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REVIEW ARTICLE

Caffeine and headache: specific remarks☆

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Abstract Caffeine is the most widely used psychostimulant worldwide. Excessive caffeine consumption induces a series of both acute and chronic biological and physiological changes that may give rise to cognitive decline, depression, fatigue, insomnia, cardiovascular changes, and headache. Chronic consumption of caffeine promotes a pro-nociceptive state of cortical hyperexcitability that can intensify a primary headache or trigger a headache due to excessive analgesic use. This review offers an in-depth analysis of the physiological mechanisms of caffeine and its relationship with headache.

PALABRAS CLAVE
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Cafeína y cefalea: consideraciones especiales

Resumen La cafeína es la droga psicoestimulante más ampliamente utilizada en el mundo. El exagerado consumo de cafeína induce una serie de cambios biológicos y fisiológicos de forma aguda y crónica, que se pueden traducir en déficit cognitivo, depresión, fatiga, insomnio, cambios cardiovasculares y cefalea. El consumo crónico de cafeína promueve un estado pronociceptivo y de hiperexcitabilidad cortical que puede exacerbar una cefalea primaria o desencadenar una cefalea por uso excesivo de analgésicos. El objetivo de la revisión es profundizar en los aspectos fisiológicos de la cafeína y su relación con la cefalea.

Introduction

Caffeine is the world's most widely consumed psychostimulant drug. In the USA, over 87% of the population consumes some amount of caffeine every day.[1] Caffeine intake in healthy adults is not recommended to exceed 400-450 mg/day. In the USA, however, nearly 30% of the

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population consumes over 500 mg/day, and this tendency is most frequently seen among people aged 35 to 64.[2] Excessive caffeine consumption causes acute and long-term biological and physiological changes deriving in cognitive deficits, depression, fatigue, insomnia, cardiovascular problems, and headache, among others.[3]

At high doses, caffeine has an antinoceptive effect and acts as an adjuvant to other analgesics. In the long-term, however, excessive caffeine consumption may increase the risk of medication overuse headache and lead to chronification of some primary headaches. Caffeine may also cause physical dependence which may manifest as withdrawal syndrome.[4] The International Headache Society does not list caffeine among substances potentially causing analgesic-overuse headache but rather as a substance that may cause headache when regular consumption over 200 mg/day for more than 2 weeks is discontinued abruptly.[5] The purpose of our review article is to gain a better understanding of the physiological effects of caffeine and its association with headache, whether as a trigger factor for medication overuse headache or as a substance exacerbating primary headache.

Caffeine: action mechanism and its association with the pathophysiology of headache

Caffeine, a chemical compound found in coffee, was isolated in 1819 by German chemist Friedrich Ferdinand Runge; this researcher coined the term 'Kaffein', which became 'caffeine' in English.[6] Caffeine, also known as trimethylxanthine, is a naturally occurring alkaloid in some plants. It is synthesised from adenosine and metabolised by cytochrome P450 (CYP1A2) into different active metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%).[6] Caffeine has an oral bioavailability of almost 100% and a half-life ranging from 4 to 9 hours, depending on several factors: it is shorter in smokers and longer in women who are pregnant or taking oral contraceptives.[6]

Caffeine molecules, which are structurally similar to adenosine, bind to adenosine receptors in the cell surface without activating them, thereby acting as competitive inhibitors.[6] Adenosine is a purine nucleotide released by adenosine triphosphate (ATP) from astrocytes. It acts at the neuronal level thanks to the action of P1 receptors; these receptors are also known as adenosine receptors and they are G protein-coupled.[7] Four subtypes of adenosine receptors have been described to date: A_1, A_{2A}, A_{2B}, and A_3. A_1 receptors are the subtype of adenosine receptors with the widest distribution throughout the brain and spinal cord, and they also have the greatest affinity for caffeine (Fig. 1).[7] In general terms, adenosine inhibits the release of excitatory neurotransmitters leading to decreased cortical excitability. Caffeine induces a state of cortical hyperexcitability due to its inhibitory effect on adenosine receptors; this process increases alertness and improves cognitive function.[7]

In this context, the hypothesis that caffeine has an analgesic effect and may be useful in acute management of headache may seem paradoxical. However, the analgesic action of caffeine is based on its powerful vasoconstrictor effect, which counteracts the vasodilator effect of purines.[8] This is the basis for the 'purinergic' hypothesis for migraine, a theory proposed in 1989 which suggests that purines trigger migraine attacks due to their powerful vasodilator effect.[9] Some studies have supported the purinergic hypothesis as an epiphenomenon rather than the factor triggering migraine. Guieu et al.[10] observed elevated plasma levels of adenosine during migraine attacks whereas Brown et al.[11] showed that administering exogenous adenosine precipitated migraine. Based on the above, it seems reasonable that caffeine would have an analgesic effect and be useful for acute management of headache. In addition to its powerful vasoconstrictor effect, caffeine may act as an analgesic given its ability to inhibit the synthesis of leukotrienes and prostaglandins, which are clearly involved in the pathophysiology of migraine.[12]

Some studies in animal models have shown that prostaglandin E2, when acting via EP4 receptors, promotes vasodilation of the middle cerebral and middle meningeal arteries, the main arteries involved in the vascular pathophysiology of migraine.[13] Furthermore, other studies have shown that prostaglandin E2 promotes the release of calcitonin gene-related peptide, a multifunctional neuropeptide that regulates peripheral vascular tone and sensory transmission and has been directly associated with migraine pathophysiology.[14] Thus, the effect of caffeine on prostaglandin synthesis induces an antinociceptive state.

The analgesic effect of caffeine is also favoured by its action as an adjuvant to other anaesthetics; caffeine promotes gastric absorption due to increased production of cyclic AMP.[15] Some studies have shown that adding caffeine to an analgesic reduces the dose necessary to achieve the same effect by 40%.[16]

Caffeine is thus an analgesic whose mechanism relies on its powerful vasoconstriction effect and the ability to inhibit prostaglandin synthesis, and to promote the absorption of other analgesics. Despite these remarkable effects, long-term caffeine consumption in patients with migraine triggers a cascade of physiological changes that may deliver 3 different clinical situations: exacerbation of primary headache, caffeine-withdrawal headache, and analgesic-overuse headache.

Caffeine in patients with headache: an aggravator of primary headache or a trigger of analgesic-overuse headache?

The question of whether caffeine exacerbates primary headache or triggers analgesic-overuse headache is difficult to answer based on available evidence. On the pathophysiological level, long-term caffeine overuse (>450 mg/day) causes a series of metabolic changes that may exacerbate primary headache and even trigger analgesic-overuse headache. Long-term effects of caffeine overuse result from over-regulation and hypersensitivity of adenosine receptors.[17] This process may explain the marked physical dependence resulting from long-term caffeine overuse. It also serves as the basis for understanding withdrawal syndrome: when caffeine consumption is interrupted abruptly, adenosine receptors become available, leading to vasodilation and significant increases in cerebral blood flow.[17]