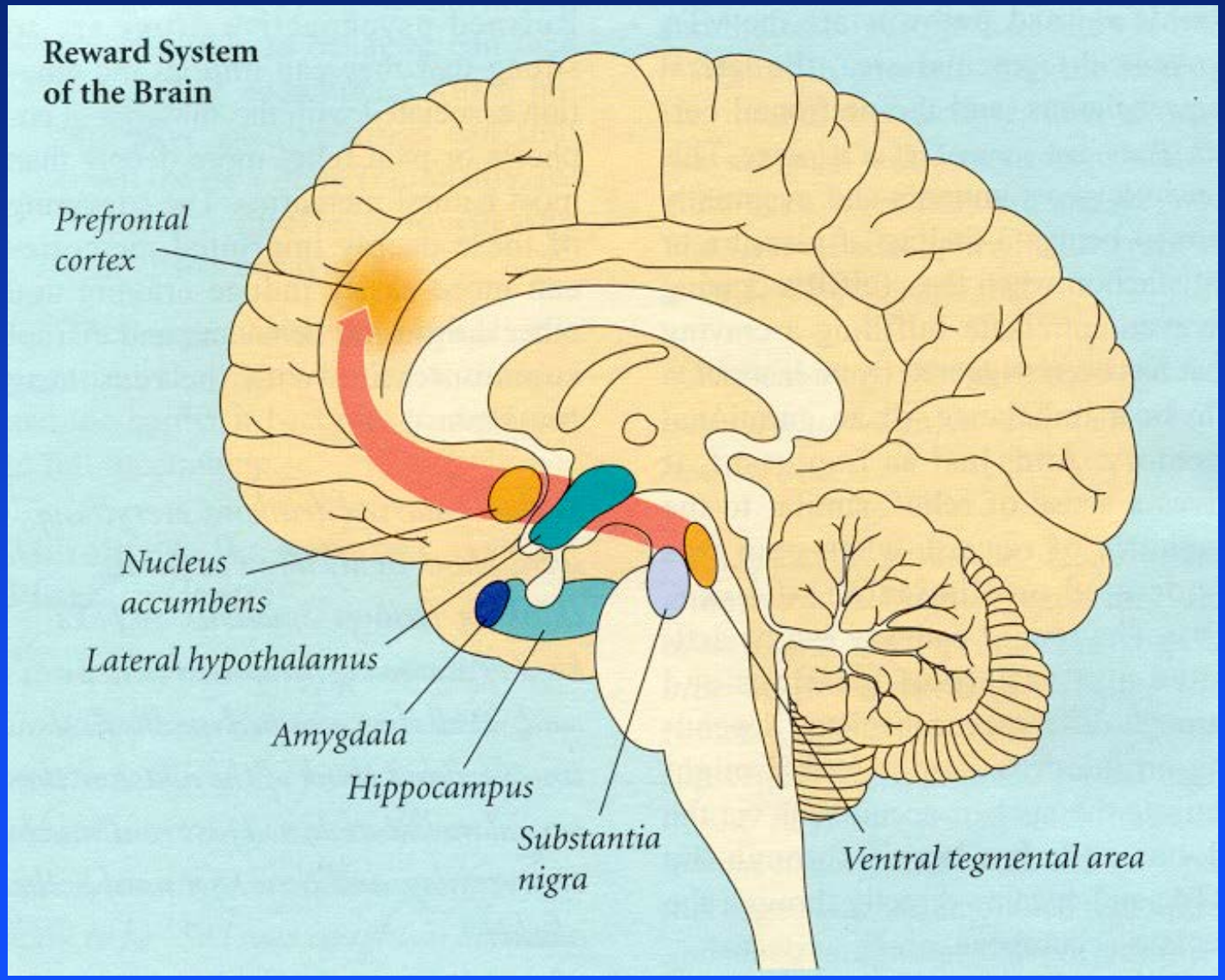


Coordinate body movement, balance

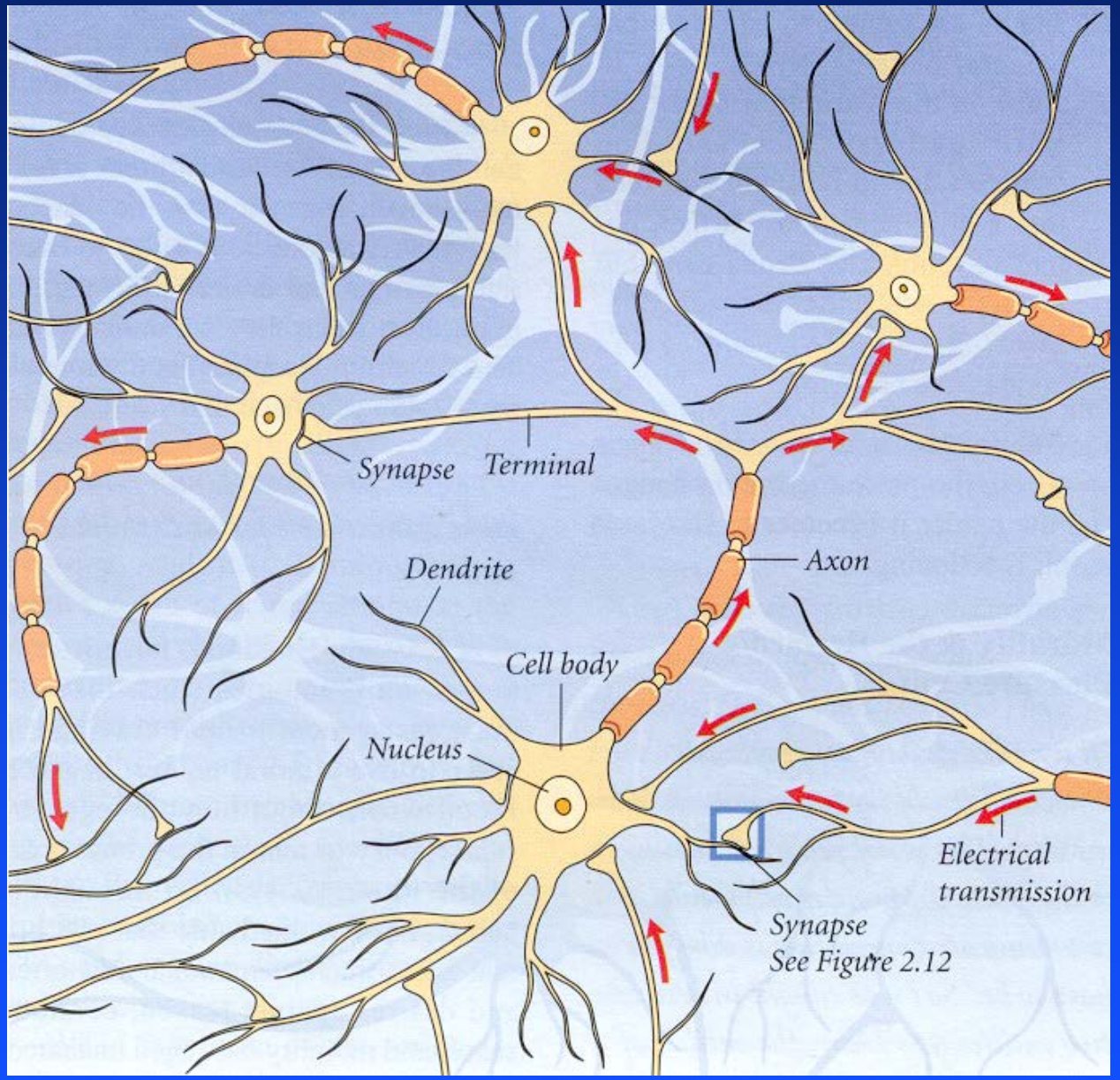
Hearing, taste, smell

Metabolism, temperature, activity level, appetite, sexual desire, reproductive cycles

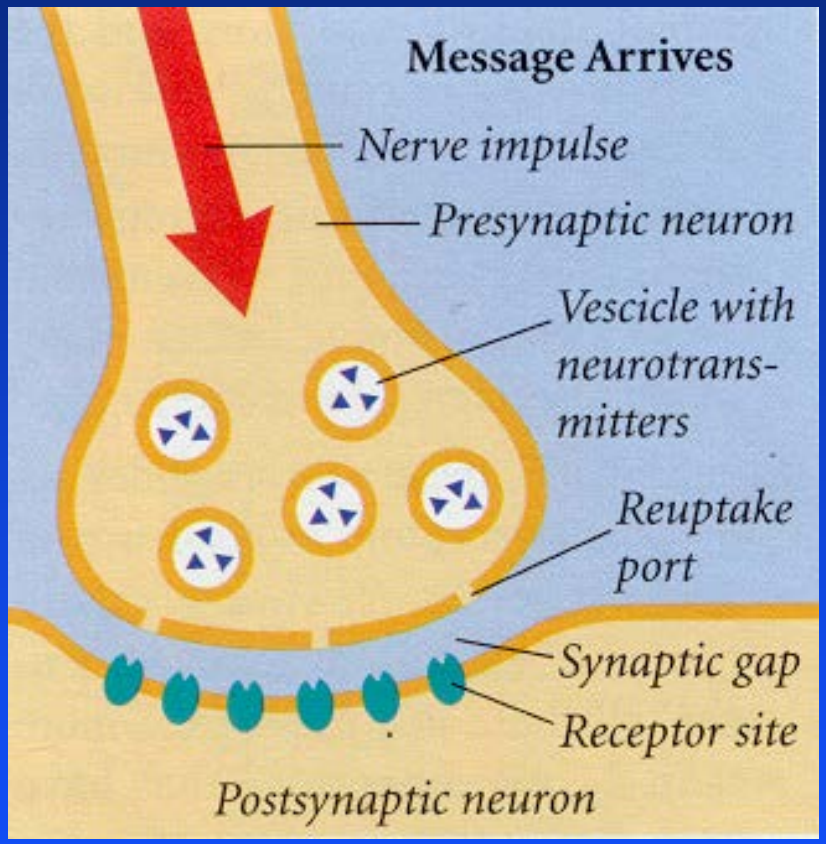
Reward/Pleasure Center

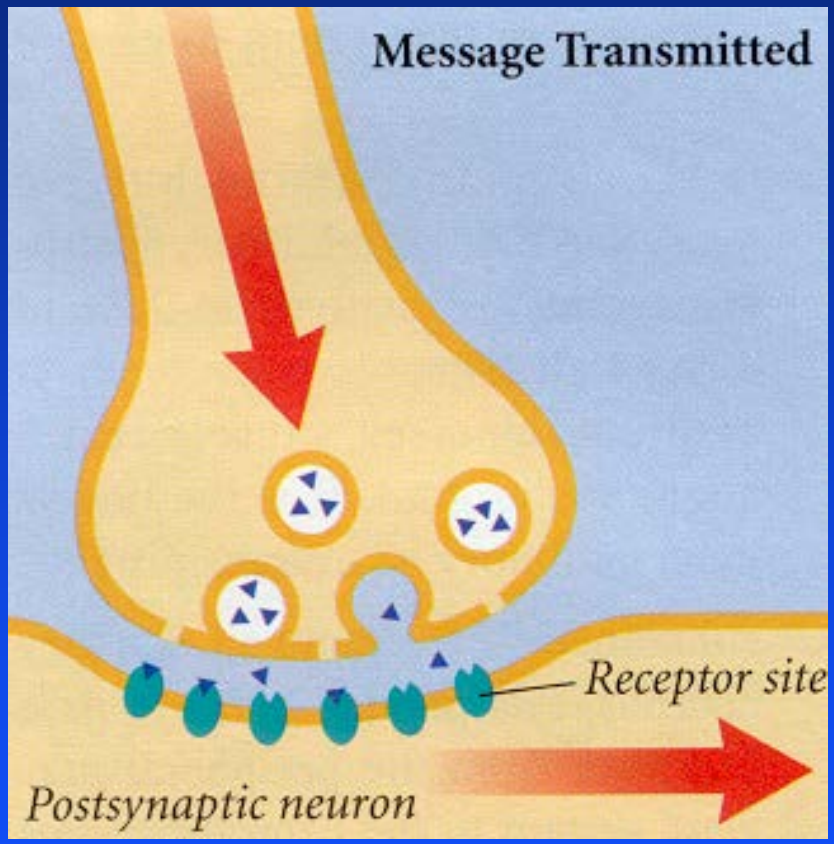


Neurons


Synapse
Terminal
Dendrite
Axon
Cell body
Nucleus
Electrical transmission
Synapse
See Figure 2.12

Synapse


Message Arrives
Nerve impulse
Presynaptic neuron
Vescicle with neurotrans-mitters
Reuptake port
Synaptic gap
Receptor site
Postsynaptic neuron


Message Transmitted
Receptor site
Postsynaptic neuron

Alcohol Affects Neuro-transmitter Function in the Brain

- Potentiates **GABA** receptor function
- Inhibits **Glutamate** receptor function
- Increases **Dopamine** concentration
- Increases **Seratonin** release
- Stimulates **Opiate Neuropeptide** Release

Affect on Dopamine, Serotonin, and Endogenous Opiates (BAC ~ .01--.05 g/dL)

- Dopamine stimulates pleasure centers and functions in positive reinforcement
  - alcohol increases Dopamine concentrations in nucleus acumbens and other reward centers
- Serotonin functions in mood, sleep and positive reinforcement
  - alcoholics and thrill seekers have low serotonin levels and alcohol consumption (and thrill activities) brings theses levels up to normal.
  - Serotonergic drugs have reduced alcohol consumption by alcoholics.
- Endorphins and Enkephalins are natural neural peptides that bind to opiate receptors and produce euphoric effects.
  - Endorphins and Enkephalins are released by the brain when exposed to alcohol
  - Euphoria seems to stimulate further drinking

Affect on GABA function (BAC >=.06 g/dL)

- GABA is major inhibitory neurotransmitter controlling “arousal state” and sensory and motor activity
- Alcohol Potentiates GABA receptor function
- GABA receptor is site of action of
  - sedative/anesthetic barbiturate, pentobarbitol
  - sedative/anxiolytic benzodiazipines
- RO 15-4513 overcomes motor impairment

Affect on Glutamate Function (BAC ~.02--.2 g/dL)

- Glutamate is major excitatory neurotransmitter
- Alcohol inhibits NMDA glutamate receptor function
- Impaired NMDA Glutamate Receptor Function Causes:
  - cognitive impairment and amnesia
  - inability to learn new information
- Alcohol parallels action of PCP or “angel dust”

Effect of Chronic Use

- Tolerance
  - changes in number and types of GABA receptors
  - Increase in number of glutamate receptors
- Withdrawal
  - increased Anxiety within hours -- GABA
  - seizures -- Glutamate
- Dependence
  - changes in Dopamine and Seratonin function appear to be long lasting

What Causes a Hangover?

- Pounding Headache
  - Caused by reduced blood pressure in cranial vessels
  - Toxicity/withdrawal
- General Lethargy
  - Caused by buildup of lactic acid and acidosis by release of acetic acid
- Hypersensitivity to Light and Sound
  - Alcohol withdrawal leads to increased excitability, depressed mood, and sensitivity to stimuli
- Queasy Stomach
  - Empty stomach, overly acidic
  - Also due to withdrawal
- What about taking a drink to relieve hangover symptoms?

Alcohol and Sex

- Physiological responses
  - Erections slower to rise and quicker to fall
  - Reduction in vaginal lubrication
- Psychological Perceptions
  - 45% of men and 68% if women say alcohol enhances sexual enjoyment
- Rutgers study (2-3 standard drinks)
  - Subjects who thought they drank alcohol were most highly aroused (those that did not actually get alcohol were slightly less aroused)
  - Subjects who expected tonic but actually got alcohol were less aroused than those that expected alcohol but did not.

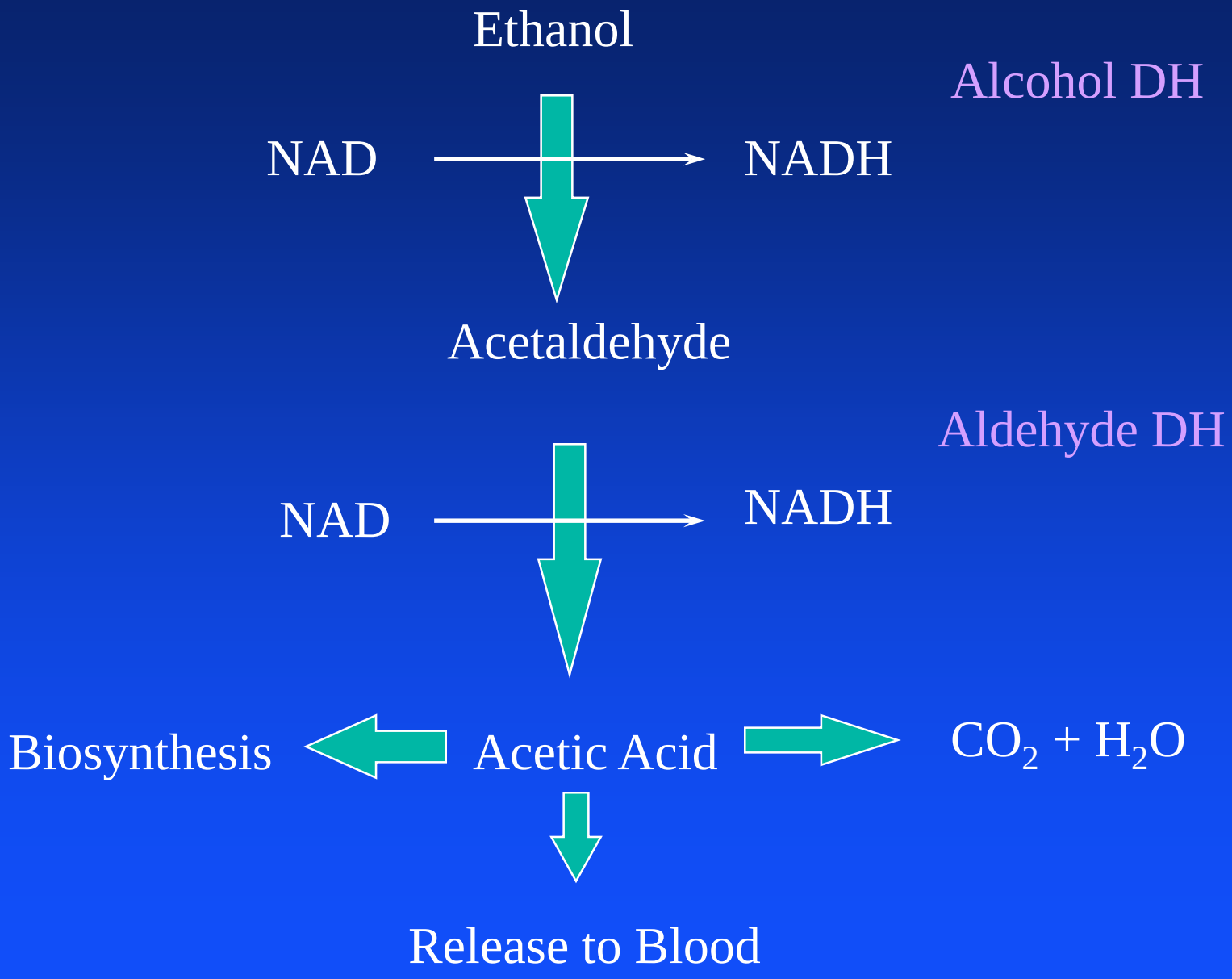
Medications for Alcohol Dependence

Drugs Used in Alcohol Dependence Treatment

- Disulfiram (Antabuse)
  - Inhibits aldehyde dehydrogenase
  - Produces negative reinforcement on alcohol consumption
- Naltrexone
  - Blocks euphoric effect of opiod receptor activation
- Acamprosate (Campral)
  - Reduces symptoms of alcohol withdrawal by inhibiting Glutamate receptor and potentiating GABA receptor

Important Metabolic Interactions and Health Concerns

Major Pathway for Alcohol Metabolism



Interaction with other Drugs

- Ethyl ester of Cocaine
  - potentiates cocaine “high”
- Aspirin and Cimetidine Inhibits Gastric ADH
- Liver Drug Detoxification Impaired
  - Depleted NAD impairs livers ability to clear other drugs

Metabolic Fates of Excess Ethanol and Acetaldehyde

- Ethyl esters of Fatty Acids and Cholesterol
  - may cause heart damage, impair energy metabolism, disrupt cell membranes
- Protein Modification by Acetaldehyde
  - enzymes inactivated by imine adducts
- Ethanol can also be oxidized by MEOS/Cytochrome P450
  - MEOS oxidation produces harmful free radicals

Other Metabolic Processes Affected by Alcohol Metabolism

- High NADH/NAD ratio:
  - Impaired Energy Metabolism and increased production of lactic acid
  - Inhibits Lipid Degredation in Liver
  - Stimulation of fat synthesis and increases in LDL and HDL levels
  - Inhibition of oxidative steps in testosterone synthesis

Other Metabolic Processes Affected by Alcohol Metabolism

- Acetaldehyde Adducts
  - tubulin-mediated protein exocytosis and endocytosis inhibited....insulin, etc
  - Impaired Protein Synthesis Type II Muscle Fibers depleted
  - In alcoholics, acetaldehyde reacts with dopamine to become tetrahydroisoquinoline (THIQ) in the brain. It is thought that accumulation of THIQ is related to addiction.