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Invited review

Neurochemical and metabolic effects of acute and chronic alcohol in the human brain: Studies with positron emission tomography

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ABSTRACT

The use of Positron emission tomography (PET) to study the effects of acute and chronic alcohol on the human brain has enhanced our understanding of the mechanisms underlying alcohol's rewarding effects, the neuroadaptations from chronic exposure that contribute to tolerance and withdrawal, and the changes in fronto-striatal circuits that lead to loss of control and enhanced motivation to drink that characterize alcohol use disorders (AUD). These include studies showing that alcohol's reinforcing effects may result not only from its enhancement of dopaminergic, GABAergic and opioid signaling but also from its caloric properties. Studies in those suffering from an AUD have revealed significant alterations in dopamine (DA), GABA, cannabinoids, opioid and serotonin neurotransmission and in brain energy utilization (glucose and acetate metabolism) that are likely to contribute to compulsive alcohol taking, dysphoria/depression, and to alcohol-associated neurotoxicity. Studies have also evaluated the effects of abstinence on recovery of brain metabolism and neurotransmitter function and the potential value of some of these measures to predict clinical outcomes. Finally, PET studies have started to provide insights about the neuronal mechanisms by which certain genes contribute to the vulnerability to AUD. These findings have helped identify new strategies for prevention and treatment of AUD.

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1. Introduction

Alcohol affects several neurotransmitter systems, including gamma-aminobutyric acid (GABA), opioids, glutamate, serotonin, DA, endocannabinoids, and acetylcholine, (reviewed in (Eckardt et al., 1998; Wiers et al., 2016)) as well as brain energetics (Gorini et al., 2013; Saba et al., 2015) (Fig. 1). These various effects mediate the diversity of alcohol's pharmacological actions in the brain, including its acute rewarding, cognitive, and behavioral effects (i.e., executive function, sedation, motor incoordination) but also neuroadaptations from chronic abuse including addiction (Zoethout et al., 2011).

This review focuses on brain imaging studies that used positron emission tomography (PET) to evaluate the effects of acute and chronic alcohol consumption on brain energy consumption and on neurotransmitter activity in the human brain.

2. Acute effects of alcohol

2.1. Brain energetics

Most PET studies that investigated the impact of acute alcohol administration in the human brain assessed its effects on cerebral blood flow (CBF) and on brain glucose metabolism. Inasmuch as both CBF and glucose metabolism are markers of brain function, these studies aimed to assess which brain regions were affected by alcohol and how this, in turn, was associated with the behavioral changes observed during intoxication. Although, typically, decreases in glucose metabolism are associated with decreases in CBF and vice versa, this was not the case during alcohol intoxication. Specifically, while studies consistently showed that acute alcohol decreased brain glucose metabolism, the CBF studies showed that, in some regions (i.e., cerebellum) CBF decreased, whereas in others (i.e., prefrontal and temporal cortices) it increased (Volkow et al., 1988), suggesting that during alcohol intoxication glucose metabolism and CBF are uncoupled. Moreover, studies showed that low to moderate doses of alcohol markedly reduced brain glucose metabolism even when they induced minimal intoxication (Volkow et al., 1990, 2006b), and even when these alcohol doses increased CBF in the human brain (Newlin et al., 1982; Sano et al., 1993; Volkow et al., 1988). This led us to hypothesize that, during intoxication, the brain uses alternative substrates for energy production, accounting for the reduction in brain glucose metabolism and its uncoupling from CBF. Specifically, we hypothesized that acetate, which is a metabolite of alcohol, would serve as a source of energy production during alcohol intoxication and that this effect would be enhanced in alcohol abusers in whom the concentrations of acetate during intoxication are higher than in non or occasional drinkers (Roine et al., 1988). When blood acetate levels increase, as occurs during alcohol intoxication (Korri et al., 1985), glial cells preferentially metabolize acetate over glucose (Cruz et al., 2005). PET imaging studies that measured brain glucose metabolism using ^{18}FDG, and brain acetate metabolism using [^{11}C]acetate, confirmed these hypotheses showing that, whereas alcohol intoxication significantly decreased brain glucose metabolism, it significantly increased brain acetate metabolism, and these effects tended to be higher in heavy alcohol users than in controls (Volkow et al., 2013a). Brain regions with the largest decrements in glucose metabolism (i.e., cerebellum, occipital cortex) were the ones with the largest increases in acetate metabolism. Notably, resting acetate metabolism in the brain was higher in heavy alcohol users than in controls, and the magnitude of that increase was associated with the doses of alcohol they had consumed (Volkow et al., 2013a). Evidence that alcohol abusers display enhanced acetate metabolism in the brain was also found in a study that used magnetic resonance spectroscopy (Jiang et al., 2013). Although acetate had been shown to serve as a source of energy in the brain, its use appears to be mostly restricted to astrocytes (Cruz et al., 2005), since they express the monocarboxylic acid transporters necessary for the transport of acetate, whereas neurons do not (Waniewski and Martin, 1998). Subsequent studies have examined whether, during alcohol intoxication, the brain relies on acetate metabolism for resting energy requirements, or whether it also metabolizes acetate for the energy needed during task-induced stimulation, which predominantly involves neuronal activation. This was assessed by measuring brain glucose metabolism during alcohol intoxication, either while being stimulated (watching a video) or when alcohol was given with no stimulation. The effects were compared to brain glucose metabolism after placebo, which was also administered with or without stimulation (Volkow et al., 2015). These studies corroborated that alcohol decreased resting brain glucose metabolism, an effect that was significantly larger in heavy drinkers (20%) than in controls (9%), and that the reductions in glucose metabolism were proportional to the daily doses of alcohol consumed. In contrast, alcohol intoxication did not reduce the regional brain glucose metabolic increases secondary to stimulation (visual and auditory regions) in either group. These findings indicate that alcohol intoxication reduces resting but not stimulation-induced increases in brain glucose metabolism. The significance of the effects of acute alcohol administration on brain energetics, as it relates to its pharmacological effects, are unclear. However, it is possible that the energetic component of alcohol might contribute to its rewarding effects, just as the calorie content of glucose contributes to its reinforcing effects (Wang et al., 2014). Indeed, calorie-containing sugars trigger DA release in the ventral striatum, even when injected into the systemic circulation (Oliveira-Maia et al., 2011).

2.2. Neurotransmitters

The ability to measure changes in neurotransmitters in the brain with PET is limited to those neurotransmitters for which there are radioligands whose binding to their targets is inhibited by the endogenous neurotransmitter. The difference in binding of the radiotracer to its target with and without an intervention (e.g., drug exposure) is then used to estimate relative changes in the extracellular levels of the neurotransmitter. Currently, evidence for the ability to measure changes in neurotransmitter levels with PET in the human brain exists for DA (Laruelle et al., 1996; Volkow et al., 1994), serotonin (Nord et al., 2013; Selvaraj et al., 2012; Sibon et al., 2008), endogenous opiates and GABA (Stokes et al., 2014). There is also preliminary evidence for the potential to measure