Topical review

Caffeine and pain

Jana Sawynok*

Department of Pharmacology, Dalhousie University, Halifax, NS, Canada B3H 1X5

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A R T I C L E   I N F O

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1. Introduction

Caffeine is widely consumed for its central nervous system stimulant effects such as increased alertness and decreased fatigue. It is present in a variety of beverages (coffee, tea, energy drinks) and some foods (chocolate, desserts); it is also available as a drug where it is used as a stimulant, or is added to analgesics in over-the-counter formulations (Table 1). Estimated daily consumption is 168–220 mg/day in North America, and 390–410 mg/day in Scandinavian countries [11]. Population-based surveys in the US confirm such intake levels (193 mg/day) and note high consumption rates (85–95% of adults) [9]. Pharmacological actions of caffeine are attributed primarily to block of adenosine A1, A2A, and A2B receptors; it has a lower affinity for A3 receptors [11]. Caffeine also can inhibit phosphodiesterase, promote Ca2+ release and block GABA_A receptors, but concentrations required to elicit these effects are one hundred times higher and unlikely to be reached by normal dietary use of caffeine [11].

The effects of caffeine on pain are of interest for several reasons. (1) Caffeine is present in analgesic formulations and exhibits adjuvant properties, increasing the analgesic effect of the primary constituent. (2) Following chronic caffeine use, withdrawal headaches occur; on the other hand, habitual caffeine over-consumption is associated with generation of headaches. (3) Caffeine, in lower doses than implicated in adjuvant analgesia, blocks antinociception by several agents in preclinical studies, and dietary caffeine could interfere with the analgesic actions of these agents. (4) Adenosine is implicated in antinociception resulting from acupuncture, and caffeine use may interfere with the effectiveness of this modality. This topical review will address each of these caffeine pain stories.

2. Caffeine as an adjuvant analgesic

Caffeine has been added to formulations containing aspirin, acetaminophen and other non-steroidal anti-inflammatory drugs (NSAIDs) for some time. It was probably originally added to offset potential sedative effects of analgesics, but is now regarded as an adjuvant analgesic. Clinical studies published in the 1960s and 1970s indicated that caffeine-containing analgesics produced effects similar to those of the analgesics alone, but in the 1980s, an analysis of 30 unpublished studies (post-operative pain, headache) derived a relative potency of 1.41 for analgesics (aspirin, acetaminophen) containing 65 mg caffeine, and this established its reputation as an adjuvant analgesic [21]. More recent meta-analyses of adjuvant actions of caffeine suggest that caffeine may be useful for enhancing relief of headache pain [43], but for postsurgical pain, caffeine adds little to the analgesic action of acetaminophen and aspirin [41,42], while additive effects with ibuprofen are inconsistent [27].

The effects of caffeine in combination with acetaminophen, aspirin and other NSAID analgesics have been examined in detail in a series of preclinical studies. An analysis using a single test, the uric acid functional impairment model, examined several dose combinations of caffeine with several analgesics [14]. In the acetaminophen–caffeine study, sixteen dose combinations were examined (100–10, -18, -32, -56; 178–10, -18, -32, -56; 316–10, -18, -32, -56; 562–10, -18, -32, -56 mg/kg) – antinociception was augmented in a mid-dose range particularly at acetaminophen 316 mg/kg and caffeine 32 mg/kg. A 3-zone model was proposed, whereby only in the ascending part of a sigmoidal curve did caffeine augment the action of acetaminophen. Subsequent studies indicated caffeine 18–32–56 mg/kg also augmented antinociception by aspirin, several other NSAIDs [14] and ibuprofen [22] in this model.

There is an extensive preclinical literature on intrinsic antinociceptive actions of caffeine, and this has been reviewed recently [28]. While the effects of caffeine depend on the nature of the test,
Table 1

<table>
<thead>
<tr>
<th>Intake level</th>
<th>Total intake (mg/day)</th>
<th>Single dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>&lt;100</td>
<td>30–75</td>
</tr>
<tr>
<td>MODERATE</td>
<td>101–200</td>
<td>76–150</td>
</tr>
<tr>
<td>HIGH</td>
<td>201–1000</td>
<td>151–300</td>
</tr>
</tbody>
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Caffeine content: coffee 100–200 mg, specialty coffees up to 500 mg, tea 25–50 mg, soft drinks 30–50 mg, energy drinks 100–300 mg, frozen desserts 50–80 mg, drugs 65–200 mg [www.cspinet.org/new/cafchart.htm][18].

The dose of caffeine, and species tested, several studies report intrinsic antinociception in different models generally at doses of 25–100 mg/kg. Antinociception is attributed to block of adenosine A$_{2A}$ and A$_{2B}$ receptors, and such actions may also contribute to adjuvant analgesia [28]. Additional non-adenosine based mechanisms, such as changes in the activity and synthesis of cyclo-oxygenase enzymes at certain sites also are implicated in adjuvant analgesia [10].

3. Caffeine and headaches

Acute administration of caffeine has been reported to produce intrinsic analgesic actions in some headache studies [5,36]. At higher doses (300–500 mg) caffeine relieved post-dural puncture headaches [4,40], but repeated administration of lower doses did not produce such an effect [6]. Vasoconstrictor actions of caffeine (secondary to adenosine receptor blockade) are implicated in relief of headache [32].

Following chronic caffeine ingestion, cessation of intake leads to a withdrawal syndrome in which headache and fatigue are prominent; symptoms have an onset of 12–24 h, peak at 24–48 h, and last about 1 week [16]. Headaches were originally recognized in the context of withdrawal from high intake levels (>600 mg/day), but even moderate intake levels (100 mg/day) lead to withdrawal headaches [15]. Caffeine withdrawal has been recognized as a factor in peri-operative headaches, as prior to surgery, “nothing by mouth after midnight” has been routine practice. Retrospective studies reported a relationship between caffeine consumption and headaches in the perisurgical interval [8,37].

A subsequent prospective study determined the effect of restoring caffeine consumption on the day of surgery, and reported elimination of peri-surgical headaches [17]. A further study investigated the effect of caffeinated beverages versus intravenous caffeine on the incidence of post-operative headaches and found both procedures reduced headache [38]. Collectively, these studies suggest that attention to caffeine intake, and restoration of intake on the day of surgery, can be helpful in alleviating post-operative headaches.

In contrast to the above scenarios, in which caffeine is beneficial in resolving headaches, habitual caffeine consumption is associated with development of headaches such as migraine and chronic daily headache. Several studies from different countries report a significant correlation between caffeine consumption and headache [32]. Furthermore, a case study in children with chronic daily headache who consumed caffeine-containing beverages reported headache resolution when these were withdrawn [19]. These observations suggest that reduction in caffeine intake may be beneficial in leading to headache resolution in certain instances.

4. Caffeine and other analgesic drugs

In the past decade, an increasing number of preclinical studies have reported that doses of caffeine lower than those that exhibit adjuvant analgesic effects inhibit antinociception by several agents (Table 2). These results are interpreted to reflect involvement of adenosine A$_1$ receptors because: (a) A$_1$ receptor agonists produce antinociception in nociceptive, inflammatory and neuropathic tests, and (b) selective A$_1$ receptor antagonists mimic the blocking effect of caffeine. Low doses of caffeine inhibit antinociception by amitriptyline, venlafaxine, carbamazepine and oxcarbazepine, all of which are currently used, or are being explored, as analgesics for neuropathic pain in humans; they also inhibit actions of allopurinol which is used to treat gout, cizolirtine which is an experimental analgesic, and even antinociception by acetaminophen in some models.

The ability of low doses of caffeine to inhibit antinociception in preclinical studies raises the possibility that dietary caffeine intake could interfere with analgesic efficacy in a clinical setting. Ideally, a clinical trial would evaluate, in a prospective manner, the effects of caffeine on analgesic agents. However, given the widespread use of caffeine, potential adaptive changes that occur following long-term use of caffeine, and challenges in recruiting trial participants who would agree to give up caffeine consumption in order to participate in blinded trials, this approach may not be optimal for exploring the issue. The experience with another drug in which adenosine is implicated in its mechanism of action may be instructive for considering trial design.

Methotrexate, in low doses, is an effective therapy for rheumatoid arthritis. In a rat model of arthritis, it relieves the severity of symptoms by an action that involves adenosine A$_{2A}$ receptors on inflammatory cells – caffeine completely suppresses this activity [24,25]. In clinical studies, the effects of caffeine intake on methotrexate actions in rheumatoid arthritis were initially examined by monitoring caffeine consumption and dividing into low (89 mg/day), medium (151 mg/day) and high (259 mg/day) intake levels – subjects in the high intake group had less improvement than those in the low intake group [26]. This study involved newly recruited subjects (N = 39) and a methotrexate dose of 7.5 mg/day. A subsequent analysis of a larger number of subjects (N = 264) on established doses of methotrexate (16 mg/day) found no differences in outcomes between low (39 mg/day), medium (165 mg/
kg) and high (422 mg/day) caffeine intake groups [2]. Similarly, analysis of subjects with psoriatic arthritis (N = 150) treated with methotrexate exhibited no difference in methotrexate dosing requirements between low (<120 mg/day), moderate (120–180 mg/day) and high (>180 mg/day) caffeine intake levels [33]. The latter study further noted a wide range of doses of methotrexate to treat this condition, and no correlation between methotrexate and caffeine intake levels. The pragmatic methodology used in these trials provides a means by which the potential influence of caffeine intake on analgesic and other effects of established drug modalities could be examined.

5. Caffeine and non-pharmacological modalities

Acupuncture is used widely to manage chronic pain. The mechanistic basis of experimental acupuncture, particularly electroacupuncture, involves multiple endogenous mediators (e.g. endorphins, monoamines, peptides, hormones) [44]. Acupuncture in traditional Chinese medicine (manual acupuncture) involves insertion and twirling of needles and may involve further peripheral mechanisms and mediators. Tissue analysis of the consequences of needle insertion and manipulation reveal engagement of collagen fibres and fibroblasts and changes in their tension kinetics within connective tissue [20]. Recently, it was demonstrated that needle insertion and manipulation leads to increased tissue levels of ATP, ADP, AMP and adenosine [13]. Adenosine mediates acupuncture analgesia via A1 receptor activation because inhibition of adenosine metabolism (using deoxycoformycin to inhibit adenosine deaminase) augmented the magnitude and duration of analgesia, and analgesia was eliminated by deletion of the A1 receptor gene [13]. Caffeine can block adenosine A1 receptors in modest doses, and could inhibit acupuncture analgesia [45].

The implication of peripheral adenosine in acupuncture analgesia necessitates some new perspectives in evaluating the efficacy of acupuncture in clinical trials. Future studies should determine whether chronic caffeine intake alters the effectiveness of acupuncture. While one might consider abstinence from caffeine for an interval prior to an acupuncture session (e.g. for 4 h), the effects of acupuncture on chronic pain are usually assessed after a series of sessions (e.g. twice weekly for 6 weeks), and effects on pain determined post-intervention and at several follow up intervals. In this setting, chronic intake patterns are likely of greater relevance. It is important to note that caffeine (200 mg) has been reported to inhibit the efficacy of transcutaneous electrical nerve stimulation, TENS, when given prior to the stimulation in a small experimental pain trial (N = 17 subjects) in humans [23]. The potential influence of chronic caffeine intake on TENS analgesia for chronic pain indications therefore also warrants attention. In another setting, prior caffeine intake (within 2–4 h) increased dose requirements for i.v. adenosine used to treat supraventricular tachycardias [3].

6. Conclusions

Caffeine is the most widely consumed psychoactive agent in the world. Given its widespread use, and the ability of low doses of caffeine to interfere with antinociception in preclinical studies, it is necessary to consider the effects of acute and chronic caffeine intake in several clinical settings. There are challenges to conducting prospective trials, but useful information can be obtained by simply monitoring intake levels in a structured manner. Adenosine is now implicated in analgesia by acupuncture and TENS, and the effect of caffeine intake on these non-pharmacological modalities also needs to be considered. Both caffeine intake and withdrawal can lead to headaches in some situations, and levels of caffeine intake warrant direct clinical attention. These considerations expand attention to effects of caffeine on pain well beyond its well-known role as an adjuvant analgesic.

Conflict of interest statement

There are no conflicts of interest pertaining to this manuscript.

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References


