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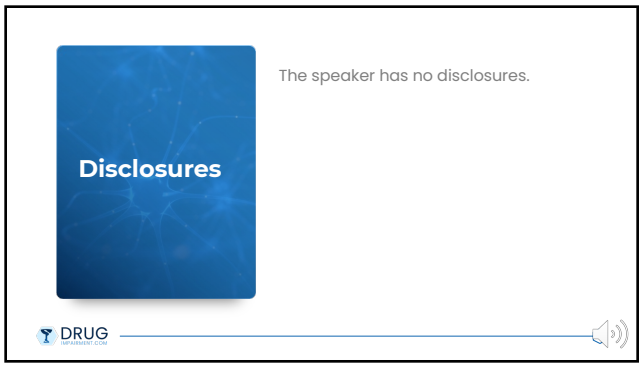
Disclosures
The speaker has no disclosures.
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Alcohol Tolerance
Dr. Zeb Graham, PharmD

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Learning Objectives

1. Explain alcohol metabolism and describe its role in tolerance
2. Describe the biochemical effects of alcohol on the human brain at the molecular level
3. Distinguish between various types of alcohol tolerance and their mechanisms
4. Explain the Mellanby Effect and its implications

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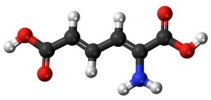
Metabolism of Alcohol

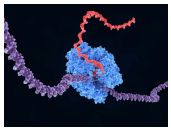
Key Enzymes

Alcohol Dehydrogenase
Acetaldehyde Dehydrogenase

Pharmacokinetics

Response of Human Body to the Presence of EtOH





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What Happens to Alcohol in the Human Body?

General Metabolic Pathway

Ethanol (EtOH) → Acetaldehyde → Acetate

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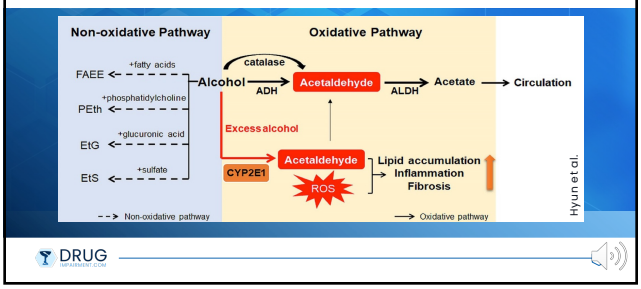
The Bigger Picture-EtOH Metabolism



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EtOH Metabolic Products

1. Acetaldehyde

-Toxic byproduct of EtOH metabolism that must undergo additional metabolism

2. Acetate

-Can be a toxic metabolite of EtOH metabolism that ultimately is cycled into other biochemical pathways

(1) and (2) Increase as EtOH Consumption Increases

-Various physiological consequences, both short and long term

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Pharmacokinetics of EtOH

Absorption

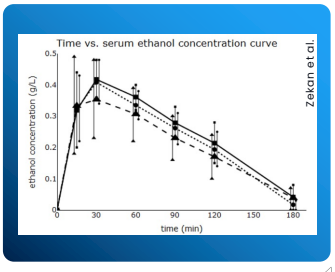
-Primarily through small intestine (>80%)

Distribution

-Very small molecule (Ethanol)
-Easily moves around the body through membranes and tissues
-Seeks water

Elimination

-90% is metabolized; 5-10% eliminated (unchanged) in expired air or urine



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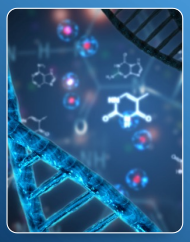
Biochemical Basis for EtOH Tolerance



- Primary (Molecular) Targets of EtOH
- EtOH Effects on the Human Brain
- EtOH Effects on Neurotransmitter Systems

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Molecular Targets of EtOH

NMDA	$GABA_A$	nACHRs	L-Type Ca^{2+} Channels
N-Methyl D-Aspartate	Gamma-Amino Butyric Acid (subtype A)	Nicotinic Acetylcholine Receptors	

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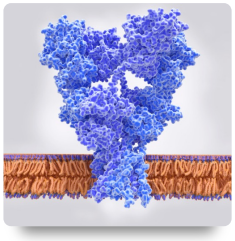
N-MDA-R (Ionotropic)



Glutamatergic System

N-MDA Receptors are an integral part of neurotransmission in the brain

Ethanol Effects

DECREASES excitatory neurotransmission. Accomplished primarily by blocking Ca^{2+} from entering intracellular space

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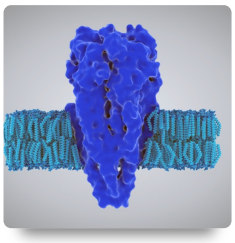
$GABA_A$ (Ionotropic)



GABAergic System

Gamma Amino-Butyric Acid (GABA) plays an important role in neurotransmission in the brain

Ethanol Effects

INCREASES inhibitory mechanisms of neurotransmission. Accomplished primarily opening the chloride (Cl^-) channel in presynaptic neurons

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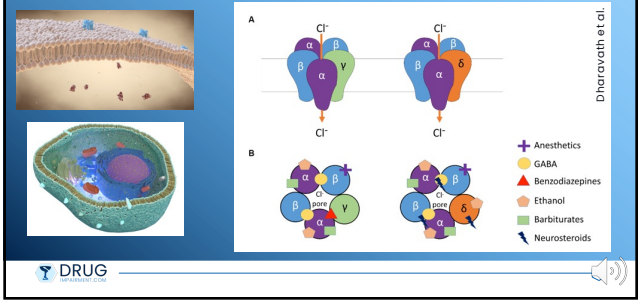
$GABA_A$ (Ionotropic)



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EtOH and Neurotransmitters in the Brain

Glutamate

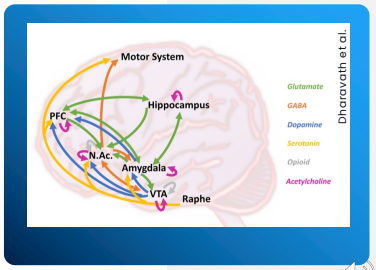
Stimulates PFC, N. Ac., Amygdala, Hippocampus, Motor System

GABA

Motor System, N. Ac., Amygdala

Dopamine

VTA, N. Ac., PFC



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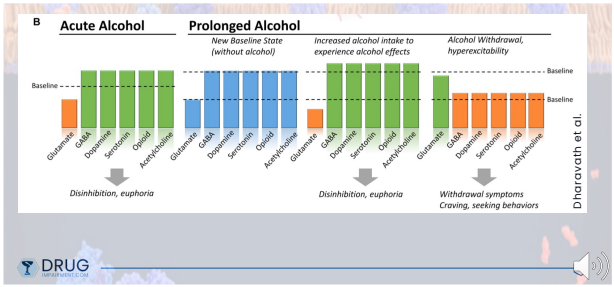
EtOH Effects on Neurotransmitter Systems



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Classifying EtOH Tolerance

PHARMACODYNAMIC	Overall effect(s) of EtOH on the human body
METABOLIC	ADME of EtOH; Metabolic pathways of EtOH
BEHAVIORAL	Management of inhibition in the presence of EtOH

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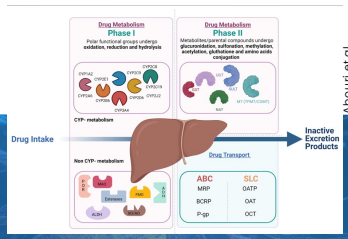
Metabolic Tolerance-EtOH

MEOS

- Microsomal Ethanol Oxidation System (MEOS)
- CYP2E1
- Liver
- ROS



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Pharmacodynamic Tolerance

CNS Alteration

-Significant changes in neurochemical receptors, both in number and in sensitivity

-More EtOH (than before) to achieve same effects (euphoria, altered mood, etc.)

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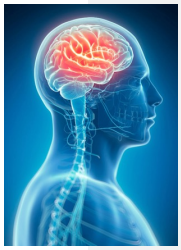
-A need for markedly increased amounts of alcohol to achieve intoxication or desired effect

-A markedly diminished effect with continued use of the same amount of alcohol.



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Behavioral Tolerance

Assessed by Brain and Body Interaction

ACUTE	RAPID	CHRONIC
15-30 minutes	8-24 hours	>24 hours of intermittent or continuous dosing

Amount of time to observe onset of tolerance after EtOH exposure

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Tolerance-Physiology or Behavioral Response(s)?

"The mind exercises a considerable effect upon drunkenness, and may often control it powerfully. When in the company of a superior whom we respect, or of a female in whose presence it would be indelicate to get intoxicated, a much greater portion of liquor may be withstood than in societies (i.e., company) where no such restraints operate"

***The Anatomy of Drunkenness* (1832)**
-R. MacNish

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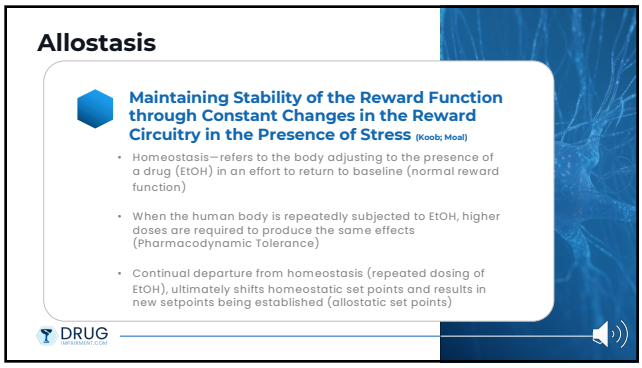
Allostasis
Maintaining Stability of the Reward Function through Constant Changes in the Reward Circuitry in the Presence of Stress (Koob; Moal)
• Homeostasis—refers to the body adjusting to the presence of a drug (EtOH) in an effort to return to baseline (normal reward function)
• When the human body is repeatedly subjected to EtOH, higher doses are required to produce the same effects (Pharmacodynamic Tolerance)
• Continual departure from homeostasis (repeated dosing of EtOH), ultimately shifts homeostatic set points and results in new setpoints being established (allostatic set points)
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Tolerance ≠ Dependence
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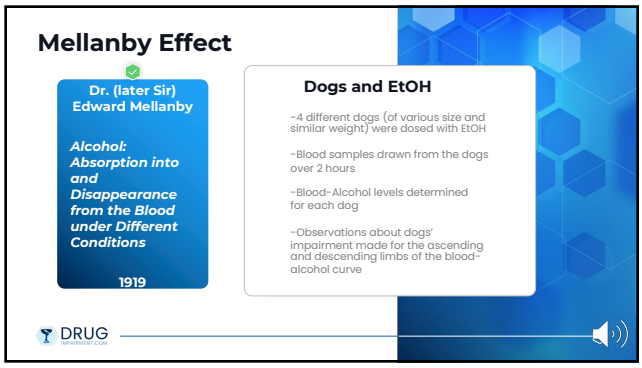
Mellanby Effect
Dr. (later Sir) Edward Mellanby
Alcohol: Absorption into and Disappearance from the Blood under Different Conditions
1919
Dogs and EtOH
-4 different dogs (of various size and similar weight) were dosed with EtOH
-Blood samples drawn from the dogs over 2 hours
-Blood-Alcohol levels determined for each dog
-Observations about dogs' impairment made for the ascending and descending limbs of the blood-alcohol curve
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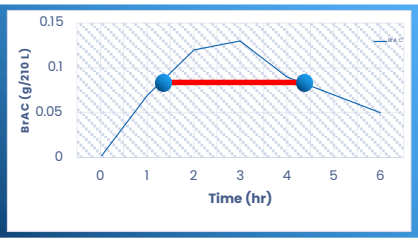
Mellanby Effect



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Mellanby Effect

Observations	Conclusions
• Watched for dogs dragging their toenails on the ground, struggling to get up after falling down, stumbling	• Psychomotor impairment is more pronounced and evident on the ascending limb of the BAC curve than it is on the descending limb (at the same BAC)
• Signs of intoxication were gone after 2 hours	• The body's CNS was the victim of 'sudden attack' (EtOH)
• Signs of intoxication were observable ONLY on the ascending limb	• CNS may have to 're-learn to coordinate its activities' after being subjected to EtOH
• Noted the inherent subjectivity of assigning impairment to dogs' movement (or lack of movement)	

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Mellanby Effect → "ACUTE TOLERANCE"

Impairment only while BAC rising?

Impairment is observed on the ascending limb of the BAC because humans develop an "acute" (behavioral) tolerance to EtOH; observed impairment isn't present on descending limb of the BAC curve at the same BAC.

Any scientific studies that support this hypothesis?

A Systematic Review of the Evidence for Acute Tolerance to Alcohol—the "Mellanby Effect"

(Holland; Ferner) (2017)

-Subjects felt more intoxicated while their BAC's were rising

-Subjects didn't feel as intoxicated at the same BAC while their BAC's were declining

The "Mellanby Effect" in Alcoholised e-Scooter Drivers

(Zube et al.) (2022)

-16 subjects demonstrated a "slight" Mellanby Effect when they drove a predefined course on scooters

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A Systematic Review of the Evidence for Acute Tolerance to Alcohol—the "Mellanby Effect" (Holland; Ferner)

CONCLUSIONS

"Mellanby Effect" Observed

-Subjects felt a higher degree of intoxication on the ascending limb of the BAC-time curve

-Subjects were more willing to drive on the descending limb than at the same BAC observed on the ascending limb

All EtOH Effects are Dependent

-Drinking history
-Degree of intoxication

DRIVING

When measured objectively, the skills required to safely drive were "generally worse" on the descending limb of the BAC-time curve.

More willing to drive
+
Driving ability negatively impacted

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The "Mellanby Effect" in Alcoholised e-Scooter Drivers

(Zube et al.)

- 16 subjects dosed with EtOH; Blood Drawn
- Numerical score assigned to subjects as they drove a closed course

CONCLUSIONS

"Slight" Mellanby Effect in E-Scooter Operators

Data Indicate a "possible" Mellanby Effect when operating an E-scooter

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EtOH Tolerance-SUMMARY

- **GABAergic and Glutamatergic Systems**
  - -Imbalance and Dysregulation of these Systems Offers Some Explanation of Tolerance
- **Multiple Types of Tolerance**
  - -Pharmacodynamic, Metabolic, Behavioral
- **Tolerance vs. Dependence**
  - -Not Interchangeable Terms
- **Mellanby Effect**
  - -Feeling Less Intoxicated on the Way Down than on the Way up (BAC-time)
  - -Implications for Driving Impaired

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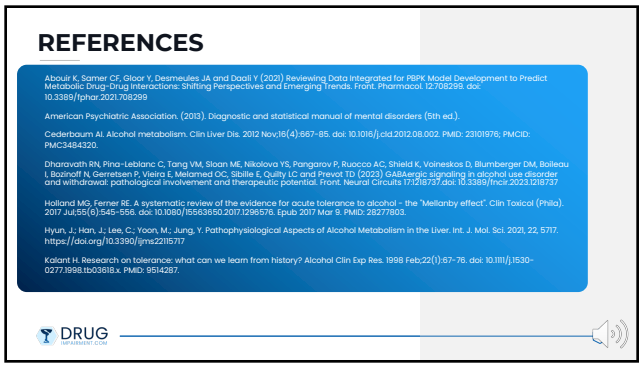
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