ALCOHOL AND THE BRAIN

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Although it used to be thought that ethanol, like other alcohols, acted as a non-specific solvent, recent research has shown that the primary action of alcohol is to produce selective alterations in the function of several neurotransmitters, probably by acting on membrane bound receptors. These neurotransmitters and their receptors are also the targets of other abused drugs. In addition the brain circuits underlying the actions of alcohol, and dependence on it, are also becoming understood and seem to be the same as those underlying heroin and cocaine dependence.

This interaction of alcohol with neurotransmitters can be considered in the context of current classification of neurotransmitters into primary (amino acid) and secondary or modulatory neurotransmitters (amines and peptides). Alcohol has a clear action on both the primary inhibitory neurotransmitters GABA and glutamate. Through an interaction at the GABA-A receptor alcohol increases brain inhibition, so calming the brain, which leads to sedation, unsteadiness and contributes to the loss of memory. However, at high doses, alcohol can over-stimulate these receptors leading to coma, respiratory depression and death. Different subtypes of the GABA receptors are expressed in different brain regions and new data suggest that certain subtypes mediate specific actions of alcohol, which is already leading to new approaches to treatment. Genetic variations in these subtypes have now been shown to affect the sensitivity to alcohol and so may help predict vulnerability and possibly direct interventions.

Glutamate is the major excitatory neurotransmitter in the brain. At levels producing profound intoxication, alcohol blocks one of the three major subtypes of this receptor (the NMDA receptor). This contributes to the amnesic and sedative actions of alcohol. The brain attempts to compensate for this interference with its function by increasing the number of these receptors, so that when alcohol is withdrawn there is an excess of excitatory stimulation that results in neuronal death (brain damage).

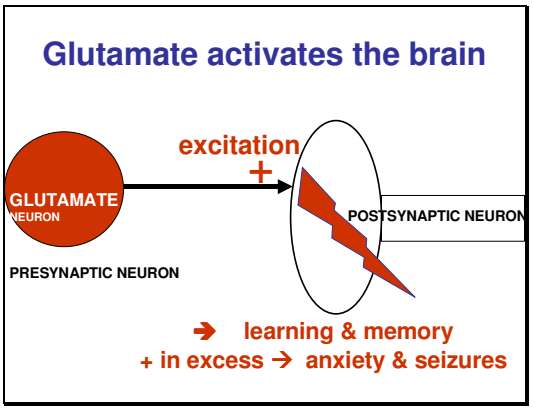
Alcohol has many actions on amine and peptide function in the brain and alterations in some of these neurotransmitter systems, especially 5HT (serotonin), have been found to be a predisposition to alcohol abuse. Dopamine release is a common feature of many abused drugs, especially stimulants and opiates, and it is likely that part of the pleasurable actions of alcohol are mediated by this neurotransmitter, and also by the release of endorphins. This latter effect helps explain why the opiate antagonist naltrexone is effective in preventing relapse.

ALCOHOL AND THE BRAIN

Alcohol has significant actions on the primary neurotransmitters, GABA and glutamate, and on the modulatory neurotransmitters, amines and peptides.

ALCOHOL & GLUTAMATE

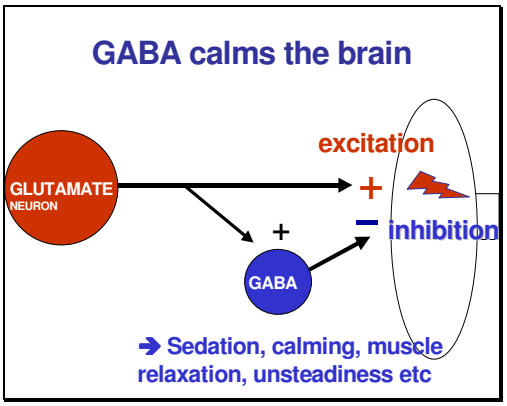
Glutamate is the main excitatory neurotransmitter in the brain. It is critical to learning and memory but in excess causes anxiety and seizures.



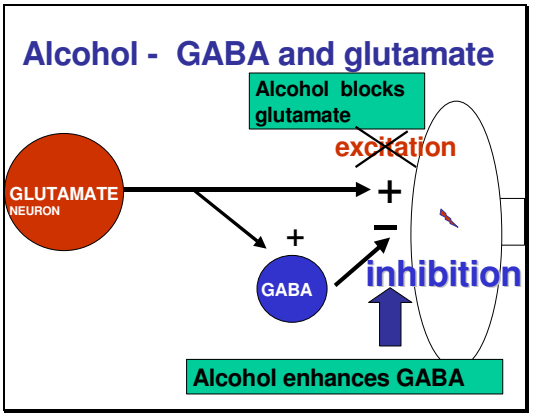
- In order to prevent excessive excitability, which will result in seizures (fits), the brain has developed a sophisticated system with projections to neurons that release inhibitory transmitters occurring where most glutamate is released.
- Alcohol blocks a particular subtype of the glutamate receptor called the NMDA receptor. Normally, activation of the NMDA receptor by glutamate allows calcium ions to flux through the membrane but the ethanol molecules block the flow of these ions through the channel, causing amnesia and also sedation and then death
- The brain makes more NMDA receptors in an attempt to compensate for the blockade by alcohol. As a result, one of the most obvious features of chronic alcohol use is the upregulation of NMDA receptors.
- With more NMDA receptors, there is more excitation possible in the brain. This can make the brain go into a hyperexcitable state when abstaining from alcohol, causing seizures and excitotoxic brain damage. This is a significant feature of the alcohol withdrawal syndrome.
- The alcohol induced brain damage that alcoholics experience is probably due to the excessive brain stimulation experienced during repeated withdrawal.
- Acamprosate (a new treatment for alcoholism) can reduce the hyperexcitable brain states by acting as a partial glutamate antagonist, offsetting the effects of alcohol on the glutamate system.

ALCOHOL & GABA

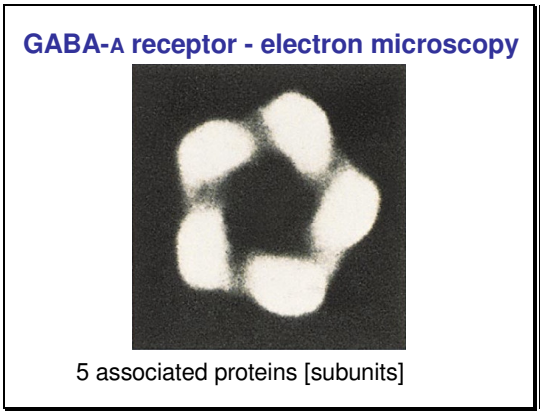
- GABA is the main inhibitory neurotransmitter in the brain. This inhibition causes sedation and muscle relaxation but in excess unsteadiness and amnesia.
- GABA release is simultaneously produced when glutamate is activated, so reducing the degree of excitation and allowing fine adjustments of the primary neurotransmission in the brain.

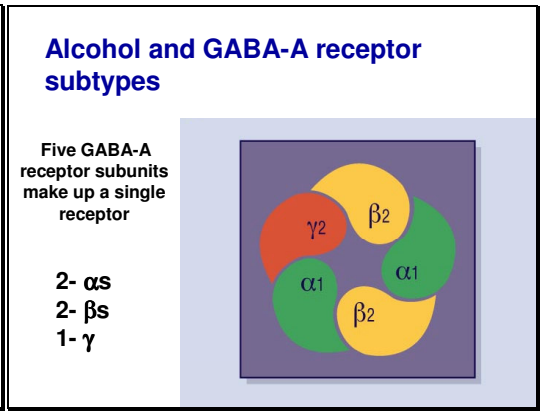


- Alcohol blocks glutamate transmission (excitation) and increases GABA transmission (inhibition). The net effect of intoxication is to produce a very profound reduction in excitation in the brain, which can lead to coma.

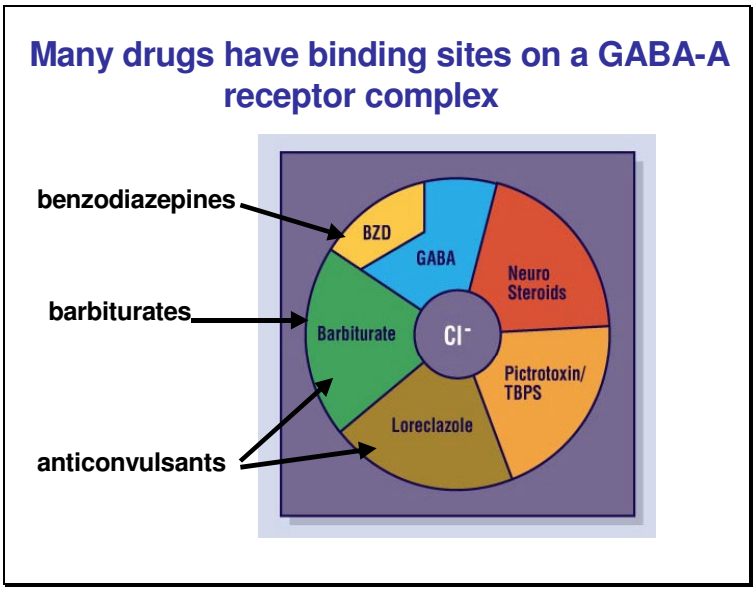


- Alcohol has a biphasic action on GABA receptors. It acts like benzodiazepines at low doses, enhancing GABA-A receptor function and causing disinhibition, sedation, clumsiness and inatttention. It acts like barbiturates at high doses, mimicking GABA action by opening chloride channels leading to coma and eventually leading to terminal respiratory depression.
- The receptor is a protein made of 5 sub-units combining to form an ion channel, and occurring in a particular combination to function correctly. The movement of ions through that channel regulates the excitability of surrounding cells.

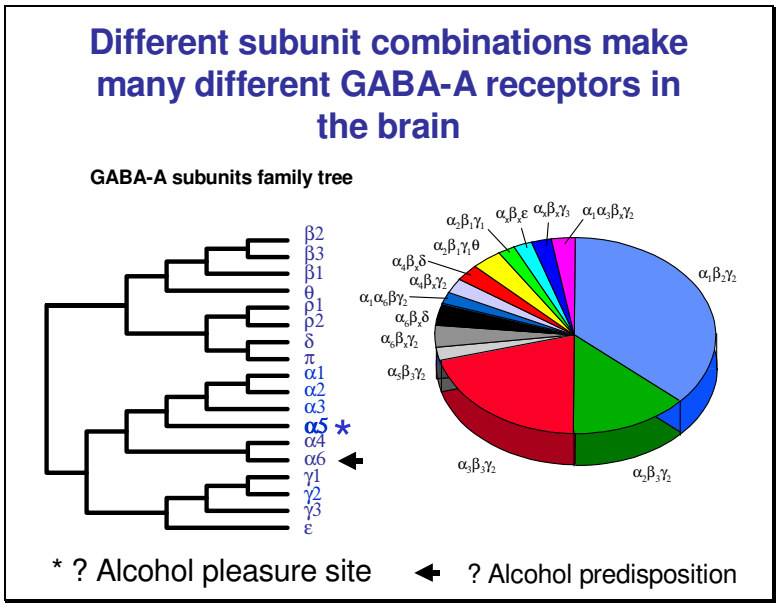




- On the complex of 5 proteins there are binding sites for many different drugs including benzodiazepines, barbiturates and anticonvulsants.
- Alcohol can interfere with the function of this receptor because it has a binding site on the GABA-A receptor complex near the barbiturate site.
- At low doses, it causes the ion channel to open wider allowing more ion flux. At high doses the channel can remain open preventing the normal adaptive mechanisms of the brain operating and explaining the acute toxicity of alcohol.

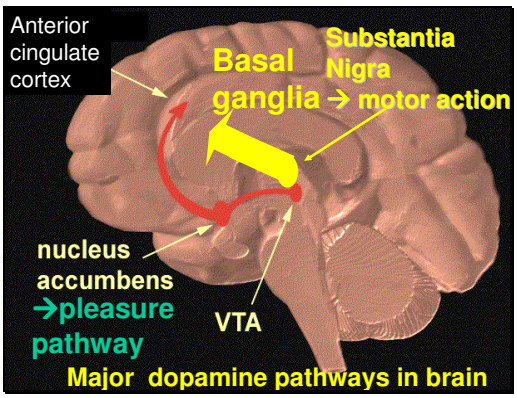


- Alcohol use downregulates the GABA-A receptors particularly in the frontal decision-making parts of the brain. There are significant differences in the density of GABA receptors in the brains of male alcoholics compared with normal controls.
- A multitude of different variants (subtypes) of the GABA-A receptors exist in the brain and their density varies, some combinations being very common and others rare.
- Different sub-types of GABA receptors mediate the different effects of alcohol.
- The alpha 5 subunit is very highly expressed in the hippocampus, a part of the brain involved in memory. It is possible this subtype mediates the pleasurable effects of alcohol.
- The alpha 1 subunit is particularly expressed in the cortex and cerebellum, areas related to higher cognitive functions. Alcohol increases inhibition of these receptors inducing sedation, ataxia and discoordination.
- Genetic variation in these receptors or receptor sub-types may predispose to alcohol dependence and account for variations in individual propensity to misuse. The alpha 6 subunit has been linked to the predisposition to alcohol dependence.
- There is also growing evidence that GABA receptors are involved in tolerance to the effects of alcohol, dependence and withdrawal effects.



ALCOHOL & AMINES

- A common pleasure circuit exists in the brain in which dopamine plays a key role. This system includes the anterior cingulated cortex and the nucleus accumbens, parts of the brain involved in motivated behaviour.
- Pleasurable experiences can cause release of dopamine in the pathway. This is critical for the learning association between the experience of pleasure and what you did to get it.
- Dopamine is thought to be the core transmitter mediating the effects of reinforced behaviour, particularly for drugs of misuse.

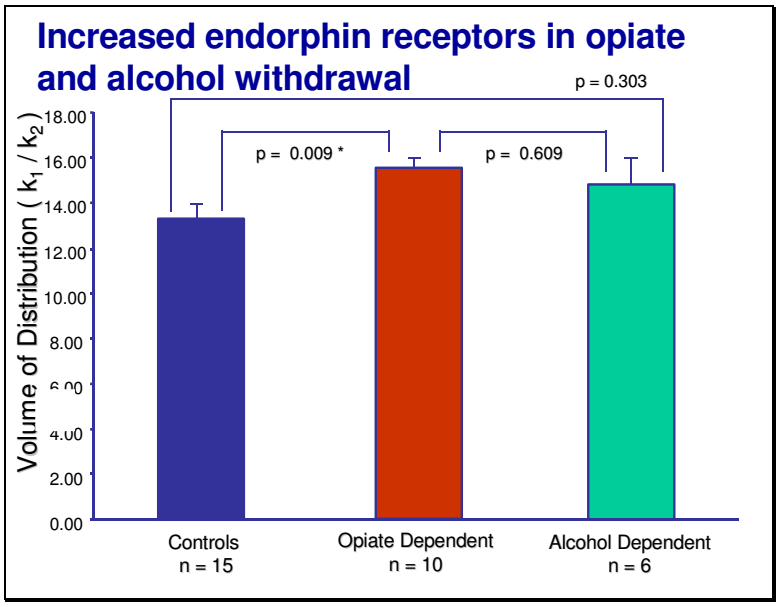


- Alcohol, like stimulants and opiates, releases dopamine activating the pleasure pathways of the brain.
- Serotonin (5HT) is a neurotransmitter manipulated by antidepressant drugs like Prozac, which boosts 5HT in the brain.
- Low 5HT receptor function is linked to alcohol dependence and chronic use may damage 5HT function in the brain. Other factors, including poor parenting and chronic stress, may also predispose individuals to alcohol dependence through reducing 5HT function.

- Drugs that promote serotonin, like the SSRIs (Selective Serotonin Reuptake Inhibitors), may have some utility in treating certain forms of alcoholism.
- Alcohol abuse may also damage the noradrenaline system, involved in attentional processes.
- Post-mortem studies show that heavy alcohol use is associated with the same magnitude of loss of noradrenaline neurons as seen in conditions like Alzheimer's disease. This may contribute to the chronic dementia seen in long-term alcohol users.

ALCOHOL & ENDORPHINS

- The brain's endorphin system is a natural system activated in response to stress in order to calm down the brain and attenuate pain.
- The receptors for the endorphins are also those on which morphine and heroin work to produce analgesia and pleasurable effects.
- Alcohol releases endorphins. This may be its primary means of producing pleasurable effects with dopamine release acting as a secondary mechanism.
- Naltrexone may have some utility in the treatment of alcohol dependence because it blocks the endorphin receptors in the brain. When endorphins are released they promote memories of experiencing pleasure, explaining why naltrexone has some therapeutic effect, preventing relapse in alcohol dependents.
- As with the glutamate system, there is an upregulation of endorphin receptors with chronic heroin and cocaine use, and preliminary evidence for similar effects with alcohol abuse. This could explain the similarities between the physical withdrawal symptoms and the propensity to relapse associated with alcohol and hard drug dependence.



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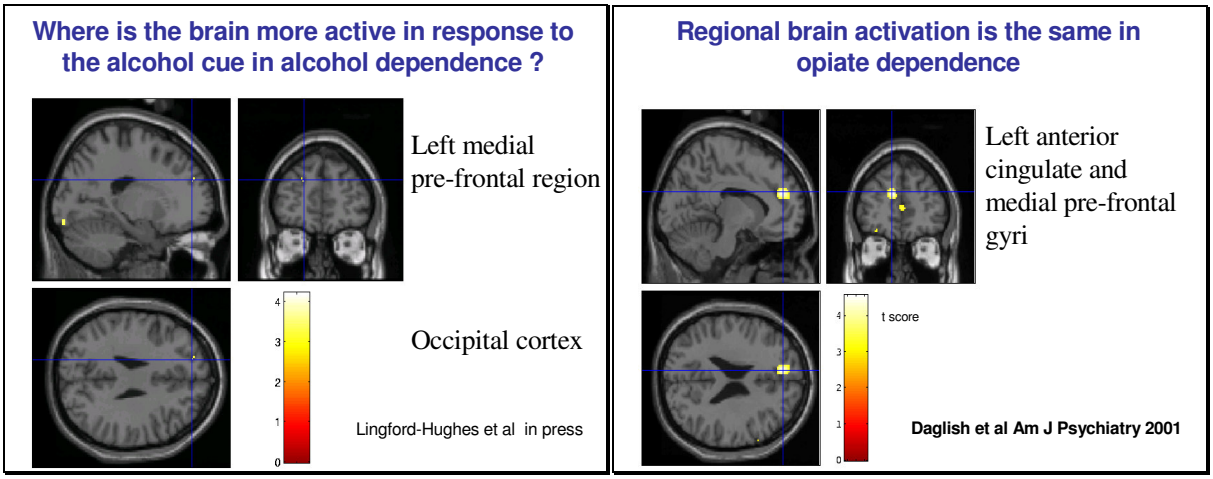
BRAIN CIRCUITS OF ALCOHOL

- Using PET or fMRI it is possible to detect changes in brain activity caused by exposure to, and craving for, a particular drug induced by specific images, smells or tastes.

- Regional brain activation is seen in similar areas in response to different drugs, from alcohol to heroin. Activation is greater with some drugs than others, which may be an indicator of the strength of the craving, but the regions activated are the same indicating a shared circuit of action.



- The common circuits associated with alcohol dependence are the same as those associated with other drugs such as heroin and cocaine. There is a commonality of action on the endogenous pleasure systems in the brain.

CONCLUSIONS

- Brain mechanisms for both legal and illegal drugs are beginning to become understood.
- Alcohol activates multiple neurotransmitters, even more so than other drugs.
- Brain receptors are involved in tolerance, withdrawal and possibly dependence to all drugs including alcohol.
- There are significant commonalities with other drugs in terms of addictive mechanisms.
- There is a need to look at patterns of receptor subtypes in persons with alcohol dependency.
- The effects of alcohol on the main neurotransmitters, glutamate and GABA, explains many of the problems with intoxication and the acute dangers of alcohol, i.e. the anesthetic effect of the drug, the ability to kill people by overdose or by virtue of accident.
- The modulatory transmitters, like dopamine and 5HT, contribute to alcohol dependence and craving. Chronic use profiles are like those of other drugs of abuse.