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Alcohol-induced headaches: Evidence for a central mechanism?

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ABSTRACT

Alcoholic drinks (ADs) have been reported as a migraine trigger in about one-third of the migraine patients in retrospective studies. Some studies found that ADs trigger also other primary headaches. The studies concerning the role of ADs in triggering various types of primary headaches published after the International Headache Society classification criteria of 1988 were reviewed, and the pathophysiological mechanisms were discussed. Many studies show that ADs are a trigger of migraine without aura (MO), migraine with aura (MA), cluster headache (CH), and tension-type headache (TH). While data on MO and CH are well delineated, those in MA and TH are discordant. There are sparse reports that ADs are also triggers of less frequent types of primary headache such as familial hemiplegic migraine, hemicrania continua, and paroxysmal hemicrania. However, in some countries, the occurrence of alcohol as headache trigger is negligible, perhaps determined by alcohol habits. The frequency estimates vary widely based on the study approach and population. In fact, prospective studies report a limited importance of ADs as migraine trigger. If ADs are capable of triggering practically all primary headaches, they should act at a common pathogenetic level. The mechanisms of alcohol-provoking headache were discussed in relationship to the principal pathogenetic theories of primary headaches. The conclusion was that vasodilatation is hardly compatible with ADs trigger activity of all primary headaches and a common pathogenetic mechanism at cortical, or more likely at subcortical/brainstem, level is more plausible.

Key words: Alcohol, headache, migraine, migraine pathogenesis, trigger

Introduction

Many foods are considered capable of triggering migraine attack, but the relationship is frequently equivocal.^[1] Perhaps, only alcohol has what is to be considered a sure dietary trigger, but its importance is still debated. Many retrospective studies show that alcoholic drinks (ADs) act as migraine triggers, at least occasionally, in about one-third of migraine patients, and as frequent/consistent trigger in about 10% of patients.^[2] Some studies report that ADs are also a trigger of tension-type headache (TH).^[1]

In the International Headache Society (IHS) classification, alcohol-induced headache is included as secondary headaches, in the section "Headache attributed to a substance or its withdrawal."^[3] However, problems for the classification of headache triggered by alcohol using IHS criteria were recently discussed.^[4] One is the differentiation between hangover headache and migraine attack triggered by alcohol in diagnosed migraine patients.^[5-7]

Alcohol being a common trigger in the principal types of primary headaches, suggest that these headaches can share a pathogenetic mechanism and that this trigger acts at the start of the neuronal pathway involved in headache provocation. To define this important issue, we have reviewed alcohol as a trigger of primary headaches and discussed the possible correlation of the results

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with the principal pathogenetic theories of the primary headaches.

Methods

This review was performed using a literature search on PubMed from 1988 (date of the first IHS classification) to December 2014. Search terms of “alcohol,” “wine,” “food trigger,” “dietary trigger,” “migraine,” “headache” were used. Additional sources were identified via manual search of bibliographies, references lists, and previous peer reviews. Review was restricted to studies written in English. Original studies were selected if they reported in the results a numeric percentage of headache patients referring any ADs as a trigger factor. Thirty-five papers were found corresponding to these criteria. Other studies useful for the correlation of the results with the pathogenesis of the primary headaches where also selected.

Results

Migraine without aura

A recent review reports that in retrospective studies performed in different countries, about one-third of migraine patients indicate alcohol as a migraine trigger, and all ADs may act as trigger.^[2] Fourteen studies reveal a percentage higher than 20% (mean 31.9%) [Table 1].^[8-21] However, some of these studies show that alcohol acts as a trigger at least occasionally in a high percentage, but as a frequent/consistent trigger in only 10% of patients.^[18,19] In other eight studies performed in India, Japan, Turkey, China, and Italy, the percentages of alcohol or wine as migraine without aura (MO) trigger are very low (0–11%).^[22-29] In Italy and Turkey, the low percentage was confirmed by many studies.^[23,25-28] Prospective studies on alcohol as migraine trigger are few. One prospective study carried out in Austria (the Pamina study), examines a wide spectrum of factors related to migraine through the application of sophisticated statistical analysis, and provides evidence for the limited importance of nutrition (comprising alcoholic beverages) in the precipitation of migraine.^[30] A broad observational general practice study (Spain, France, Italy) reports alcohol as a trigger in 12% of migraine patients but prospectively only in 4% of migraine attacks.^[31]

Migraine with aura

Six studies report ADs as a trigger of migraine with aura (MA), four of them by the same Danish group [Table 2].^[8,12,17,19,32,33] Four studies report ADs trigger MA attack in a percentage similar to that found in MO

Table 1: Percentage of migraine without aura patients who report alcoholic drinks as a trigger

Author (country, year)	Patients (n)	Percentage
Rasmussen and Olesen (DK 1992) ^{[8]†}	58	27
Rasmussen (DK 1993) ^{[9]*}	119	20
Scharff <i>et al.</i> (US 1995) ^{[10]†}	69	35
Peatfield (UK 1995) ^{[11]*}	347	30
Russell <i>et al.</i> (DK 1996) ^{[12]†}	222	39
Bánk and Márton (HU 2000) ^{[13]†‡}	78	30
Spierings <i>et al.</i> (US 2001) ^{[14]*}	38	42
Ierusalimsky and Moreira Filho (BR 2002) ^{[15]†}	100	28
Henry <i>et al.</i> (FR 2002) ^{[16]*,†,‡}	880	23
Zivadinov <i>et al.</i> (HR 2003) ^{[17]†,‡}	720	32
Wöber <i>et al.</i> (AT 2006) ^{[18]†,‡}	66	50
Kelman (US 2007) ^{[19]*,†,‡}	1750	37
Fukui <i>et al.</i> (BR 2008) ^{[20]*}	200	34
Andress-Rothrock <i>et al.</i> (US 2010) ^{[21]*}	200	20
Takeshima <i>et al.</i> (JP 2004) ^{[22]†}	213	1
Karli <i>et al.</i> (TR 2005) ^{[23]†}	33	6
Yadav <i>et al.</i> (IN 2010) ^{[24]†}	182	0
Finocchi and Sivori (IT 2012) ^{[25]†}	100	4
Mollaoglu (TR 2013) ^{[26]†,‡}	126	3
Panconesi <i>et al.</i> (IT 2013) ^{[27]*,†,‡}	401	5
Baldacci <i>et al.</i> (IT 2013) ^{[28]†‡}	120	5
Wang <i>et al.</i> (CN 2013) ^{[29]*}	394	11

*Migraine, †MO, ‡MA. MO: Migraine without aura, MA: Migraine with aura

Table 2: Percentage of migraine with aura patients who report alcoholic drinks as a trigger. Comparison with migraine without aura

Author (country, year)	MA/MO patients (n)	MA %	MO %
Rasmussen and Olesen (DK 1992) ^[8]	38/58	7	27
Russell <i>et al.</i> (DK 1996) ^{[12]*}	111/222	27	39
Ulrich <i>et al.</i> (DK 2000) ^{[32]†}	169	9	
Zivadinov <i>et al.</i> (HR 2003) ^{[17]‡}	258/462	35	30
Kelman (US 2007) ^{[19]§}	419/855	>MO	37
Hauge <i>et al.</i> (DK 2010) ^[33]	347	30	

*4% coexisting with MO, †7% coexisting with MO, ‡7% coexisting with MO, §No specification if MA coexists with MO in some patients, †40% coexisting with MO. MO: Migraine without aura, MA: Migraine with aura

patients (about 30%). In these studies, MA coexists with MO in a variable percentage of patients or this was not specified.^[12,17,19,33] Two studies report a much lesser percentage (<10%).^[8,32] Other studies, carried out in Japan, Turkey, and Italy, find that ADs never precipitated MA, but these studies also report that ADs rarely precipitate MO and TH.^[22,23,27]

A recent detailed study shows a high number of factors that triggered MA attack, and more importantly, a high number of factors that frequently precipitated MA attack.^[33] In this study, about 30% of patients with current MA (at least one attack within the last year) report ADs as a trigger, and only about 10% indicate ADs to trigger often or always an attack. For patients

having both current MA and MO attacks, ADs are reported as a trigger of MO in 51% of patients and of MA in 40% of MA patients. In a further evaluation of patients indicating at least one trigger factor where exposure often or always triggers an attack of MA, 17% of them report ADs as a trigger: In 90% of these cases, ADs cause only 0–25% of their MA attacks while in the other 10% of cases, 26–50% of attacks.^[34] All ADs trigger MA attacks, in 80% of cases within 3 h, and consistent with other studies, red wine is frequently indicated.^[12,17] A prospective study shows that white wine, red wine, beer, and spirits do not influence the risk of MA, similarly to MO or headache, while sparkling wine increases the risk of MA.^[35]

Tension-type headache

Five studies report ADs as TH trigger in approximately the same percentage (30%) of MO patients [Table 3].^[9,10,14,17,18] However, the most extensive study also includes TH patients with coexisting migrainous headaches.^[17] Peatfield find that 21% of TH with migraine features, but only 2% of pure TH, report sensitivity to ADs while Ulrich states that ADs provoke TH in MA and MO patients but not in TH patients.^[11,36] In these two studies, red wine is the most common ADs involved in triggering TH attacks, in accordance with another study.^[18] Other studies find that ADs rarely precipitated both migraine and TH.^[22,23,27,29] Furthermore, an old prospective study reports that ADs trigger vascular headaches but not TH.^[37]

Cluster headache

More than 50% of patients indicate ADs are triggers of cluster headache (CH) attacks in chronic CH and in episodic CH only during bouts [Table 4].^[38–45] Studies in Asiatic population, similarly to an older study on Italian population, show a smaller percentage of CH patients reporting ADs as a trigger, which may be due in part to different alcohol habits.^[46–49] This great variability appears even considering only CH patients who consume alcohol.^[39,46,47]

One study shows that ADs trigger CH attack within 2 h in 82% of cases, red wine being the most implicated.^[40] However, others report beer as the most common trigger.^[43] Curiously, several reports show transitory remission as a result of alcohol consumption and also delay of the following attack through consumption of large amounts of alcohol.^[40,45] Almost 50% of CH patients stated they drank alcohol.^[40,41,43,47] Some reports suggest increased alcohol consumption, and even alcohol abuse, in CH population.^[50,51] Other studies do not support this, finding almost 50% change drinking habits, avoiding alcohol.^[52,53] In fact, CH

Table 3: Percentage of tension-type headache patients who report alcoholic drinks as a trigger. Comparison with migraine patients

Author, (country, year)	TH/M patients (n)	TH %	M %
Rasmussen and Olesen (DK 1993) ^{[9]‡}	167/119	27	20
Scharff (US 1995) ^[10]	52/69	31	35
Peatfield (UK 1995) ^[11]	40/347	2	30
Ulrich <i>et al.</i> (DK 1996) ^[36]	44	0	
Spierings <i>et al.</i> (US 2001) ^{[14]*}	17/38	29	42
Zivadinov <i>et al.</i> (HR 2003) ^{[17]†,‡}	1319/720	30	32
Takeshima <i>et al.</i> (JP 2004) ^{[22]†,‡}	412/213	1	1
Karli <i>et al.</i> (TR 2005) ^[23]	31/33	6	6
Wöber <i>et al.</i> (AT 2006) ^{[18]‡}	22/66	30	50
Wang <i>et al.</i> (CN 2013) ^[29]	344/720	7	11
Panconesi <i>et al.</i> (I 2013) ^[27]	47/401	0	5

*Two TH subjects with one migraine criterion, †TH group also includes subjects with migrainous headache, ‡M patients also include subjects with coexisting TH. TH: Tension-type headache, M: Migraine

Table 4: Percentage of episodic cluster headache and chronic cluster headache patients who report alcoholic drinks as a trigger

Author (country, year)	Patients (n)	Percentage
Levi <i>et al.</i> (SE 1992) ^[38]	49	79 (ECH)
Bahra <i>et al.</i> (UK 2002) ^[39]	230	63 (65 ECH, 54 CCH)
Schürks <i>et al.</i> (DE 2006) ^[40]	257	53 (51 ECH, 58 CCH)
Donnet <i>et al.</i> (FR 2007) ^[41]	113	31 (CCH)
Rainero <i>et al.</i> (IT 2010) ^[42]	110	44 (ECH+CCH)
Rozen and Fishman (US 2012) ^[43]	1134	52 (ECH+CCH)
Lin <i>et al.</i> (TW 2004) ^[46]	104	19 (ECH)
Dong <i>et al.</i> (CN 2013) ^[47]	120	27 (ECH+CCH)
Xie <i>et al.</i> (CN 2013) ^[48]	26	38 (ECH)

ECH: Episodic cluster headache, CCH: Chronic cluster headache

patients reduce alcohol consumption during cluster period.^[38,43,51]

Other primary headaches

A recent Danish study reports that familial hemiplegic migraine (FHM) share environmental migraine triggers with MA and MO, including ADs in 15% of patients.^[54] Hemiplegia continua is exacerbated by alcohol within 3 h (38% of patients).^[55] Of the other trigeminal autonomic cephalalgias (TACs), paroxysmal hemicrania is reported to be triggered by alcohol while there are no reports for short-lasting unilateral neuralgiform headache.^[56]

Discussion

Many of retrospective studies report that ADs trigger migraine attack in about one-third of MO population. A higher percentage of patients (over 50%) referring ADs as a trigger is found in CH. The role of alcohol in other types of primary headaches is less uniformly defined. The more detailed study shows that ADs are a trigger

of MA attack in a similar percentage to MO attack,^[33] confirming the data of earlier studies,^[12,17,19] but not the low percentage found in previous studies of the same Danish group.^[8,32] The same Danish group reports that the typical triggers of FHM are the same of MA, including ADs.^[54] The role of alcohol in TH is less surely defined. While many studies show that ADs trigger headache in TH patients in approximately the same percentage (30%) as in migraine patients, other studies show that ADs trigger TH in migraine patients^[36] but not in patients with pure TH.^[11,27] Moreover, the larger study also includes TH patients with coexisting migrainous headaches.^[17] This wide variability may result from the similar phenotypic features between MO and TH while MA and CH have more distinctive characteristics.^[3] ADs have been reported to trigger even more rare forms of primary headaches such as FHM, hemicrania continua, and paroxysmal hemicranias.^[54-56]

The interval between ADs intake and the start of MO is not well determined in many studies. However, it is reported that in 80% of cases, ADs can trigger MA attacks and CH attacks within 3 and 2 h, respectively; consistent with other studies,^[12,17] red wine is the principal alcohol trigger.^[34,40] Even MO induced experimentally by red wine developed for the most part within 3 h.^[57] However, all ADs provoke headache and the type of beverage most frequently consumed in a country will probably be the type of ADs most commonly reported to trigger headache.^[2,43]

In contrast to the well-defined role of ADs in MO patients found in many studies, in India, Japan, Turkey, China, and Italy, a much lower percentages of MO patients indicate ADs as a trigger, perhaps partly due to alcohol habits, that is to lower consumption or different beverage strength to Europe and US.^[22-29] Cultural differences can be responsible even of the very low percentage of MA and TH patients and of the lower percentage of CH patients referring ADs as a trigger found in these countries.^[22,23,27,29,46-48] In fact, in comparison to Europe and the US, the percentage of abstainers in India and Turkey is much higher and the alcohol consumption per capita is much lower, but this assumption is not valid for Italy and Japan. Conversely, in Brazil, the percentage of abstainers is high while the percentage of MO patients sensitive to ADs is equal to that found in Europe and US.^[58] In addition to the population, the frequency estimates vary widely based on the study approach. Reported rates of trigger factors vary with the method of the study (retrospective vs. prospective, spontaneous report vs. checklists, population vs. clinic based), and many methodological difficulties of investigation was highlighted.^[59-62] Differently to retrospective studies,

influenced by recall bias, few prospective studies provide evidence for the absence or very limited role of ADs in the precipitation of migraine.^[30,31,35]

Many population-based studies, carried in various countries show an inverse relationship between alcohol and migraine, both in MO than MA, and nonmigraine headache.^[4,63] Recently, two studies show that patients with chronic migraine compared to patients with chronic TH and with patients without headache, less likely drink alcohol.^[27,64] A possible explanation for the inverse association between alcohol use and headache disorders is that subjects with headache disorders may be abstaining from alcohol as it is a trigger for their headache attack. In fact, 90% of MA patients sensitive to ADs report abstaining or avoiding certain type of alcohol and CH patients reduce alcohol consumption during cluster periods.^[34,38,43,51] However, some observations seem not to support the explication that migraine patients consume less ADs because they trigger migraine attacks: (1) Among migraine patients who did not drink alcohol at all (about 50%), only 3% reported that abstaining from alcohol was a result of alcohol as a migraine trigger;^[27] (2) differently with we can expect if ADs trigger migraine, an higher use of ADs was reported in chronic migraine in comparison with episodic migraine;^[64] (3) the percentage of subjects who never or seldom consume ADs is higher in migraine and nonmigraine headache,^[63,65,66] which suggests that factors other than previous experience of alcohol as a trigger can contribute to reduced alcohol consumption in migraine, such as personal preference.^[4]

The possible triggering site

However, if ADs are a trigger factor of virtually all primary headaches, a fundamental question emerges: That is if ADs act at different levels in triggering the primary headaches or do they act at an initial level of a common pathogenetic pathway. The second hypothesis is more plausible, because it seems unlikely that ADs may act with different mechanisms in different forms of headaches but with similar phenotypic features.

Meningeal nociceptors activation through inflammatory/vasodilatory mechanism is suggested responsible of migraine pain: However, how these nociceptors are activated remains largely speculative. Cortical spreading depression (CSD), a transient neuronal and glial depolarization that propagates slowly across the cerebral cortex, is the putative electrophysiological event underlying migraine aura and has been proposed as the mechanism responsible for the activation of the migraine pain pathway, but many arguments against its role are reported.^[67] Whether the pain in TH originates from myofascial tissues or from central mechanisms in the

brain is still a matter for debate. However, the present consensus is that peripheral pain mechanisms have a role in episodic TH whereas central dysnociception is predominant in chronic TH.^[68] Several studies support the hypothalamic involvement in the TACs pathophysiology.^[69]

Concerning migraine pain, animal studies report that alcohol, mimicking capsaicin, provokes neurogenic inflammation in the trigeminovascular system, and vasodilatation of meningeal vessels through calcitonin gene-related peptide (CGRP) release from perivascular sensory nerve terminals.^[70] Many studies with noninvasive imaging techniques has well established that low-moderate doses of alcohol, after oral or intravenous (alcohol clamp) administration, increases cerebral blood flow. The increased cerebral perfusion, due to direct or indirect vasodilatory mechanisms, was found in most cerebral regions, stronger in women, and inversely correlated with sensitivity of alcohol.^[71-73] Therefore, alcohol may have an action similar to other strong vasodilators such histamine, CGRP, and glyceryl trinitrate (GTN), which trigger migraine. However, disagreement between cranial vasodilatation and drug-provoked headache suggests that vasodilatation *per se* could not explain the induced headache.^[74-76]

If the vasodilator action of alcohol at the trigeminovascular level can theoretically be compatible with MO and CH provocation, how can it be the trigger of aura and subsequent migraine pain or TH pain?

Other vasodilating drugs such as CGRP and nitroglycerin/GTN failed to induce migraine-like attacks and aura in patients with FHM, while in a small percentage of patient with MA, they have been reported to provoke aura symptoms associated with migraine-like headache, but a role of experimental stress cannot be excluded.^[77-80] On the other hand, there is no description in publications that histamine triggers MA. It is also difficult to sustain a direct vasodilating action of alcohol in the triggering TH if we do not believe in a pathogenetic mechanism in common between migraine and TH.

Migraine triggers, included ADs, can theoretically provoke CSD which can theoretically be responsible for MA, but also for FHM and MO. But at what level do ADs trigger CH, other TACs and TH? However, ethanol infusion decreases the propagation rate of CSD, indicating a decline of tissue excitability and in the CSD initiation mechanisms.^[81] Moreover, acute intake of ethanol acts as a central nervous system depressant and at cortical level, alcohol is reported to reduce cortical excitability or facilitate the activity of cortical

inhibitory circuits probably through the increase of gamma-aminobutyric acid neurotransmission.^[82,83]

Therefore, if ADs are definitely confirmed a common trigger of various primary headaches, some of which with phenotypic overlap, it is more plausible that they act probably at a common central cortical or subcortical levels.

A unitary hypothesis suggests that migraine triggers promote headache by the activation of subcortical distinct neuronal pathways convergent into parasympathetic innervation, which if activated results in meningeal release of vasoactive and algescic mediators capable of activating meningeal nociceptors.^[84] Another view sustains that migraine headache can be triggered in absence of nociceptor activation, simply as a consequence of disinhibition of tonic control from antinociceptive system, which may result in abnormal central processing of normal sensory signal,^[85,86] a mechanism previously theorized as “functional deafferentation.”^[87]

Another important question, previously discussed, is whether alcohol *per se* or some components of AD are responsible of headache provocation.^[2,4] However, the analgesic activity of alcohol deserve to be briefly discussed because not easily compatible with headache triggered by ADs. In fact, the anesthetic and analgesic properties of alcohol have been recorded for centuries and alcohol is frequently used as self-medication in pain syndromes.^[88,89] Some experiments show that alcohol have analgesic effect in the early hours after their administration, which is the amount of time ADs have been reported to trigger MO, MA, and CH. In fact, rats that received dural stimulation followed by alcohol showed an initial analgesic effect within the first 2 h after alcohol ingestion; however, 4–6 h later, their pain sensitivity increased.^[90] Similarly, intravenously administered alcohol has an analgesic effect in humans,^[91] while hyperalgesia is found in alcohol withdrawal.^[92] Interestingly, many experiments with “alcohol clamp,” a method of infusing alcohol to achieve and maintain a target breath/blood alcohol level for a prolonged time (3 h), do not report migraine within the 8 h of the typical study session in several hundred subjects.^[4,91,93,94] Only one study carried out on few subjects reports mild and transient headache as side effect in 17–25% of Japanese but not Caucasians male subjects.^[95] Experiments with this technique in migraine patients should be of much interest.

Conclusion

ADs have been reported to trigger the principal types of primary headaches. Certainly, ADs, even in small doses,

trigger headache in some MO patients, but what is debated is the degree, which depend, in part, from the population studied, the country where the study was performed and the study approach. While the results in MO and CH are in relative agreement, those in MA and TH are discordant. However, if the role of ADs in triggering MA and TH will be confirmed, a common trigger site should be considered. In this case, a direct action at the vascular system is hardly compatible with TH or MA. More plausible is an action at subcortical pain modulatory circuits, which in some way stimulate the neural generator of CH (hypothalamus?) and of migraine aura (cortex?, thalamus?).

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Conflicts of interest

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