Effects of Ethanol on Neurons and Neuronal Structures

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Psychology 472: Pharmacology of Psychoactive Drugs

Bi-Phasic Effects

- At low doses, (<1 drink)
  - Get some stimulation in neurons
- Higher doses (>1 drink)
  - Alters neuronal membrane (Lipid Bilayer)

Results
- Decreased amounts of Na that enters the axon
- Decreased height of the action potential
- Other consequences

The Action Potential

Result

- Alters Ca influx
  - Decreases the amount of NT that is released
- Decreases transmission speed of all neurons
  - Slows down stimulatory neurons

Behavioral Bi-Phasic Effects

- At low levels (<.05 BAC)
  - Alcohol causes you to feel good, makes you euphoric, loosens inhibitions etc.
    - Usually occurs on the ascending portion of the BAC curve
- Higher levels (> .05 BAC)
  - Euphoric feelings go away
  - Feel depressed
  - Descending portion of the BAC curve

Alters the Lipid Bilayer

The Alcohol Curve

- Decreases the amount of NT that is released
- Decreases transmission speed of all neurons
  - Slows down stimulatory neurons
Reason for the Changes
- Lower levels
  - Get increased levels of Dopamine in MFB
- Higher levels
  - Begin to sedate the brain, levels of dopamine decrease. Etc.

Effects on Receptors
- GABA
- NDMA
- Glutamate
- Opiate

GABA A Receptor
- Is an Axoaxonic receptor
  - Binds on presynaptic elements of stimulatory neurons
  - Designed to shut down stimulatory neurons
- Normally needs lots of GABA to work
  - High Affinity State

GABA Receptor
- Has Many Binding Sites
  - GABA site
    - Site for GABA to bind
  - BZ site
    - Site where BZ (α1,α2,α3,α5) and Alcohol (α4,α6) binds
    - Many types (some more sedative, others more anxiolytic)
  - Barbiturate site
    - Site where Barbiturates bind
  - Picrotoxin
    - Blocks effects of Barbiturates
  - Neuroactive steroid site

Alcohol
- Alters GABA Receptors
  - Binds on the BZ site (α4,α6)
  - Changes affinity for GABA from High to Low
  - Increases the amount of Cl influx into most stimulatory neurons
  - Further decreases the amount of Ca influx
  - Decreases the amount of NT
NDMA Receptor
*N-methyl D-aspartate*
- Is a specific type of ionotropic glutamate receptor
- Is important for synaptic plasticity and memory
- Requires both glutamate or aspartate and glycine
- When activated, lets Ca into the cell

Alcohol and NDMA Receptors
- Acts as an antagonist
- Inhibits the function of NDMA receptors
- Decreases the responsiveness of NDMA receptors to glutamate
- Have enhanced stimulation when the person withdraws from alcohol
  - Can get agitation, have epileptiform seizures, etc.

Opiate Receptors
- Alcohol triggers release of endogenous opiates (β-endorphin)
  - Causes a release of dopamine in MFB
  - Makes you feel good
- Use antagonists to reduce craving
  - Naltrexone

Serotonin Receptors
- Serotonin receptors
  - Alcohol use increases serotoninergic activity.
  - Increases secretion of dopamine from nucleus accumbens.
  - Makes you feel good
- SSRIs
  - Are effective in reducing drinking in lower-risk alcohol males.

Cannabinoid Receptors
- Chronic alcohol use stimulates formation of endogenous cannabinoid transmitter *anandamide* (an-anda-mid)
  - Leads to down regulation of cannabinoid receptors, disinhibiting nucleus accumbens.
- Cessation of drinking
  - Get hyperactive endocannabinoid reaction
  - Results in alcohol craving

Summary
- Affects the entire neuron
  - Alcohol decreases transmission speed
  - Alcohol decreases NT release
  - Alcohol increases Cl in post synaptic elements
- Shuts down structures that inhibit neurons of medial forebrain bundle
  - Get more firing in MFB
  - Feel good
**Withdrawal Management**

- Benzodiazepines
  - e.g., Chlordiazepoxide (Librium), Diazepam (Valium)
  - Increase GABA activity.
  - Decreases withdrawal symptoms; prevent seizures and DTs.
  - Long-acting, prevent withdrawal symptoms (either maintained or slowly withdrawn), allowing person to function.
  - Drawbacks: sedation, psychomotor deficits, additive interactions with alcohol, abuse and dependence liabilities.

**Anticonvulsant Mood Stabilizers**

- Fewer limitations than benzodiazepines
- Older anticonvulsants effective, but have side effects (e.g., liver and pancreatic problems).
  - e.g., Carbamazepine (Tegretol), Valproic Acid (Depakote)
- Newer anticonvulsants are less toxic and have significant potential.
  - e.g., Gabapentin (Neurontin), Oxcarbazepine (Trileptal)

**Acamprosate**

- Acamprosate (Campral)
  - First pharmacological agent designed to maintain abstinence in alcoholics after detoxification.
  - Both GABA-agonistic and NMDA-inhibitory, similar to ethanol.
  - Comparably effective to Naltrexone; combination of both drugs may be additively effective.

**Dopaminergic Drugs**

- Bupropion (Wellbutrin)
  - Works on both positive reward and withdrawal
  - Seems to involve dopaminergic reward system.

**Conclusions**

- Alcohol has many impacts on Neurons
- Creates lots of problems
- Has lots of implications for pharmacologic interventions