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Review

Alcohol sensory processing and its relevance for ingestion

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HIGHLIGHTS

- Alcohol directly activates peripheral and central taste and trigeminal pathways.
- These circuits are linked to motivationally-relevant limbic and cortical areas.
- Ethanol chemosensory signals can acquire control over subsequent alcohol seeking.
- Integration of alcohol sensory-postingestive inputs is an important area for future study.

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ABSTRACT

Alcohol possesses complex sensory attributes that are first detected by the body via sensory receptors and afferent fibers that promptly transmit signals to brain areas involved in mediating ingestive motivation, reinforcement, and addictive behavior. Given that the chemosensory cues accompanying alcohol consumption are among the most intimate, consistent, and immediate predictors of alcohol's postabsorptive effects, with experience these stimuli also gain powerful associative incentive value to elicit craving and related physiologic changes, maintenance of ongoing alcohol use, and reinstatement of drug seeking after periods of abstinence. Despite the above, preclinical research has traditionally dichotomized alcohol's taste and postingestive influences as independent regulators of motivation to drink. The present review summarizes current evidence regarding alcohol's ability to directly activate peripheral and central oral chemosensory circuits, relevance for intake of the drug, and provides a framework for moving beyond a dissociation between the sensory and postabsorptive effects of alcohol to understand their neurobiological integration and significance for alcohol addiction.

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1. Introduction

Historically, preclinical research investigating factors that motivate alcohol drinking has tended to dichotomize whether ethanol is ingested for its 'taste' or 'postingestive' effects, often with attempts to control for or minimize the influence of the former. This dichotomy derives in part from proposed criteria for a valid animal model of alcoholism put forth in the 1970s, including the tenet that intake of alcohol should be "based solely on its pharmacological properties and not be related to some other characteristic, such as the calories it provides or its gustatory or olfactory properties" [1,2]. This dissociation between ethanol's sensory and postabsorptive effects has been less prominent in the clinical research literature on alcoholism, which has frequently recognized the

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significance of alcohol chemosensory stimuli in eliciting craving and associated drug-seeking responses in alcohol-experienced individuals [3–11]. The sensory properties of alcohol have also been of significant research interest to the alcoholic beverage industry in order to identify and manipulate those sensory attributes that maximize intake [12].

Under conditions of natural self-administration, ethanol initially produces activation of peripheral and central taste and oral somatosensory pathways [13–18], as well as a multitude of visceral sensory effects (e.g., stimulation of the gut, etc.), temporally prior to entry of pharmacologically relevant levels of ethanol into brain. Thus, ethanol sensory signals gain immediate access to the CNS (within ms) in advance of the drug's delayed postabsorptive effects. With chronic exposure, sensory and postingestive inputs become intimately integrated, such that these stimuli gain meaning for the addicted organism. Importantly, these sensory pathways are linked to limbic forebrain and cortical areas involved in controlling ingestive motivation and feeding [19]. In this review, we examine evidence for the role of sensory mechanisms in alcohol intake and provide a framework for understanding the convergence of chemosensory and postingestive factors in the development and maintenance of alcohol addiction.

2. Oral sensory processing of ethanol

Ethanol is a highly salient and complex oral chemosensory stimulus, known to directly stimulate sensory receptor and brain gustatory circuits involved in sweet taste processing [13–16] as well as oral trigeminal pathways sensitive to noxious or irritant stimulus input [17,18]. A relationship between ingestion of alcohol and sweet-tasting solutions was first recognized several decades ago with observations that ethanol-preferring C57BL mice display a significantly greater intake of both nutritive (sucrose) and non-nutritive (saccharin) sweeteners relative to their non-ethanol-preferring DBA/2J counterparts [20,21]. Subsequently, direct positive correlations between alcohol and saccharin consumption were observed in randomly bred rats [22,23], multiple inbred strains of mice [24], and seven strains of rats known to differ in ethanol preference [25]. A robust association between the intake of alcohol and sweet substances (i.e., sucrose, saccharin) has held true across a variety of independently-selected lines of alcohol-preferring and -nonpreferring rats [26–30], the F_2 progeny of crosses of these lines [25,29,31–33], and rats selectively bred for the reciprocal phenotype of saccharin consumption [34], strongly supporting a common genetic basis for this relationship. In humans, genetic risk for alcoholism as indexed by a positive family history of the disorder has also repeatedly been associated with heightened preference for concentrated sweet solutions [35–37], including in children with a positive family history but no prior experience with alcohol [38].

A substantive body of behavioral and neurophysiological data has now established that alcohol directly activates gustatory receptor and central neural substrates for sweet taste. Initial conditioned taste aversion generalization studies demonstrated that conditioned aversions to the taste of alcohol generalized to sucrose mixtures in randomly bred rats [39–42], with the sweet component of the mixtures being critical whenever aversion generalization was found [40]. Conditioned taste aversions also cross-generalize between ethanol and sucrose alone in C57BL/6J mice [43,44]. Neurophysiological recordings from peripheral gustatory nerves in primates have indicated that orally applied ethanol preferentially stimulates sweet-sensitive relative to other taste fibers in the chorda tympani nerve innervating the anterior tongue [14]. Studies from our laboratory have also demonstrated that oral ethanol stimulation of the tongue and palate within a clinically relevant concentration range (3–40%) selectively activates central sweet-responsive gustatory neurons in the rodent nucleus of the solitary tract (NTS), the first brain area to receive and process taste information [13,15,16]. Moreover, the response of individual central taste-sensitive neurons to sucrose is a robust predictor of their responsiveness to ethanol ([15,16]; Fig. 1). Ethanol-induced activity in these cells was further inhibited by peripheral pharmacological blockade of oral sweet receptors, initially implicating sweet taste receptors as candidate receptors for ethanol [15]. More recently, we specifically established that knockout of the T1r3 sweet taste receptor subunit suppresses alcohol's ability to activate central sweet taste circuits in the NTS as well as eliminates behavioral alcohol preference in ethanol-preferring C57BL/6J mice, strongly supporting this receptor in the sensory detection and transduction of ethanol taste ([13]; Fig. 2). Ethanol's ability to potently

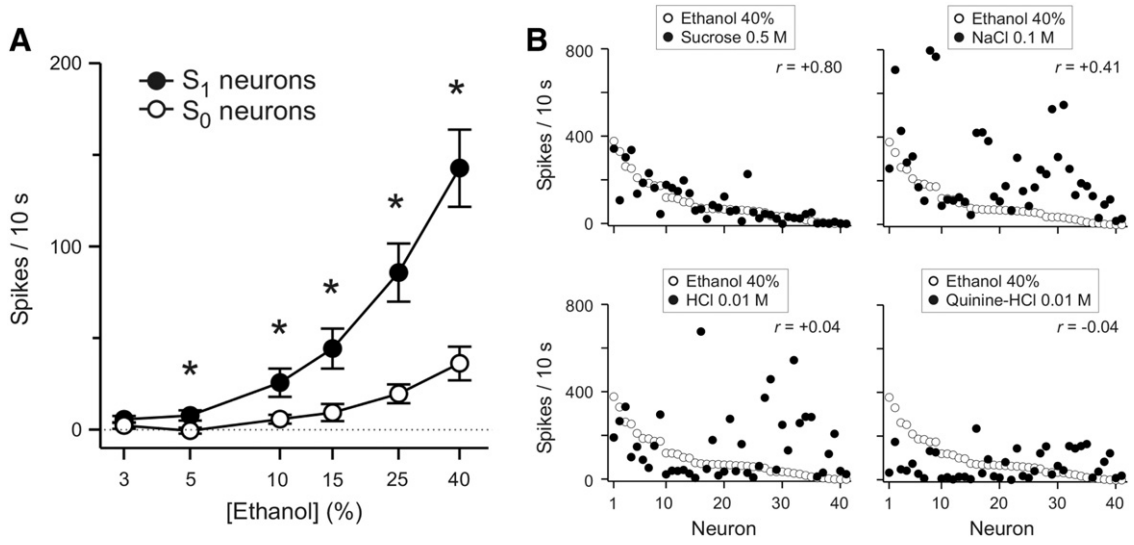

Fig. 1. A: Mean ($\pm SEM$) responses of sucrose-responsive (S_1) and sucrose-unresponsive (S_0) NTS neurons to an ethanol concentration series (3–40%) recorded from anesthetized Sprague–Dawley rats. Stimuli were presented to the anterior tongue and palate in discrete 10-s trials preceded and followed by a deionized water rinse. Responses to ethanol recorded from S_1 neurons were significantly greater than those observed in S_0 neurons for all ethanol concentrations except 3% ($^*P \leq 0.02$). B: Across-neuron patterns of response produced by standard sweet, salty, acid, and bitter tastants (filled circles) relative to that evoked by 40% ethanol (open circles). Individual neurons are rank ordered along the abscissa based on their magnitude of response to 40% ethanol. Correlation coefficients (r) calculated between the across-neuron pattern evoked by ethanol and each standard tastant are shown. Responses to ethanol were highly correlated with those to 0.5 M sucrose ($r = +0.80$), but uncorrelated with responses to HCl ($r = +0.04$) or quinine ($r = -0.04$).
Modified from [15].