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A pathophysiological perspective on wine induced headaches

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Abstract

Headaches are one of the most common reasons why patients seek help in the emergency department, and alcohol consumption is a well-known cause. Wine, in particular, is associated with headaches not only due to its alcohol content but also due to the presence of polyphenols and biogenic amines such as tyramine, putrescine, and, notably, histamine. Wine consumption is on the rise around the world and is likely to be reflected in headache prevalence. Understanding the mechanisms underlying wine-induced headaches can help in their management and prevention Therefore, we provide a comprehensive review of the pathophysiology of wine induced headaches.

Running title: Pathophysiology of wine induced headaches

Keywords: wine, headache, pathophysiology

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Introduction

Headache is the fourth most common reason why patients seek help in the emergency department. In the United States, it accounts for up to 2-3% of all medical visits to this department. In other countries, however, this number reaches even 5% [1].

According to the 3rd edition of The International Classification of Headache Disorders (ICHD-3), we distinguish primary and secondary headaches and unclassified headaches. Primary headaches include: migraine, tension headache and cluster headache [2].

Statistically, the largest percentage of headaches are primary headaches, and migraine dominates among them [3].

Many patients associate migraine attacks with the consumption of certain foods, the most common of which are chocolate, alcohol, especially red wine, and cheese [4].

Red wine has been known as a trigger for migraine headaches since ancient times. The current version of the International Headache Society (IHS) defines headaches related to alcohol consumption as the so-called alcohol-induced headache, which, according to ICHD-3, can be divided into immediate ones, which appear up to 3 hours after drinking alcohol and disappear within 72 hours after stopping its consumption. , and a delayed headache that occurred within 5-12 hours after drinking alcohol and disappeared within 72 hours [5].

Drinking wine is associated with headaches not only due to the consumption of alcohol itself, but mainly due to the flavonoids and tannins it contains, as well as biogenic amines such as tyramine, putrescine and, above all, histamine [6].

Wine consumption is on the rise around the world, which is likely to be reflected in headache prevalence. Therefore, we provide a comprehensive review of the pathophysiology of wine induced headaches.

Biogenic amines

Biogenic amines are low molecular weight organic compounds containing nitrogen, known for their biological activity. These compounds are present in various living organisms, as well as in a wide range of foods and beverages, including wine [7,8]. Their formation is primarily attributed to the decarboxylation of amino acids or the amination and transamination of ketones and aldehydes. Biogenic amines include histamine derived from histidine, tyramine from tyrosine, tryptamine from tryptophan, and cadaverine from lysine, reflecting their amino acid precursors [8].

Histamine, a key biogenic amine implicated in the pathophysiology of headaches, is subject to regulatory limits in certain countries, with permissible concentrations in wine ranging from 2 to 10 mg/L [8]. In clinical trial by Aebelholt Krabbe et al., researches administered intravenous histamine infusions at doses of 0.16, 0.33, and 0.66 μg/kg/min to three groups: 13 healthy, non-headache-prone individuals, 10 patients with chronic tension-type headache, and 25 patients with episodic migraine. Among the healthy controls, none experienced pulsatile headaches. In contrast, within the migraine cohort, 13 patients developed severe pulsatile headaches, 9 reported moderate intensity, 2 experienced mild headaches, and only 1 patient did not exhibit any headache symptoms. Injection of the H1 receptor antagonist, mepyramine, resulted in near-immediate resolution of the headache. In contrast, the H2 receptor antagonist, cimetidine, demonstrated significantly less efficacy but still performed better than placebo [9]. Since histamine cannot cross the blood-brain barrier and H1 receptors are located in the endothelium of cerebral arteries, it is plausible that migraine attacks may originate from the walls of intracerebral arteries rather than from the brain itself [10].

Another potential mechanism by which histamine may trigger headaches is through histamine intolerance. Due to limited data, the prevalence of this condition is difficult to ascertain, though some estimates suggest it affects 1–3% of the population [11]. Histamine intolerance presents with a broad spectrum of nonspecific gastrointestinal and extraintestinal symptoms, given the widespread presence of histamine receptors in various organs and tissues. In a study by Schnedl W.J. et al., researchers thoroughly evaluated the symptoms of 133 patients diagnosed with histamine intolerance. The second most common symptoms were neurological, including headaches, dizziness and palpitations [12].

The metabolism of biogenic amines in the human body primarily involves enzymes like diamine oxidase (DAO) and monoamine oxidase (MAO). Individuals with lower activity of these enzymes may have an impaired ability to degrade these amines, leading to their accumulation and an increased risk of headaches [13]. For instance, those with a genetic deficiency in DAO may experience histamine intolerance, manifesting as headaches after wine consumption. In a randomized, double-blind trial conducted by Izquierdo-Casas et al., 100 patients diagnosed with episodic migraine according to the IHS criteria and confirmed DAO deficiency were randomly assigned to two groups. One group received DAO enzyme supplementation, while the other was given a placebo for one month. The results showed significant variability in the duration of migraine attacks between the placebo and DAO-supplemented groups. Notably, a statistically significant reduction in pain duration was observed in the DAO group, with mean attack durations decreasing from 6.14 to 4.76 hours. In contrast, the placebo group experienced a smaller, non-significant reduction, with attack durations decreasing from 7.53 to 6.68 hours. Both groups experienced a similar reduction in the frequency of attacks and pain intensity scores [14].

Research suggests that of all biogenic amines, histamine contained in wine is the main cause of headaches. Individuals with enzymatic deficiencies, such as reduced DAO activity or histamine intolerance, are particularly vulnerable to these headaches.

Alcohol

Headache is one of the most frequently reported symptoms of hangover syndrome (HS) [15]. The alcohol hangover is defined as the combination of negative physical and mental symptoms that can occur the day after a single episode of alcohol intake, which begins when the blood alcohol concentration approaches zero [16]. The underlying mechanisms of HS remain an area of significant research. The current understanding of HS pathogenesis suggests a complex interplay between alcohol-induced metabolic and endocrine disorders, oxidative stress, inflammation, disturbances in water-electrolyte balance, and acid-base balance [17].

The majority (90-98%) of alcohol consumed is metabolized by oxidative processes within the liver, with the remaining 2-10% excreted unaltered through breath, sweat and urine [18]. The initial phase entails the oxidation of ethanol to acetaldehyde, which is catalyzed by the alcohol dehydrogenase (ADH) enzyme. In order for the reduction of the alcohol to occur, a vitamin-related cofactor, nicotinamide adenine dinucleotide (NAD), is required to accept the transfer of hydrogen atoms and electrons from the ethanol. This process culminates in the formation of NADH and protons (H+). This reaction is reversible. The subsequent phase is catalyzed by aldehyde dehydrogenase (ALDH) and comprises the oxidation of acetaldehyde to acetate, which also requires NAD as a cofactor. In contrast to the preceding reaction, this one is irreversible. A significant proportion of the acetate generated by the oxidation of acetaldehyde is transported from the liver to peripheral tissues, where it is converted to acetyl coenzyme A (CoA), a pivotal metabolite [19]. An additional pathway for the oxidation of ethanol to acetaldehyde, especially at high concentrations is the microsomal ethanol oxidizing system (MEOS). The CYP2E1 enzyme plays a key role in this process, which requires the cofactor nicotinamide adenine dinucleotide phosphate (NADP) [18]. Furthermore, a minor third pathway has been described, involving the activity of catalase in liver peroxisomes. In this pathway, ethanol functions as an electron donor for the reduction of hydrogen peroxide to water [20].

The role of ethanol and acetaldehyde in the pathology of alcohol-induced hangover symptoms remains a topic of debate in the scientific community. Given that ethanol readily crosses the blood-brain barrier (BBB), its effects on the brain may have a significant impact on the onset of the symptoms commonly associated with a hangover, such as headaches, where the underlying pathogenesis involves central processes [21]. Acetaldehyde, despite its toxic nature, does not easily cross the BBB due to its rapid metabolism by enzymes [22]. Nevertheless, acetaldehyde can be produced directly in the brain from ethanol via catalase, which can result in oxidative stress [23]. The final products of the metabolism of ethanol are acetate (acetic acid) and water, both of which are readily capable of crossing the BBB [24].

Ethanol has been demonstrated to upregulate the expression levels of the transient receptor potential cation channel subfamily V member 1 (TRPV1) and Toll-like receptor 4 (TLR4) receptors. Both receptors have been shown to trigger a neuroinflammatory response that promotes the manifestation of alcohol induced headache (AIH). Additionally, other compounds, including histamine, serotonin (5-HT), and condensed tannins, have been observed to upregulate TRPV1 and TLR4, neuroinflammatory conditions, and AIHs [25]. Nicoletti et al. demonstrate that neurogenic trigeminal inflammation and ethanol-induced meningeal vasodilation are the result of TRPV1 activation, which in turn leads to the release of calcitonin gene-related peptide (CGRP) and substance P [26]. It has been demonstrated that activated TLR4 co-localises with adaptor proteins, specifically cluster of differentiation 14 (CD14) and myeloid differentiation protein 2 (MD2), within lipid rafts [27]. TLR4 transmits signals to adaptor proteins, including TIR-domain-containing adaptor-inducing IFNβ (TRIF) and myeloid differentiation primary response gene88 (MyD88). Both adaptor proteins have been demonstrated to induce the activation of nuclear transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activator protein 1 (AP-1) and interferon regulatory factor 3 (IRF3). Subsequently, these transcription factors promote the release of cytokines, including Interleukin-1 beta (IL-1β), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP-1) and inflammatory mediators such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), which leads to inflammatory response [28–30].

The results of the study conducted on animals indicate a potential correlation between blood acetate levels and the occurrence of hangover headaches. The administration of acetate to rats in a headache model resulted in the development of trigeminal pain, whereas a similar correlation was not observed for acetaldehyde [31]. Furthermore, it is noteworthy that the concentration of acetaldehyde in the bloodstream has been shown to potentially exert an indirect influence on the severity of the post-drinking syndrome, either through oxidative stress or via the inflammatory response [32].

Two other hypotheses regarding alcohol-related headache relate to cortical spreading depolarization (CSD) and vascular lesions. However, Pancone-

si et al. puts forward the proposition that CSD and vascular lesions may be considered mere concomitant phenomena, whereas AIH is essentially the consequence of the previously described neuroinflammation [33]. A substantial body of evidence from numerous studies has demonstrated that low to moderate alcohol consumption increases cerebral blood flow [34–36]. Consequently, alcohol may elicit effects that are comparable to those of other vasodilators with potent effects, such as histamine, CGRP and glyceryl trinitrate (GTN), which are known to trigger migraine [37]. CSD can be defined as a process whereby there are alterations in ion homeostasis, an increase in mitochondrial activity, a rise in energy demand and an increase in cerebral blood flow [38]. CSD has been proposed as a mechanism that is responsible for the activation of the pain pathway in migraine, but many arguments against its role have been reported [39]. It has been postulated that CSD is primarily associated with long-term alcohol intake and has not been shown to cause headache in acute alcohol consumption tests [40,41].

Moreover, the consumption of alcohol can precipitate the onset of headaches in individuals with Asian flush syndrome, a condition characterized by an aldehyde dehydrogenase 2 (ALDH2) deficiency. Affecting 35%-40% of the East Asian population, it is one of the most common inherited enzyme deficiencies. The metabolism of alcohol by individuals with ALDH2 deficiency results in the accumulation of acetaldehyde within the body, due to the absence of ALDH2 activity. The effects are manifested by alcohol-induced facial flushing, tachycardia, nausea and headaches. These effects result from a variety of actions of acetaldehyde in the body, which include the release of histamine [42–44].

Furthermore, disturbances in the endocrine and immune systems, dehydration, hypoglycemia and sleep disturbances have been identified as potential contributors to the development of hangovers and consequent headaches [45,46].

It is crucial to acknowledge that components in alcoholic beverages can either exacerbate the effects of alcohol, leading to symptoms such as headaches, or, conversely, diminish its impact [47].

Red wine in comparison with other alcoholic beverages

Red wine contains various substances, such as histamine, tyramine, sulfites, and flavonoid phenols, which besides alcohol, may trigger migraines [5]. A study conducted by Peatfield et al. provided evidence that white wine and champagne could also potentially trigger migraine attacks [48]. In contrast to white wine and beer, red wine is a potent trigger of 5-HT release from human platelets. Thus, red wine could potentially cause more severe headaches than other beverages [49,50]. In a study conducted by Littlewood et al., red wine was compared with a mixture of vodka and lemonade to provoke migraine-like episodes. The evidence suggests that the migraine-provoking agents in alcoholic beverages are neither alcohol nor tyramine, as none of the individuals consuming the vodka mixture experienced migraine-like attacks [51]. On the other hand, retrospective data analysis from the National Statistics Institute of Spain database showed that migraine prevalence was negatively associated with alcohol consumption in the preceding 12 months [52]. Triptans, a group of serotonin receptor agonists, are used as abortive medications in the treatment of migraines [53]. Evidence suggests these drugs interact with alcohol. Nedergaard et al. conducted a retrospective study on patients who regularly consume triptans. They found that red wine was the most frequently reported migraine trigger among self-reported alcoholic beverages. In order to explain the mechanism of this phenomenon, they hypothesized that regular intake of triptans may sensitize the vascular 5-HT2 receptors involved in red wine-induced headaches [54].

Polyphenols as aldehyde dehydrogenase inhibitors

Polyphenols have been extensively studied due to their potential benefits in reducing lipid peroxidation and oxidative stress, enhancing insulin sensitivity, improving cognitive function, and lowering blood pressure [55]. Phenolic compounds are characterized by the presence of at least one aromatic ring with one or more hydroxyl groups attached. To date, over 8,000 distinct phenolic structures have been identified, many occurring in commonly consumed foods. Phenolics vary greatly in complexity, ranging from simple, low molecular weight compounds with a single aromatic ring to large and complex tannins and derived polyphenols. They are typically classified based on the number and arrangement of their carbon atoms and are frequently found in conjugation with sugars and organic acids. Naturally occurring phenolics in plant tissues can be broadly categorized into two main groups: flavonoids and non-flavonoids [56]. Flavonoids are further divided into anthocyanidins, flavonols, flavanols, hydrolyzable and condensed tannins, flavanones, flavones, and chalcones. Non-flavonoid phenolics, on the other hand, encompass compounds such as hydroxycinnamic acids, hydroxybenzoic acids, stilbenes, tyrosol, and hydroxytyrosol [55].

Wine is often recognized for its high phenolic content, which varies significantly based on factors such as the grape variety, aging, and fermentation processes. Research indicates that red wine contains nearly ten times the total phenolic compounds compared to white wine. The phenolic content of red wine typically ranges from approximately 1,000 mg/L to nearly 6,000 mg/L [55,57].

In an in vitro study conducted by Devi et al., one of the quercetin (compound belonging to flavonol group) metabolites, quercetin-3-glucuronide , demonstrated significant inhibition of ALDH2, with an inhibition rate of 78.69%. Other tested polyphenolic compounds exhibited inhibition activities ranging from 14.77% to 27.69%, except for epicatechin (one of flavan-3-ols) , which showed minimal inhibition at 0.34%. Quercetin-3-glucuronide was found to have half maximal inhibitory concentration (IC50) value of 9.62 μM, in comparison to disulfiram, a drug used for the treatment of chronic alcoholism, which has an IC50 of 1.45 μM [58].

In a study by Goldberg et al., researchers administered 10 mg of quercetin per 70 kg of body weight in 100 mL of white wine or other beverages such as grape juice, as well as a simulated vegetable homogenate or suspension. The administration in white wine resulted in a peak serum level of 126.8 μg/L of total quercetin (free and conjugated) 30 minutes post-administration, which was considerably higher than the levels observed in the other two media. Approximately 20% of the total quercetin was present in the free form [59]. Data suggest that glucuronidation is the predominant metabolic pathway for quercetin in humans [60,61]. However, it is important to note that quercetin-3-glucuronide is not the only metabolite formed through this process, other metabolites are also produced during glucuronidation [61]. These studies provide new insights into why red wine is more frequently reported to cause headaches compared to other alcoholic beverages.

Conclusions

Wine-induced headaches are caused by complex mechanisms that are influenced by multiple components, including alcohol and biogenic amines such as histamine and polyphenols. Histamine causes vasodilatation of the brain vessels and local inflammation, in which antihistamine agents may be helpful. Alcohol and its metabolites induce metabolic and endocrine disorders, oxidative stress, inflammation, and water-electrolyte imbalance. Polyphenols present in wine, such as quercetin, can escalate the effects of alcohol by inhibiting ALDH2, which is an important enzyme in alcohol metabolism. A better understanding of these underlying mechanisms can help in the management and prevention of wine-induced headaches.

Ethical approval
This conducted study is not related to either human or animal use.

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Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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