Review Article

Thirst sensation and oral dryness following alcohol intake

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Summary   Substantial acute and chronic intakes of alcohol or ethanol (EtOH) severely influence oral sensations, such as thirst and oral dryness (dry mouth, xerostomia). Thirst sensation and oral dryness are primarily caused by the activation of neurons in brain regions, including the circumventricular organs and hypothalamus, which are referred to as the dipsogenic center, and by a decrease in salivary secretion, respectively. The sensation of thirst experienced after heavy-alcohol drinking is widely regarded as a consequence of EtOH-induced diuresis; however, EtOH in high doses induces anti-diuresis. Recently, it has been proposed that the ethanol metabolite acetaldehyde induces thirst via two distinct processes in the central nervous system from EtOH-induced diuresis, based on the results of animal experiments. The present review describes new insights regarding the induction mechanism of thirst sensation and oral dryness after drinking alcohol.

Contents

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1. Introduction

Thirst sensation is not only induced by an increase in plasma osmolality and/or a decrease in body fluid volume but also neurally and humorally related neurotransmitters, hormones and cytokines [1,2]. The thirst sensation induced by increased plasma osmolality causes water intake, whereas the thirst sensation induced by a decreased body fluid volume results in both water and salt intakes. To induce this thirst sensation, it is important to activate neurons in the circumventricular organs (CVOs), including the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO), and the hypothalamus, which are referred to as the dipsogenic center. Oral dryness, which comprises a feeling of dryness in the oral cavity, is produced by a decrease in salivary secretion [3—5] and is distinguished from thirst sensation [6—9]. In the present review, thirst sensation and oral dryness after alcohol drinking or administration are differentiated.

It is widely believed that the thirst sensation after acute alcohol intake may be attributed to a decrease in the body fluid volume via an alcohol- or ethanol (EtOH)-induced diuresis [10,11]. This hypothesis is supported by findings that EtOH reduces vasopressin (AVP) release from the nerve terminals of the posterior pituitary, which results in increased urine formation [12,13]. Low doses of EtOH induce diuresis; however, the urine volume is decreased rather than increased by substantial doses in animal experiments [14—16]. In addition, alcohol intake that is sufficient to induce a hangover in humans causes diuresis immediately afterwards and gradually shifts to anti-diuresis [17]. In the condition referred to as a hangover, in which individuals experience nausea, vomiting and dizziness, as well as thirst, the former symptoms are thought to be elicited by acetaldehyde, which comprises a metabolite of EtOH and a toxic substance [18]. Acetaldehyde is also considered to have an important key role in alcohol addiction [19]. Recently, it has been reported that acetaldehyde elicits the intake of water and salt without diuresis [16]. Moreover, a study has demonstrated that acetaldehyde has no effect on AVP release from the posterior pituitary [20]. Thus, the hypothesis of ''EtOH-induced diuresis'' must be reconsidered.

In addition to acute alcohol intake, chronic alcohol intake induces thirst sensation [21]. Acute [22] and chronic alcohol intake [23—25] also induces hyposalivation, which is a cause of oral dryness. There are many unknown points. The purpose of this review is to provide new insights regarding the induction mechanism of thirst sensation and oral dryness following acute and chronic alcohol intake, with a focus on the involvement of EtOH and acetaldehyde and their effects on the dipsogenic center in the brain and salivary secretion.

2. Heavy-alcohol induces thirst sensation: can it be explained by EtOH-induced diuresis?

On the subsequent morning after heavy-alcohol drinking, many individuals experience thirst sensation and oral dryness as well as other unpleasant feelings [18,26]. It is widely believed that the thirst sensation induced by alcohol drinking causes alcohol-induced diuresis [12]. This idea is based on a suppression of AVP release from the posterior pituitary [27] and a decrease in plasma AVP [12] by EtOH. EtOH inhibits calcium currents in neurosecretory neurons in the hypothalamus [28] and the terminals of the posterior pituitary [10,11,29], and it potentiates voltage-gated potassium channels [30]. Carney et al. have reported that EtOH-induced diuresis is not a result of the inhibition of AVP secretion; instead, it results from an alteration of AVP-induced water permeability within the proximal tubule in the kidney [31]. In the case of relatively heavy-alcohol drinking or administration, which may cause a hangover, the urine volume is decreased with an increase in plasma AVP or remains unchanged [14—16,21,32]. One study indicates the biphasic responses of early alcohol-induced diuresis and late anti-diuresis following alcohol drinking in humans [17]. Immunocytochemical studies indicate an increase in c-Fos immuno-positive neurons in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus, which include AVP neurons, following EtOH administration [33—35]. A recent study has reported that the AVP-enhanced green fluorescent protein (eGFP) expression levels were increased in the SON and PVN but decreased in the posterior pituitary in transgenic rats, which suggests that AVP was released from the posterior pituitary by EtOH administration [16]. To date, there is no decisive conclusion regarding whether EtOH elicits diuresis or anti-diuresis. However, it is clear that EtOH-induced diuresis is not always the cause of thirst sensation following heavy-alcohol drinking.

3. Acetaldehyde induces thirst sensation

3.1. Activation of renin—angiotensin system

Following ingestion and absorption, EtOH is metabolized into acetaldehyde via the enzymes alcohol dehydrogenase

(ADH), cytochrome P450, and catalase, which convert alcohol [36]. More than 90% of EtOH is metabolized by ADH. Acetaldehyde is subsequently further metabolized by aldehyde dehydrogenase (ALDH) to acetate. Acetaldehyde is highly reactive and may lead to hangover symptoms, such as nausea, vomiting, dizziness and headache [18]. Acetaldehyde is quickly degraded with a half-life of several minutes in vivo by ALDH [37]. Furthermore, after alcohol drinking, a specific amount of acetaldehyde is maintained and sustained in the body for several hours because EtOH may be a resource for it. To avoid the problems associated with degradation and maintain effective concentrations of acetaldehyde in the body, which are both experimentally and clinically similar to the concentrations following EtOH administration (or drinking) [34,38], the ALDH inhibitors cyanamide and disulfiram are administered in combination with EtOH or acetaldehyde [39]. The combination of acetaldehyde and cyanamide induced water and salt intake in contrast to acetaldehyde alone [16]. The acute administration of EtOH and acetaldehyde inhibits calcium currents, prostaglandin and nitric oxide and induces the relaxation of venous smooth muscle [40–42] as well as suppresses blood pressure several hours after their administration [16,43,44]. The suppression of blood pressure causes renin secretion, which results in an increase in angiotensin II in the plasma [16]. Fitts and Hoon have reported that EtOH intake increases the plasma renin activity and plasma angiotensin II level and induces water and salt intakes [45]. Furthermore, many studies demonstrate that EtOH intake increases renin and angiotensin II [46]. Several brain regions in the CVOs and the hypothalamus lack the blood–brain barrier [1]. Angiotensin II in the plasma affects and activates neurons in these regions via the activation of non-selective calcium currents and the suppression of transient potassium I_A currents via AT_1 receptors [47–50]. The activation signals of neurons in these regions elicit the behaviors of water and salt intakes through the thalamocortical pathways [1,51]. Taken together, it is hypothesized that acetaldehyde induces decreases in blood-pressure, which result in the activation of the renin–angiotensin system, and thirst sensation, as shown in Fig. 1. EtOH also induces decreases in blood-pressure [43,52]; thus, it may be involved in the pathway. Nevertheless, the novel hypothesis does not completely deny a hypothesis of EtOH-induced diuresis. The experiments regarding EtOH and acetaldehyde administrations were acutely performed with intraperitoneal one-shot injections; thus, the concentrations of EtOH and acetaldehyde would be rapidly increased in the animal body [16]. When individuals drink alcohol in normal life, the plasma concentration of EtOH would gradually increase. Therefore, the concentration must be low at the initiation of alcohol drinking and may produce urine. When the plasma concentration of acetaldehyde (or EtOH) subsequently becomes high, the mechanism shown in Fig. 1 would primarily be active. Thus, the thirst-inducible process after heavy-alcohol drinking is time-dependent.

Fluid intake induced by acetaldehyde has important physiological implications. Acetaldehyde comprises a strongly toxic substance [18]. Acetaldehyde is intrinsically produced in the body [53,54]; however, it is quickly degraded [37]. Acetaldehyde threatens the survival of life if it abnormally increases. Therefore, acetaldehyde should be quickly
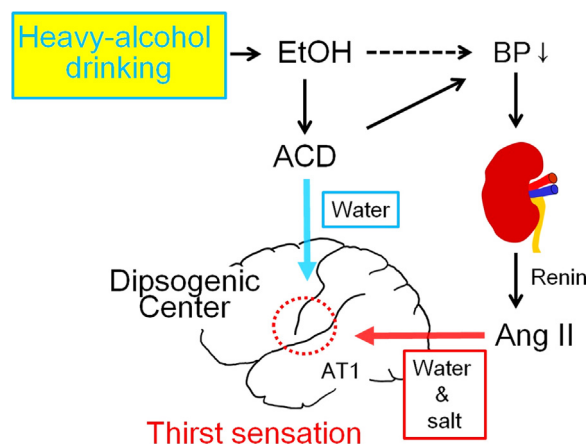

Figure 1 A hypothetical schema for the induction mechanism of thirst sensation after acute heavy-alcohol drinking. The ethanol (EtOH) metabolite acetaldehyde (ACD) suppresses arterial blood pressure (BP). This suppression enhances renin release from the juxtaglomerular cells of the kidney, which results in an increase in angiotensin II (Ang II) in the plasma. The increased Ang II induces thirst sensation, which induces the actions of both water and salt intakes, through AT1 receptors in the dipsogenic center (red arrow). EtOH also induces decreases in blood-pressure [43,52]; thus, it may be involved in the pathway. ACD also directly affects neurons in the dipsogenic center, which only affect water intake (blue arrow). The hypothesis has primarily been constructed based on our recent report [16]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

diluted or removed from the body. The increased fluid intake induced by acetaldehyde appears necessary for the former purpose, that is, for the dilution of acetaldehyde.

3.2. Direct effect of acetaldehyde on neurons in the dipsogenic center of the brain

The penetration of acetaldehyde into the central nervous system from the blood is restricted by the high ALDH activity at the blood–brain barrier [55], whereas its penetration into the cerebrospinal fluid is relatively high [56]. Acetaldehyde is immediately degraded into acetate by ALDH, which abundantly exists in the blood vessel wall; thus, it is considered that acetaldehyde has minimal effects on parenchymal cells in the brain. However, it is indicated that even low doses of acetaldehyde have direct effects on parenchymal cells [57]. In individuals with heavy-alcohol drinking or alcoholics, high doses of acetaldehyde are present in the plasma. In these cases, acetaldehyde leads to blood–brain barrier breakdown and harms parenchymal cells in the brain [58,59].

Acetaldehyde excites neurons in the ventral tegmental area [57,60]. It also primarily excites neurons in the SFO with a rather high concentration compared with other brain regions [16,61]. The threshold concentration of acetaldehyde (approximately $30\,\mu M$) was compatible with the plasma concentration after EtOH loading [34,38]. CVOs lack a blood–brain barrier; thus, they would encounter high concentrations of acetaldehyde. Furthermore, an i.c.v. injection of acetaldehyde selectively induces water but not

salt intake without a change in blood pressure [16]. These findings suggest that acetaldehyde directly affects neurons in the CVOs with a substantially increased concentration of acetaldehyde compared with other brain regions, which occurs via a distinct process from the renin—angiotensin system as described in Section 3.1 (Fig. 1).

The direct central action of acetaldehyde on thirst-related neurons, which results in an induction of only water intake, has another physiological implication. Pure water intake induces more urine output compared with an electrolyte solution [62]. Thus, acetaldehyde must be excluded from the body with urine via this action.

3.3. Involvement of dopaminergic system

EtOH and acetaldehyde affect dopaminergic neurons in the ventral tegmental area, which sends fibers to the nucleus accumbens, a primary site of EtOH reinforcement, and is related to reward-seeking behavior and addiction [57,63]. In addition, the nucleus accumbens is important for electrolyte balance [64]. Comparatively high doses of EtOH decreased the firing rates of dopaminergic neurons in the ventral tegmental area, whereas low doses of EtOH had the opposite effect [65,66]. It has been reported that an i.c.v. injection of dopamine suppresses water intake [67]. These findings are consistent with the suppression of dopamine release by a high dose of EtOH, which, in turn, may represent an additional pathway that increases thirst sensation (or sodium appetite) after heavy-alcohol drinking.

3.4. Degranulation of mast cells

Alcohol exposure affects a number of biological factors of mast cells, such as degranulation, differentiation, gene expression, proliferation, and migration [68]. Acetaldehyde enhances the degranulation of mast cells [69—71]. Mast cells contain histamine, renin, chymase, tryptase, and other immunologically active substances [72,73]. Histamine elicits both water and salt intakes, similar to angiotensin II [74—78]. The intracranial injection of histamine is effective for the induction of the behavior; thus, it is possible that the histaminergic pathway in the brain is involved in the responses. Histamine is also a well-known vasodilation factor [79]. Izumi and Hayakari have reported that histamine, which is released by the degranulation of mast cells in the application of compound 48/80, suppresses blood pressure and consequently activates the renin—angiotensin system, which results in the induction of thirst sensation [80]. Reports indicate that acetaldehyde stimulates the secretion of histamine from mast cells [70,81]. Thus, the histamine released from mast cells may be involved in the induction of thirst sensation via multiple histaminergic pathways after heavy-alcohol drinking.

Mast cells also secrete renin [71,72] and chymase [82]. One report indicates that acetaldehyde induces renin release from mast cells [71]. However, an experiment using the mast cell membrane stabilizer cromolyn indicates that the plasma renin activity enhanced by acetaldehyde is not changed by the stabilizer while fluid intake induced by acetaldehyde is suppressed (unpublished observation). In addition, acetaldehyde also secretes chymase from mast cells; however, rat chymase does not produce angiotensin II while human chymase activates the production [82,83]. Cytokines released from mast cells, such as tumor necrosis factor (TNF)-α [84] and interleukin (IL)-1β [85—87], do not increase, but suppress water intake. In contrast, IL-6 has no effects [87]. Thus, these substances described in the present paragraph may not be, at least, main induction factors regarding the thirst sensation after heavy-alcohol drinking.

Mast cells exist everywhere in the body. Their well-known locations include the dura mater of the brain [88—90], the lung [70], the heart [72] and the abdominal cavity [81]. Mast cells that contain histamine are present in several brain regions, such as the dura mater [89], thalamus [91] and median eminence [92]. The thalamus contains relay nuclei of thirst signals sensed in the CVOs and the hypothalamus. Therefore, the histamine released from mast cells may activate neurons in the relay nuclei and may subsequently modulate thirst sensation.

3.5. Involvement of endocannabinoids

The homeostatic response that regulates fluid balance is modulated by endocannabinoids [93,94]. Water intake is mediated, in part, through endocannabinoid CB1 receptors [93]. The receptors and the synthesizing and degrading enzymes for the endocannabinoid system are distributed in the CVOs, including the SFO [95]. Alcohol increases the system or suppresses the degradation of endocannabinoids in the brain [96]. Acetaldehyde-induced behavior is suppressed by CB1 receptor antagonists [97]. The endocannabinoid system also appears to be involved in the dopaminergic reward system. Thus, the CB1 receptor is a potential candidate target to explain thirst sensation after alcohol drinking [96].

4. Chronic intake of EtOH and thirst sensation

Alcohol abuse causes diseases in many organs, such as the digestive and endocrine organs, central nervous system, muscle, and heart [98]. Several cases are associated with thirst sensation, such as diabetes mellitus [99]. Diabetes mellitus causes polyuria, as a result of osmotic diuresis, when the glucose levels are so high that glucose is excreted in the urine. Polyuria causes polydipsia, which is excessive thirst. In the central nervous system, the decrement of AVP neurons in the hypothalamus in alcoholics is dose-related and time-dependent [100—102]. While the AVP response to osmotic stimulation is preserved, the plasma AVP level is decreased in alcoholics [102]. The volume of the SFO is increased; however, the volume of the area postrema, which is another circumventricular organ, is decreased in chronic EtOH treatment, whereas the number of cells in two brain regions is not changed in rodents [103]. Thus, the chronic administration of alcohol alters the center in the brain responsible for body fluid balance. Alcoholics without specific complications, such as hypertension, kidney or liver disease, diabetes mellitus, diabetes insipidus, brain disease, delirium, head trauma, or pituitary dysfunction, also exhibit thirst sensation [21]. In alcoholic patients and experimental animals chronically administered EtOH, the plasma concentrations of acetaldehyde, renin activity and angiotensin II

are enhanced [21,104,105]. Based on the same concept as acute alcohol intake indicated in Section 3.1, it is possible that enhanced angiotensin II evokes thirst sensation. However, chronic alcohol intake induces hypertension [105,106]; thus, the process of angiotensin II production may be different compared with acute alcohol intake.

5. Oral dryness induced by EtOH and acetaldehyde: change in salivary secretion

Chronic alcohol intake may increase oral dryness [107]. Accumulating evidence suggests that EtOH or acetaldehyde increases cell death [108]. Chronic alcohol intake also causes an enhancement of TNF-α expression and leads to the induction of acinar cell apoptosis [109]. There are other effects of chronic alcohol intake on the salivary glands: fat accumulation in the salivary glands, swelling and atrophy of acinar cells, and changes in the salivary flow rate [23–25]. Clinically, many studies demonstrate a decrease in salivary secretion in alcoholic patients [23–25,110]. In these cases, significant correlations have been identified between decreased salivary secretion and periodontal disease [25] as well as caries [24]. Moreover, conflicting evidence indicates an increase in salivary secretion in alcoholic patients [111,112]; however, so far, no available information has been reported regarding the mechanisms of the increased salivary secretion. No report indicates the acetaldehyde effect on salivary secretion in chronic alcohol treatment and alcoholics.

Acute heavy-alcohol drinking causes a decrease in the secretion and a change in the electrolyte concentration in the saliva as well as a decrease in protein synthesis in the salivary glands [113,114]. Prestifilippo et al. demonstrate that the inhibitory effect induced by EtOH on salivary secretion is mediated by the endocannabinoid system [22].

6. Conclusion

In the present review, thirst sensation following heavy-alcohol intake is reported to be induced by the EtOH metabolite acetaldehyde via two distinct processes (Fig. 1). Furthermore, the possibility that thirst sensation is induced via the dopamine and endocannabinoid systems and mast cells, as well as EtOH-induced diuresis, is discussed. However, many components regarding the induction mechanisms of thirst sensation and oral dryness after alcohol intake or drinking remain to be clarified.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgment

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