Review Article

Thirst sensation and oral dryness following alcohol intake

Kiyotoshi Inenaga*, Kentaro Ono, Suzuro Hitomi, Ayu Kuroki, Izumi Ujihara

Division of Physiology, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita, Kitakyushu 803-8580, Japan

Received 15 April 2016; received in revised form 28 September 2016; accepted 8 December 2016

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.

© 2016 The Authors. Published by Elsevier Ltd on behalf of Japanese Association for Dental Science. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

1. Introduction ..............................................................................................................................................79
2. Heavy-alcohol induces thirst sensation: can it be explained by EtOH-induced diuresis? ..............................................................................................................................................79
3. Acetaldehyde induces thirst sensation .................................................................................................................79
3.1. Activation of renin–angiotensin system ............................................................................................................79

* Corresponding author at: Division of Physiology, Kyushu Dental University, 2-6-1 Manazuru, Kokurakita, Kitakyushu, Fukuoka, 803-8580, Japan. Fax: +81 93 582 8288. E-mail address: inenaga2211@yahoo.co.jp (K. Inenaga).

1 Present address: 3-6-3, Hanatachibana, Shingu, Kasuya, Fukuoka, 811-0103, Japan.

http://dx.doi.org/10.1016/j.jdsr.2016.12.001 1882-7616/© 2016 The Authors. Published by Elsevier Ltd on behalf of Japanese Association for Dental Science. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 hormonally 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
the blood-pressure, and acetaldehyde suppresses IA currents, \(\text{Angiotensin II}\) receptors in the dipsogenic center (red arrow). EtOH also induces decreases in blood-pressure \([43,52]\); thus, it may be involved in the pathway. Acetaldehyde in the plasma affects and activates neurons in these regions via the activation of non-selective calcium currents and the suppression of transient potassium \(I_K\) currents via \(\text{AT}_1\) 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 \(\text{renin–angiotensin}\) 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 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 vasodilator 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

This research was supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (JSPS KAKENHI 26462819 (K.I.)).

References

[1] Fitzsimons JT. Angiotensin, thirst, and sodium appetite. Physiol Rev 1998;78:583—686.
[2] McKinley MJ, Cairns MJ, Denton DA, Egan G, Mathai ML, Uschakov A, et al. Physiological and pathophysiological influences on thirst. Physiol Behav 2004;81:793—803.
[3] Atkinson JC, Fox PC. Salivary gland dysfunction. Clin Geriatr Med 1992;8:499—511.
[4] Niew Amerongen AV, Veerman EC. Current therapies for xerostomia and salivary gland hypofunction associated with cancer therapies. Support Care Cancer 2003;11:226—31.
[5] Sreebny LM. Saliva in health and disease: an appraisal and update. Int Dent J 2000;50:140—61.
[6] Ito K, Morikawa M, Inenaga K. The effect of food consistency and dehydration on reflex parotid and submandibular salivary secretion in conscious rats. Arch Oral Biol 2001;46:353—63.
[7] Sato N, Ono K, Honda E, Haga K, Yokota M, Inenaga K. Pilocarpine-induced salivation and thirst in conscious rats. J Dent Res 2006;85:64—8.
[8] Borella TL, De Luca Jr LA, Colombari DS, Menani JV. Central muscarinic receptor subtypes involved in pilocarpine-induced salivation, hypertension and water intake. Br J Pharmacol 2008;155:1256—63.
[9] Inenaga K, Ono K. Oral dryness and thirst — the central effect of acetylcholine on drinking behavior —. J Oral Biol 2010;52:344—54.
[10] Wang XM, Lemos JR, Dayanithi G, Nordmann JJ, Treistman SN. Ethanol reduces vasopressin release by inhibiting calcium currents in nerve terminals. Brain Res 1991;551:338—41.
[11] Wang XM, Dayanithi G, Lemos JR, Nordmann JJ, Treistman SN. Calcium currents and peptide release from neurohypophysial terminals are inhibited by ethanol. J Pharmacol Exp Ther 1991;259:705—11.
[12] Eisenhofer G, Johnson RH. Effect of ethanol ingestion on plasma vasopressin and water balance in humans. Am J Physiol 1982;242:R522—7.
[13] Eisenhofer G, Johnson RH. Effects of ethanol ingestion on thirst and fluid consumption in humans. Am J Physiol 1983;244:R568—72.
[14] Colbern DL, ten Haaf J, Tabakoff B, van Wimersma Greidanus TB. Ethanol increases plasma vasopressin shortly after intraperitoneal injection in rats. Life Sci 1985;37:1029—32.
[15] Pohorecky LA. Effect of ethanol on urine output in rats. Alcohol 1985;2:659—66.
[16] Uijhara I, Hitomi S, Ono K, Kakinoki Y, Hashimoto H, Ueta Y, et al. The ethanol metabolite acetaldehyde induces water and salt intake via two distinct pathways in the central nervous system of rats. Neuropharmacology 2015;99:589—99.
[17] Tainainen H, Laitinen K, Tahтела R, Kilanmaa K, Valimaki MJ. Role of plasma vasopressin in changes of water balance accompanying acute alcohol intoxication. Alcohol Clin Exp Res 1995;19:759—62.
[18] Penning R, McKinney A, Verster JC. Alcohol hangover symptoms and their contribution to the overall hangover severity. Alcohol Alcohol 2012;47:428—52.
[19] McBride WJ, Li TK, Deitch RA, Zimatinik S, Smith BR, Rodd-Henricks ZA. Involvement of acetaldehyde in alcohol addiction. Alcohol Clin Exp Res 2002;26:114—9.
[20] Hashimoto H, Noto T, Nakajima T, Kato N. Effect of ethanol and acetaldehyde on the release of arginine-vasopressin and oxytocin from the isolated hypothalamo-hypophyseal system of rats. Endocrinol Jpn 1985;32:489—96.
[21] Collins GB, Brosnihan KB, Zuti RA, Messina M, Gupta MK. Neuroendocrine, fluid balance, and thirst responses to alcohol in alcoholics. Alcohol Clin Exp Res 1992;16:228—33.
Prestifilippo JP, Fernandez-Solari J, Medina V, Rettori V, Elverdin JC. Role of the endocannabinoid system in ethanol-induced inhibition of salivary secretion. Alcohol Alcohol 2009;44:443–8.

Dutta SK, Orestes M, Vengulek S, Kwo P. Ethanol and human saliva: effect of chronic alcoholism on flow rate, composition, and epidermal growth factor. Am J Gastroenterol 1992;87:350–4.

Dukic W, Dobrijevic TT, Katunaric M, Lesic S. Caries prevalence in chronic alcoholics and the relationship to salivary flow rate and pH. Cent Eur J Public Health 2013;21:43–7.

Waszkiewicz N, Jelski W, Zalewska A, Szulc A, Szmitkowski M, Zwierz K, et al. Salivary alcohol dehydrogenase in non-smoking and smoking alcohol-dependent persons. Alcohol 2014;48:611–6.

Penning R, van Nuland M, Flervoet LA, Olivier B, Verster JC. The pathology of alcohol hangover. Curr Drug Abuse Rev 2010;3:68–75.

Dopico AM, Lemos JR, Treistman SN. Alcohol and the release of vasopressin and oxytocin. In: Alcohol and hormones. Totowa: Human Press Inc.; 1995. p. 209–26.

Widmer H, Lemos JR, Treistman SN. Ethanol reduces the duration of single evoked spikes by a selective inhibition of voltage-gated calcium currents in acutely dissociated supraoptic neurons of the rat. J Neuroendocrinol 1998;10:399–406.

Wang X, Wang G, Lemos JR, Treistman SN. Ethanol directly modulates gating of a dihydropridine-sensitive Ca2+ channel in neurohypophysial terminals. J Neurosci 1994;14:5453–60.

Dopico AM, Bukiya AN, Martin GE. Ethanol modulation of mammalian BK channels in excitable tissues: molecular targets and their possible contribution to alcohol-induced altered behavior. Front Physiol 2014;5:466.

Carney SL, Gillies AH, Ray CD. Acute effect of ethanol on renal electrolyte transport in the rat. Clin Exp Pharmacol Physiol 1995;22:629–34.

Cooper RG, Musabayane CT. Effects of ethanol on plasma chloroquine, arginine vasopressin (AVP) concentrations and renal hydro-electrolyte handling in the rat. Ren Fail 2000;22:785–98.

Chang SL, Patel NA, Romero AA. Activation and desensitization of Fos immunoreactivity in the rat brain following ethanol administration. Brain Res 1995;679:89–98.

Kinosita H, Jessop DS, Roberts DJ, Ameno K, Ijiri I, Hishida S, et al. Effects of acetaldehyde on c-fos mRNA induction in the paraventricular nucleus following ethanol administration. Alcohol Alcohol 2002;37:432–5.

Kolodziejaska-Akiyama KM, Cha YM, Jiang Y, Loh HH, Chang SL. Ethanol-Induced FOS immunoreactivity in the brain of mu-opioid receptor knockout mice. Drug Alcohol Depend 2005;80:161–8.

Zimatkin SM, Deitrich RA. Ethanol metabolism in the brain. Addict Biol 1997;2:387–99.

Isse T, Oyama T, Matsuno K, Uchiyama I, Kawamoto T. Aldehyde dehydrogenase 2 activity affects symptoms produced by an intraperitoneal acetaldehyde injection, but not acetaldehyde lethality. J Toxicol Sci 2005;30:315–28.

Tsuchamoto S, Muto T, Nagoya T, Shimamura M, Saito M, Tainaka H. Determinations of ethanol, acetaldehyde and acetate in blood and urine during alcohol oxidation in man. Alcohol Alco- hol 1989;24:101–8.

Eriksson CJ. The role of acetaldehyde in the actions of alcohol (update 2000). Alcohol Clin Exp Res 2001;25:155–325.

Edgarhin H, Altura BM. Ethanol and contraction of venous smooth muscle. Anesthesiology 1976;44:311–7.

Greenberg SS, Xie J, Wang Y, Kolls J, Shellito J, Nelson S, et al. Ethanol relaxes pulmonary artery by release of prostaglandin and nitric oxide. Alcohol 1993;10:21–9.

Morales JA, Ram JL, Song J, Brown RA. Acetaldehyde inhibits current through voltage-dependent calcium channels. Toxicol Appl Pharmacol 1997;143:70–4.

Kawano Y, Abe H, Kojima S, Ashida T, Yoshida K, Imanishi M, et al. Acute depressor effect of alcohol in patients with essential hypertension. Hypertension 1992;20:219–26.

Satoh Y, Ide Y, Sugano T, Koda K, Momose Y, Tagami M. Hypotensive and hypertensive effects of acetaldehyde on blood pressure in rats. Nihon Arukoru Yakubutsu Igakki Zasshi 2008;43:188–93.

Fitts DA, Hoon RG. Ethanol-induced changes in plasma proteins, angiotensin II, and salt appetite in rats. Behav Neurosci 1993;107:339–45.

Linkola J, Fyhrquist F, Ylikahri R, Renin, aldosterone and cortisol during ethanol intoxication and hangover. Acta Physiol Scand 1979;106:75–82.

Nagatomo T, Inenaga K, Yamashita H. Transient outward current in adult rat supraoptic neurons with slice patch-clamp technique: inhibition by angiotensin II. J Physiol 1995;485:87–96.

Okuya S, Yamashita H. Effects of atrial natriuretic polypeptide on rat hypothalamic neurons in vitro. J Physiol 1987;389:717–28.

Ono K, Honda E, Inenaga K. Angiotensin II induces inward currents in subfornical organ neurons of rats. J Neuroendocrinol 2001;13:517–23.

Ono K, Toyono T, Honda E, Inenaga K. Transient outward K+ currents in rat dissociated subfornical organ neurons and angiotensin II effects. J Physiol 2005;568:979–91.

Hollis JH, McKinley MJ, D’Souza M, Kampe J, Oldfield BJ. The trajectory of sensory pathways from the lamina terminals to the insular and cingulate cortex: a neuroanatomical framework for the generation of thirst. Am J Physiol Regul Integr Comp Physiol 2008;294:R1390–401.

Strickland JA, Woolies WR. Effect of acute and chronic ethanol on the agonist responses of vascular smooth muscle. Eur J Pharmacol 1988;152:83–91.

Ostrovsky YuM. Endogenous ethanol—its metabolic, behavioral and biomedical significance. Alcohol 1986;3:239–47.

Gill K, Menez JF, Lucas D, Deitrich RA. Enzymatic production of acetaldehyde from ethanol in rat brain tissue. Alcohol Clin Exp Res 1992;16:910–5.

Hipolito L, Sanchez MJ, Polache A, Granero L. Brain metabolism of ethanol and alcoholism: an update. Curr Drug Metab 2007;8:716–27.

Peso AR, Hillbom ME, Eriksson L. Acetaldehyde penetrates the blood–liquor barrier of goats. Toxicol Lett 1981;8:57–62.

Melis M, Diana M, Enrico P, Marinelli M, Brodie MS. Ethanol and acetaldehyde action on central dopamine systems: mechanisms, modulation, and relationship to stress. Alcohol 2009;43:531–9.

Haorah J, Knipe B, Leibhart J, Ghorpade A, Persidsky Y. Alcohol-induced oxidative stress in brain endothelial cells causes blood-brain barrier dysfunction. J Leukoc Biol 2005;78:1223–32.

Doggett TM, Breslin JW. Acute alcohol intoxication-induced microvascular leakage. Alcohol Clin Exp Res 2014;38:2414–26.

Fodda M, Dosia G, Spiga S, Diana M. Acetaldehyde increases dopaminergic neuronal activity in the VTA. Neuropsychopharmacology 2004;29:530–6.

Diana M, Peana AT, Sirca D, Lintas A, Melis M, Enrico P. Crucial role of acetaldehyde in alcohol activation of the mesolimbic dopamine system. Ann N Y Acad Sci 2008;1139:307–17.
Perez-Idarraga A, Aragon-Vargas LF. Postexercise rehydration: potassium-rich drinks versus water and a sports drink. Appl Physiol Nutr Metab 2014;39:1167–74.

Quertemont E, Tambour S, Tirelli E. The role of acetaldehyde in the neurobehavioural effects of ethanol: a comprehensive review of animal studies. Prog Neurobiol 2005;75:247–74.

Na ES, Morris MJ, Johnson RF, Beltz TG, Johnson AK. The neural substrates of enhanced salt appetite after repeated sodium depletions. Brain Res 2007;1171:104–10.

Ericson M, Molander A, Lof E, Engel JA, Soderpalmer B. Ethanol elevates accumbal dopamine levels via indirect activation of ventral tegmental nicotinic acetylcholine receptors. Eur J Pharmacol 2003;467:85–93.

Burkhardt JM, Adermark L. Locus of onset and subpopulation specificity of in vivo ethanol effect in the reciprocal ventral tegmental area-nucleus accumbens circuit. Neurochem Int 2014;76:122–30.

Miyahara N, Ono K, Hitomi S, Hirase M, Inenaga K. Dopamine modulates neuronal excitability pre- and post-synaptically in the rat subfornical organ. Brain Res 2012;1474:44–52.

Law B, Fix C, Barton B, Carver W. A role for mast cells in alcohol-induced tissue damage and remodeling. J Clin Exp Pathol 2015;5:2.

Ruiu CM, Gomes JC. Effects of ethanol, acetaldehyde, and acetic acid on histamine secretion in guinea pig lung mast cells. Alcohol 2000;20:133–4.

Kawano T, Matsue H, Kondo Y, Machida I, Saeki S, Tomari S, et al. Acetaldehyde induces histamine release from human airway mast cells to cause bronchoconstriction. Int Arch Allergy Immunol 2004;134:233–9.

Aldi S, Marino A, Tomita K, Corti F, Anand R, Olson KE, et al. E-NTPDase1/CD39 modulates renin release from heart mast cells during ischemia/reperfusion: a novel cardioprotective role. FASEB J 2015;29:61–9.

Reid AC, Brazin JA, Morrey C, Silver RB, Levi R. Targeting cardiac mast cells: pharmacological modulation of the local renin-angiotensin system. Curr Pharm Des 2011;17:3744–52.

Amin K. The role of mast cells in allergic inflammation. Respir Med 2012;106:9–14.

Goldstein DJ, Halperin JA. Mast cell histamine and cell dehydroxanthin. Nature 1977;267:250–2.

Fox GB, Pan JB, Esbenshade TA, Bitner RS, Nikkel AL, Miller T, et al. Differential in vivo effects of H3 receptor ligands in a new mouse dopisgenesis model. Pharmacol Biochem Behav 2002;72:741–50.

Eidi M, Oryan S, Eidi A, Sepehrara L. Effect of morphine, naltrexone and histamine system on water intake in adult male rats. Eur J Pharmacol 2003;478:105–10.

Lecklin A, Eriksson L, Leppluoto J, Tarhanen J, Tuomisto L. Metoprine-induced thirst and diuresis in Wistar rats. Acta Physiol Scand 1999;165:325–33.

Magrani J, de Castro ESE, Athanazio R, Improta L, Fregoneze JB. Involvement of central H1 and H2 receptors in water intake induced by hyperosmolality, hypovolemia and central cholinergic stimulation. Physiol Behav 2006;89:241–9.

Hall JE, Guyton AC. Textbook of medical physiology. Philadelphia, PA: Elsevier; 2016.

Izumi H, Hayakari M. The role of the renin-angiotensin system in compound 48/80-induced thirst in rats. Eur J Pharmacol 1986;130:279–86.

Koivisto T, Kailoavaara P, Salaspuro M. Acetaldehyde induces histamine release from purified rat peritoneal mast cells. Life Sci 1999;64:183–90.

Brecher AS, Dubord R. Effect of acetaldehyde upon cathepsin G and chymase. NRAS implications. Dig Dis Sci 2008;53:1311–5.

Kanemitsu H, Takai S, Tsuneoyoshi H, Nishina T, Yoshikawa K, Miyazaki M, et al. Chymase inhibition prevents cardiac fibrosis and dysfunction after myocardial infarction in rats. Hypertens Res 2006;29:57–64.

Calapai G, Mazzaglia G, Cilia M, Zingarelli B, Squadrito F, Caputi AP. Mediation by nitric oxide formation in the preoptic area of endotoxin and tumour necrosis factor-induced inhibition of water intake in the rat. Br J Pharmacol 1994;111:1328–32.

Luz PA, Andrade L, Miranda N, Pereira V, Fregoneze J, De Castro e Silva E. Inhibition of water intake by the central administration of IL-1beta in rats: role of the central opioid system. Neuropeptides 2006;40:85–94.

Calapai G, Parente L, Nava F, Facciola G, Marciano MC, Caputi AP. Interleukin-1 inhibits drinking behaviour through prostaglandins, but not by nitric oxide formation. Life Sci 1997;60:457–64.

van Haasteren GA, van der Meer MJ, Hermus AR, Linkels E, Klootwijk W, Kaptein E, et al. Different effects of continuous infusion of interleukin-1 and interleukin-6 on the hypothalamic-hypophyseal-thyroid axis. Endocrinology 1994;135:1336–45.

Dropp JJ. Mast cells in mammalian brain. Acta Anat (Basel) 1976;94:1–21.

Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. Cephalalgia 1997;17:166–74.

Tore F, Reynier-Rebuffel AM, Tuncel N, Callebert J, Aubineau P. Effects of sepsis on mast cells in rat dura mater: influence of L-NMMA and VIP. Br J Pharmacol 2001;134:1367–74.

Florenzano F, Bentivoglio M. Degranulation, density, and distribution of mast cells in the rat thalamus: a light and electron microscopic study in basal conditions and after intracerebroventricular administration of nerve growth factor. J Comp Neurol 2000;424:651–69.

Panula P, Yang HY, Costa E. Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci U S A 1984;81:2572–6.

Verty AH, McFarlane JR, McGregor IS, Mallet PE. Evidence for an interaction between CB1 cannabinoid and oxytocin receptors in food and water intake. Neuropsychopharmacology 2004;47:593–603.

Ruginsk SG, Vechiatto FM, Uchoa ET, Elias LL, Antunes-Rodrigues J. Type 1 cannabinoid receptor modulators watts modulate homeostatic responses. Am J Physiol Regul Integr Comp Physiol 2015;309:R1358–68.

Suarez J, Romero-Zerbo SY, Rivera P, Bermudez-Silva FJ, Perez J, De Fonseca FR, et al. Endocannabinoid system in the adult rat circumventricular areas: an immunohistochemical study. J Comp Neurol 2010;518:3065–85.

Basavarajappa BS. The endocannabinoid signaling system: a potential target for next-generation therapeutics for alcoholism. Mini Rev Med Chem 2007;7:769–79.

Plescia F, Brancato A, Marino RA, Cannizzaro C. Acetaldehyde as a drug of abuse: insight into AM281 administration on operant-conflict paradigm in rats. Front Behav Neurosci 2013;7:64.

Molina PE, Gardner JD, Souza-Smith FM, Whittaker AM. Alcohol abuse: critical pathophysiological processes and contribution to disease burden. Physiology (Bethesda) 2014;29:203–15.

Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Invest 2010;1:212–28.

Harding AJ, Halliday GM, Ng JL, Harper CG, Kril JJ. Loss of vasopressin-immunoreactive neurons in alcoholics is dose-related and time-dependent. Neuroscience 1996;72:699–708.

Silva SM, Paula-Barbosa MM, Madeira MD. Prolonged alcohol intake leads to reversible depression of corticotropin-
releasing hormone and vasopressin immunoreactivity and mRNA levels in the parvocellular neurons of the paraventricular nucleus. Brain Res 2002;954:82–93.

[102] Jahn H, Doring WK, Krampe H, Sieg S, Werner C, Poser W, et al. Preserved vasopressin response to osmotic stimulation despite decreased basal vasopressin levels in long-term abstinent alcoholics. Alcohol Clin Exp Res 2004;28:1925–30.

[103] Castaneyra-Perdomo A, Perez-Delgado MM, Meyer G, Carmona-Calero E, Perez-Gonzalez H, Gonzalez-Hernandez T, et al. Alcohol effects on the morphometric development of the subfornical organ and area postrema of the albino mouse. Alcohol 1991;8:65–70.

[104] Wright JW, Morseth SL, Abhold RH, Harding JW. Elevations in plasma angiotensin II with prolonged ethanol treatment in rats. Pharmacol Biochem Behav 1986;24:813–8.

[105] Thevananther S, Brecher AS. Interaction of acetaldehyde with plasma proteins of the renin-angiotensin system. Alcohol 1994;11:493–9.

[106] Marchi KC, Muniz JJ, Tirapelli CR. Hypertension and chronic ethanol consumption: what do we know after a century of study? World J Cardiol 2014;6:283–94.

[107] Sreebny LM. The cause of dry mouth: a broad panoply. Ames, Iowa: Wiley-Blackwell; 2010.

[108] Tong M, Longato L, Nguyen Q-G, Chen WC, Spaisman A, de la Monte SM. Acetaldehyde-mediated neurotoxicity: relevance to fetal alcohol spectrum disorders. Oxid Med Cell Longev 2011;11:13.

[109] Slomiany BL, Piotrowski J, Slomiany A. Chronic alcohol ingestion enhances tumor necrosis factor-alpha expression and salivary gland apoptosis. Alcohol Clin Exp Res 1997;21:1530–3.

[110] Friedlander AH, Marder SR, Pisegna JR, Yagiela JA. Alcohol abuse and dependence: psychopathology, medical management and dental implications. J Am Dent Assoc 2003;134:731–40.

[111] Abelson DC, Mandel ID, Karmiol M. Salivary studies in alcoholic cirrhosis. Oral Surg Oral Med Oral Pathol 1976;41:188–92.

[112] Scott J, Woods K, Baxter P. Salivary flow rate, protein and electrolyte concentrations in chronic alcoholic patients. J Biol Buccale 1988;16:215–8.

[113] Proctor GB, Shori DK, Preedy VR. Protein synthesis in the major salivary glands of the rat and the effects of re-feeding and acute ethanol injection. Arch Oral Biol 1993;38:971–8.

[114] Enberg N, Alho H, Loimaranta V, Lenander-Lumikari M. Saliva flow rate, amylase activity, and protein and electrolyte concentrations in saliva after acute alcohol consumption. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:292–8.