BACKGROUND

Neuropharmacology of Alcohol

- Alcoholism is a chronic relapsing disorder characterized by periods of heavy alcohol consumption followed by unsuccessful attempts at abstinence. This brain disease affects approximately 17 million Americans and results in tremendous social, legal, and medical costs to society that have been estimated at more than $184 billion per year.

- The neural substrates that underlie alcohol reward are not fully understood, but several studies have shown the relationship between the mesolimbic dopaminergic system and alcoholism.

- Alcohol increases dopamine release in synapic terminals of the nucleus accumbens (NAc) and somatodendritic regions of the VTA, stimulates the spontaneous activity of VTA dopamine neurons (Imperato & Di Chiara, 1986; Campbell et al., 1996; Hodge et al., 1997; Ikemoto et al., 1998; Koob et al., 2003; Brodie et al., 1999; Xiao et al., 2007), and alcohol consumption can be altered by dopamine and dopamine receptor manipulation (Samson et al., 1993; Price & Middaugh, 2004).

- However, the mechanism by which alcohol affects dopamine neurotransmission has yet to be fully elucidated.

Alcohol, Glutamate, & the VTA

- Glutamate provides excitatory input that is a key regulator of dopamine cell activity (Oberoi & Clark, 1997).

- D1-like receptors are located on glutamatergic synaptic terminals on VTA dopaminergic neurons (Li & Hagg, 1997) and stimulation of D1 receptors increases glutamate release in the VTA (Kailvias & Duffy, 1995).

- Since alcohol stimulates VTA dopamine release, it is possible that alcohol can increase glutamate release in the VTA through an indirect mechanism. In midbrain slices, acute alcohol facilitates glutamatergic transmission (Xiao et al., 2008) and systemic alcohol administration increases glutamate release in the NAc of rats (Dochshurer et al., 2000).

RESULTS

- We hypothesized that alcohol consumption would significantly increase VTA glutamate levels compared to saccharin-only consumption when measured with glutamate-oxidase coated biosensors.

METHODS

Alcohol Drinking Procedure

- Rats were trained to drink an alcohol-containing “Supersac” (ET) solution (10% alcohol, 3% glucose, 0.125% saccharin) during daily 30 min sessions in their home cage. A separate group of rats were also trained to drink a non-alcohol Saccharin solution (3% alcohol, 3% glucose, 0.125% saccharin) during daily 30 min sessions in their home cage.

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- Analysis of blood alcohol concentrations (BACs) during the drinking sessions revealed significant alcohol consumption.

- Analysis of the cumulative change in glutamate between the groups revealed a significant increase in VTA glutamate transmission in ET-drinking animals compared to Saccharin-drinking animals (t(7)=5.040, p<.001).

DISCUSSION

- Using enzyme-based detection of extracellular glutamate, we were able to show near real-time increases in glutamatergic transmission in the VTA restricted to alcohol administration.

- Our study is the first to show increased glutamatergic neurotransmission in the VTA during voluntary alcohol consumption.

- The mechanism by which alcohol increases glutamate levels may result from alcohol-induced dopamine release that stimulates dopamine receptors located on glutamatergic axons.

- Increased glutamate release could act as a “feed-forward” mechanism for dopamine neuron excitation.

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