https://doi.org/10.31925/farmacia.2022.6.20 **ORIGINAL ARTICLE**

THE INFLUENCE OF CAFFEINE, CELECOXIB AND THEIR COMBINATION ON ANALGESIC PROCESSES

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Abstract

Pain and inflammation are the most complex processes that occur in the human body. Pain physiology involves intricate pathways based on a level of reception, transmission pathways and a cortical level. There are numerous neurotransmitters and mediators that influence pain and inflammation as they modulate each level of pain transmission. The purpose of this paper is to determine the analgesic effect of two different substances, celecoxib and caffeine, and the way they influence each other's effects after both, single and multiple administrations to Swiss albino strain male mice. Two tests were used to determine the analgesic effect, the writhing test and the hot plate test. Following single dose administration, both caffeine and celecoxib determined an increase in the analgesic effect compared to the control group during writhing and hot plate tests. However, no dose-effect relationship could be observed for caffeine. Moreover, caffeine slightly decreased the effects of celecoxib, however without statistical significance. Following multiple dose administration, only the higher doses (10 mg/kg and 25 mg/g) of caffeine tested had analgesic effects while celecoxib showed analgesic effects only in the hot plate test. Caffeine had no influence on analgesic effects of celecoxib following multiple dose administration. The results of IL-6 and CPR determinations suggest that the analgesic effects of celecoxib could be mediated by pro-inflammatory cytokines. Caffeine did not affect IL-6 and CRP levels.

Rezumat

Durerea și inflamația reprezintă cele mai complexe procese care au loc în corpul uman. Durerea și inflamația implică mecanisme intricate bazate pe un nivel de recepție, căi de transmisie și un nivel cortical. Numeroși neurotransmițători si mediatori pot influența durerea, prin modularea fiecărui nivel de transmisie. Scopul acestei lucrări a constat în determinarea efectului analgezic a două substanțe, și anume celecoxib și cafeină, precum și modul în care acestea își influențează reciproc efectele, atât după administrare în doză unică cât si după administrare repetată la șoareci albinoși masculi rasa Swiss. În acest scop au fost utilizate două teste pentru a determina efectul analgezic, testul torsiunilor și testul plăcii încălzite. Rezultatele obtinute au arătat faptul că, după administrarea în doza unică, atât cafeina cât și celecoxibul au determinat o creștere a efectului analgezic, comparativ cu lotul martor, în cadrul ambelor teste utilizate. Totuși, nu s-a observat o relație doză-efect pentru cafeină. Mai mult decât atât, s-a observat faptul că efectul celecoxibului a fost diminuat de către cafeină, fără semnificație statistică insă. După administrare în doza repetată, doar dozele mari de cafeină (10 mg/kg și 25 mg/kg) au prezentat efecte analgezice, în timp ce celecoxibul a prezentat efecte analgezice doar în cazul testului plăcii încălzite. Cafeina nu a influențat efectul analgezic al celecoxibului după administrare de doze multiple. Rezultatele determinărilor de IL-6 și CPR sugerează că efectele analgezice ale celecoxibului ar putea fi mediate de citokinele proinflamatorii. Cafeina nu a afectat nivelul IL-6 și CRP.

Keywords: caffeine, celecoxib, analgesia

Introduction

The inflammation and pain processes are extremely complex. While pain is mostly considered a physical experience, it also has an emotional and sensorial component. It involves a physiological pathway based on a level of reception, transmission pathways and a cortical level. There are numerous neurotransmitters and mediators that influence pain, such as acetylcholine, dopamine and serotonin [1]. Apart from neurotransmitters, there are other factors that trigger inflammation and pain. Inflammation can lead to direct or secondary injury systemically or of the central nervous system that can finally lead to neurodegenerative disorders and depression or anxiety. Among these factors we can mention exposure to neurotoxic or immuno-toxic substances like aluminium [2] or smoking tobacco [3].

The purpose of this paper was to determine the analgesic effect of two different substances, celecoxib and caffeine, and the way they modulate each other's effects.

A number of substances are able to influence the process of nociception as secondary effects. As an

example, *Plantago spp.* has numerous biologically active components, some of which are capable of modulating pain. Radu *et al*. determined that polysaccharide extracts of *Plantago spp.* decreased pain [4]. The same author concluded in 2010 in two separate studies that flavonoid and iridoid extracts of *Plantago spp.* have similar effects [5, 6].

Moreover, by administering different medicinal products, we can modulate the physiological processes that lead to feeling pain. These substances are largely named analgesics. They can be either opioids (for example morphine) or non-opioids (for example, nonsteroidal anti-inflammatory drugs or NSAIDs). There are two classes of NSAIDs depending on their action mechanism. Non-selective inhibitors of the enzyme cyclooxygenase (COX) which modulate the activity of both COX-1 and COX-2 isoenzymes, and selective inhibitors of COX-2 [6]. One of the most frequently used COX-2 inhibitor is celecoxib. It has been shown in literature over the years that this selective NSAID is as effective as the non-selective ones. However, celecoxib does have a benefit, as it determines less gastrointestinal adverse reactions than the other NSAIDs [8]. Even so, in 2000, Layton *et al*. reported that the most common adverse effects of selective NSAIDs and in particular of celecoxib are still the gastrointestinal ones (dyspepsia, abdominal pain, diarrhoea and nausea) [9]. Caffeine is a widely distributed substance that the majority of people consume. For many years, caffeine has been used as an enhancer of action of other analgesic drugs. It has three mechanisms of action. It mainly acts as an antagonist of the adenosinic receptors [10, 11]. Second of all, it also inhibits all the phosphodiesterases [12]. Last, but not least, caffeine intensifies the histone de-acetylation (which determines the anti-inflammatory effects of caffeine)..

Materials and Methods

The analgesic effects of either caffeine or celecoxib as well as their combination were studied on Swiss albino strain mice, by using the writhing test and the hot plate test, as described below.

Animals used

For each experiment a group of 15 Swiss albino strain male mice was used. All of them were bred in the biological hatchery of the "Carol Davila" University of Medicine and Pharmacy, Bucharest, and weighted between 25 and 35 grams. The mice were brought in the laboratory with more than 24 hours before the tests and were accommodated in acrylic plastic cages with the floor covered by wood shavings, at a temperature between 21 and 24°C and at a relative humidity between 45 - 60%. The number of mice *per* cage was 12 with *ad libitum* access to granulated food and water.

All animal procedures were carried out with the approval of the local ethical committee for animal research of Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, in accordance with the European Communities Council Directive 86/609 on the protection of animals used for scientific purposes.

Substances tested

The substances used were: caffeine (Sigma Aldrich), celecoxib (Sigma Aldrich), sodium chloride 0.9% and acetic acid 0.75%. For the analgesic effect of caffeine doses of 1 mg/kg, 5 mg/kg, 10 mg/kg and 25 mg/kg of caffeine in dilution with sodium chloride 0.9% were used. For the analgesic effect of celecoxib doses of 1 mg/kg and 5 mg/kg in dilution with sodium chloride 0.9% were used. The concentrations were made so that a volume of 0.1 mL/10 g of mouse were administered. For the analgesic effect of the combination of caffeine and celecoxib we used caffeine at a dose of 1 mg/kg (diluted with sodium chloride 0.9%) and celecoxib (diluted with sodium chloride 0.9%) at a dose of 1 and 5 mg/kg. For the control group in the writhing test and in the hot plate test, we used sodium chloride 0.9% at a volume of dose of 0.1 mL/10 g of mouse. For the writhing test, acetic acid 0.75% was used to produce writhes and it was administered in a volume of 0.15 mL/10 g.

The substances were administrated intraperitoneally for celecoxib and acetic acid and subcutaneously for caffeine and sodium chloride 0.9%. The analgesic effects were evaluated after single dose and multiple dose administration (14 days), following the same protocol: caffeine was administered 30 minutes before the tests. Celecoxib was administered 1 hour before the tests. Acetic acid was administered 5 minutes before the writhing test.

Tests used

For the analgesic effects of caffeine and its combination with celecoxib two tests were used: the writhing test and the hot plate test.

In the testing day, for the writhing test, each mouse was administered acetic acid 0.75% v/v intraperitoneally in a volume of 0.15 mL/10 g for each mouse. Five minutes after the administration of the acetic acid and the substance used in the test (caffeine or a combination of caffeine and celecoxib) the numbers of the writhes were counted. A complete writhe is considered when the animal had a stretch and splayed out the front limbs from the hind limbs. The operation of counting the writhes was done by the same person and the time of the test was 5 minutes.

For the hot plate test, we used a metal plate, heated at 55°C and a glass cylinder of 18 cm height and 19 cm diameter. Two parameters were recorded: the first parameter was the time until the mice lick their front paws and the second was the time until they

tried to escape by jumping. The cut-off limit for the hot plate test was set at 30 seconds.

High-sensitivity CRP was determined by using a high-sensitivity immunoturbidimetric assay. Interleukin-6 (IL-6) was determined by ultra-sensitive ELISA. Plasma samples were drawn into an EDTA tube and stored at -80°C until batch analysis.

Protocol

The analgesic effects were evaluated after single dose and multiple dose administration, following the same testing protocol.

For acute effects, the evaluation was done following single dose administration. For chronic effects, the evaluation was done following 14 days administration of caffeine and celecoxib.

For testing the analgesic effect of caffeine, both during the writhing test as well as during the hot plate test, in the testing day, caffeine was administered 30 minutes before the test. For testing the analgesic effect of a combination of caffeine and celecoxib, for both of the tests used, the caffeine was administered 30 minutes before the test, while the celecoxib was administered 1 hour before the test.

CRP and IL-6 determinations were done in the 14th days of multiple dose administration study.

Statistical analysis

The results were collected and analysed using Microsoft Office-Excel. The percentage change over control was calculated using the following formula: (Control – Treated)/Control × 100 = Percentage change. A negative value for percentage change in case of hot plate test indicated an analgesic effect, while in the case of writhing test a positive value indicated an analgesic effect. For each group the average and the standard deviation were calculated, and t-Student test was applied. As for the results to be statistically significant p value was considered to be under 0.05.

Results and Discussion

Single dose administration

In case of caffeine, the results of the writhing test showed that the analgesic effect of 1 mg/kg caffeine was with 22% higher than in control group, the analgesic effect of 5 mg/kg caffeine was with 1% higher and the analgesic effect of 10 mg/kg caffeine was with 2% higher. The results are illustrated in Figure 1.

During the hot plate test, 1 mg/kg caffeine determined 12% increase in analgesia and 10 mg/kg doses of caffeine determined 2% increase in analgesia. The administration of 25 mg/kg caffeine determined a hyperalgic effect of 1%. The results are illustrated in Figure 2.

In case of celecoxib, the results of the writhing test showed that the 1 mg/kg celecoxib determined a 47% increase in the analgesic effect; 5 mg/kg celecoxib determined a 45% increase in the analgesic effect. Furthermore, the results of the writhing test showed the association of caffeine 1mg/kg and celecoxib 1 mg/kg determined a 44% increase in the analgesic effect, while the combination of caffeine 1 mg/kg and celecoxib 5 mg/kg had an increased analgesic effect of 45%. All the results are illustrated in Figure 3.

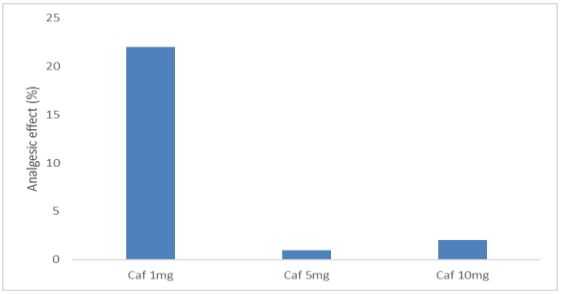

Figure 1.
Single dose study – analgesic effect at 30 minutes after the administration of caffeine in the writhing test

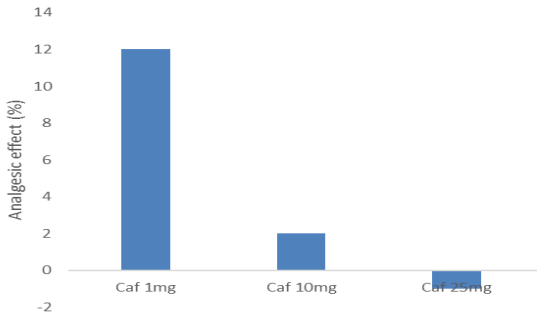

Figure 2.
Single dose study – analgesic effect at 30 minutes after the administration of caffeine in the hot plate test – "lick" parameter

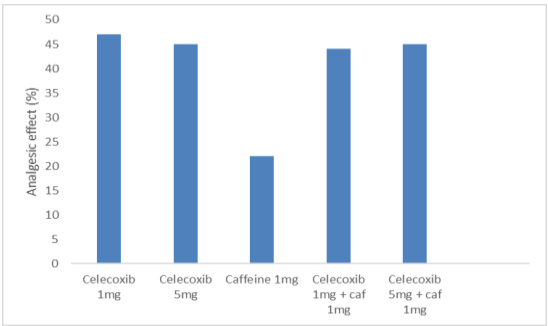

Figure 3.
Single dose study – analgesic effect of celecoxib 1 mg/kg, celecoxib 5 mg/kg, caffeine 1 mg/kg, and combinations of caffeine and celecoxib in writhing test

The hot plate test results showed that 1 mg/kg celecoxib determined an 18% increase in the analgesic effect and 5 mg/kg celecoxib determined a 19% increase in the analgesic effect. Furthermore, the hot plate test results showed that the combination of caffeine 1 mg/kg and celecoxib 1 mg/kg determined a 14% increase in the analgesic effect, and the

combination of caffeine 1 mg/kg and celecoxib 5 mg/kg led to 19% increase in the analgesic effect. All the results are illustrated in Figure 4.

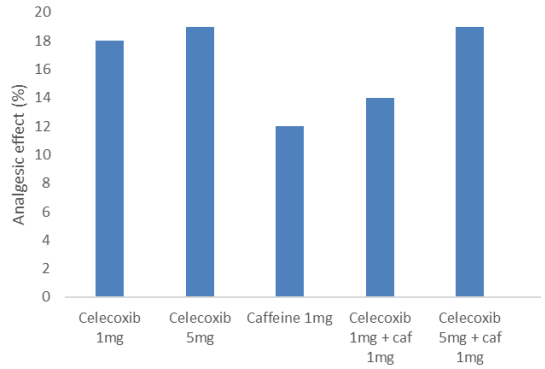

Figure 4.
Single dose study - analgesic effect of celecoxib 1 mg/kg, celecoxib 5 mg/kg, caffeine 1 mg/kg and combinations of caffeine and celecoxib in the hot plate test

Multiple dose administration

Following 14 days administration, in case of caffeine, the results of the writhing test showed that the analgesic effect of 1 mg/kg caffeine was with 2% higher than in control group, the analgesic effect of 5 mg/kg caffeine was with 1% higher and the analgesic effect of 10 mg/kg caffeine was with 19% higher than in control group. The results are illustrated in Figure 5.

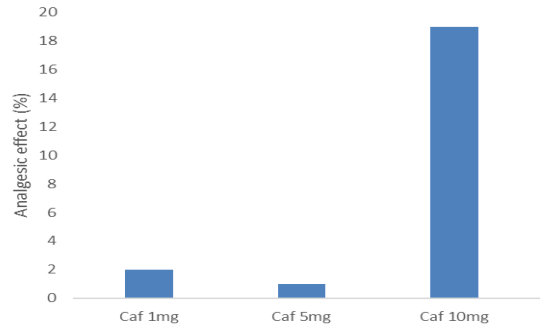

Figure 5.
Multiple dose study – analgesic effect at 30 minutes after the administration of caffeine in the writhing test

During the hot plate test, 1 mg/kg, 10 mg/kg doses of caffeine had no analgesic effect. The analgesic effect of 25 mg/kg caffeine was with 17% higher than in control group.

The results of the writhing test showed that celecoxib 1 mg/kg and 5 mg/kg had no analgesic effect after multiple dose administration. Furthermore, the results of the writhing test showed that the association of caffeine and celecoxib (10 mg/kg caffeine + 1 mg/kg celecoxib and 1 mg/kg caffeine + 5 mg/kg celecoxib) had no analgesic effects after multiple dose administration. The results are presented in Figure 6.

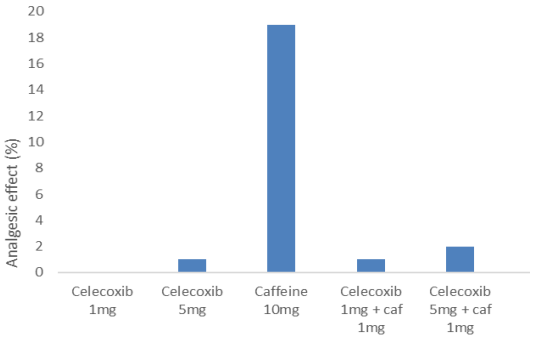

Figure 6.
Multiple dose study - analgesic effect of celecoxib 1 mg/bw, celecoxib 5 mg/bw, caffeine 1 mg/bw, combinations of caffeine and celecoxib in writhing test

The hot plate test results showed that, following multiple dose administration, 1 mg/kg celecoxib determined a 21% increase in the analgesic effect and 5 mg/kg celecoxib determined a 19% increase in the analgesic effect as compared to control group. Furthermore, the hot plate test results showed that the combination of caffeine 25 mg/kg and celecoxib 1 mg/kg determined a 20% increase in the analgesic effect, and the combination of caffeine 25 mg/kg and celecoxib 5 mg/kg led to 20% increase in the analgesic effect. All the results are illustrated in Figure 7.

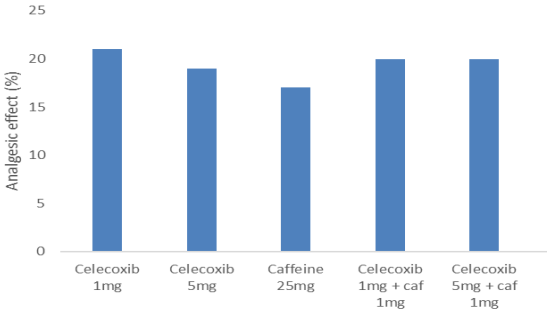

Figure 7.
Multiple dose study - analgesic effect of celecoxib 1 mg/bw, celecoxib 5 mg/bw, caffeine 1 mg/bw and combinations of caffeine and celecoxib in the hot plate test

Celecoxib 5 mg/kg significantly lowered interleukin-6 (IL-6) levels than caffeine group and control group (16.1 pg/mL *versus* 18 pg/mL and 20 pg/mL, p = 0.04). Celecoxib 5 mg/kg had significantly lowered C reactive protein (CRP) levels than caffeine and control group (320 mg/L *versus* 400 mg/L and 420 mg/L, p = 0.04).

Following single dose administration, the results in terms of analgesic effect of caffeine in the writhing test were better in the group which received caffeine at a dose of 1 mg/kg than in the others, the analgesic effect being with 22% higher than in control group. A dose of caffeine of 10 mg/kg caffeine determined

only 2% analgesic effect while 5 mg/kg caffeine resulted in only to 1% more analgesic effect than the control group.

As shown in Figure 2, in the hot plate test a dose of caffeine of 1 mg/kg had an analgesic effect with 12% more than the control group. For a dose of caffeine of 10 mg/kg we obtained an analgesic effect of 2% and at a dose of 25 mg/kg of caffeine we obtained a hyperalgic effect of 1% compared with the control group.

The results for 1 mg/kg caffeine are in line with the results of the study of Ghelardini C *et al*., that describes the antinociceptive effect of caffeine in hot-plate, abdominal constriction tests in mice and the tail flick and paw-pressure tests in rats [13].

The results for 5 mg/kg and 10 mg/kg doses are consistent with the results of Fialip J *et al*. that showed caffeine (5 to 200 mg/kg) did not produced a significant antinociceptive effect [14].

As shown in Figure 3, the highest analgesic effect compared to the test group was the one of celecoxib at a dose of 1 mg/kg (47%). However, both celecoxib doses had an analgesic effect. This result is consistent with previous published studies where celecoxib demonstrated analgesic effects [15].

Celecoxib at a dose of 5 mg/kg and the association of celecoxib 5 mg/kg and caffeine 1 mg/kg had an analgesic effect of 45% compared to the test group. The combination of caffeine at a dose of 1 mg/kg and celecoxib at a dose of 1 mg/kg had similar results to the others, of 44%.

As seen in Figure 4, during the hot plate test, celecoxib administered in a 1 mg/kg dose determined a 18% increase in the antalgic effect compared to the control group, while administering a dose of 5 mg/kg, it determined a 19% increase. When we administered 1 mg/kg of caffeine, it determined a 10% increase in the analgesic effect compared to the control. Using the combination of caffeine 1 mg/kg and celecoxib 1 mg/kg, compared to the control it determined only a 14% increase in the analgesic effect, while using caffeine 1 mg/kg and celecoxib 5 mg/kg determined a 19% increase.

During the writhing test, although the caffeine proved to have analgesic effect, a dose-effect relationship could not be established. Meanwhile celecoxib showed an analgesic effect during the writhing test at a dose of 1 mg/kg, as well as at a dose of 5 mg/kg. Speaking about the combinations of caffeine and celecoxib, during the writhing test, adding caffeine to celecoxib decreased the analgesic effect given by celecoxib alone with 1%. This decrease was not statistically significant.

During the hot plate test, the only dose of caffeine which proved to have an analgesic effect is 1 mg/kg. Comparing with the test group, the celecoxib has prolonged the delay of "lick" parameter with 44% in the hot plate test.

Following multiple dose administration, it was noticed that only the high doses of caffeine had analgesic effects. Caffeine in the dose of 10 mg/kg determined 19% analgesic effect in the writhing test, and 25 mg/kg dose of caffeine led to an increase in analgesic effect of 17% compared to the control group.

Furthermore, the results of the writhing test showed that the doses of celecoxib tested (1 mg/kg and 5 mg/kg) had no analgesic effect after multiple dose administration. The association of caffeine and celecoxib (10 mg/kg caffeine + 1 mg/kg celecoxib and 1 mg/kg caffeine + 5 mg/kg celecoxib) had no analgesic effects after multiple dose administration in the writhing test.

As for the hot plate test, the results showed that 1 mg/kg and 5 mg/kg celecoxib doses have analgesic effects following multiple dose administration. Furthermore, the hot plate test results showed that caffeine 25 mg/kg had no influence on analgesic effects of celecoxib 1 mg/kg and celecoxib 5 mg/kg.

It is hypothesized that the pro-inflammatory state is multifactorial which include dysfunction of the hypo-thalamic-pituitary-axis, vegetative nervous system, and also metabolic disorders [3].

IL-6 determinations showed that analgesic effects of celecoxib might be mediated by pro-inflammatory cytokines. Caffeine did not affect the IL-6 levels.

At the same time, celecoxib influenced the CRP levels which further support the idea that its effects might be mediated by pro-inflammatory proteins.

Further studies are needed to investigate the acute and chronic effects of various doses of caffeine and celecoxib.

Fixed drug combinations of caffein with ibuprofen or aspirin are currently available on the market; in these combinations, caffein acts as an adjuvant to the analgesic effect of ibuprofen and aspirin. However, no other NSAI drugs are used in combination with caffeine. One clinical study showed that caffeine may enhance celecoxib analgesic effect as the combination of the two drugs had higher efficacy than other medications for pain control following dental surgery [16]. Therefore, the possible association of caffein and celecoxib might be of therapeutic interest.

Starting from this, we aimed to see if caffein can influence in any way the effects of celecoxib. Since there is no literature data on this, as a first step, the influence of caffein on the analgesic effect of celecoxib was studied following single dose and multiple dose administration. After single dose administration, caffeine slightly decreased the effects of celecoxib. Caffeine had no influence on analgesic effects of celecoxib following multiple dose administration.

These results are considered important since caffeine is the best-known component of coffee, one of the most consumed beverages in the whole word [17]. Caffeine is also contained by many different beverages (tea, energy drinks or soft drinks), foods (chocolate,

cocoa), food supplements and medicines. It is very well known that concomitant intake of food [18] or specific beverages (such as grapefruit juice, coffee) [19, 20] can have a significant impact on pharmacodynamic or pharmacokinetic properties of various medicinal products and thus the potential for interaction needs to be studied. The effects of coffee or caffeine intake were investigated by various researchers [21-24]. Among the effects studied, there were investigations on the effect of caffein on inflammatory status [21] and analgesia [22, 23]. Caffeine was found to be a potent adenosine receptor antagonist [24] that provides effective analgesia when used as an adjunctive treatment in case of secondary headache syndromes [25]. The results of the study of AO More *et al*. showed, in a mouse model of postoperative pain, that moderate doses of caffeine can inhibit acupuncture-induced analgesia [23].

The efficacy of celecoxib in various painful conditions was extensively studies [26, 27].

As already mentioned, inflammation and pain processes are extremely complex and the impact of inflammation on the body and the anti-inflammatory properties of various substances are still under investigation [28, 29].

Future studies are needed to investigate the influence of caffein on other effects of celecoxib such central nervous effects (sedation, anxiety) or peripheral effects (by influencing the anti-inflammatory effect).

Furthermore, it would be interesting to see if the anti-inflammatory effect is limited to celecoxib administration alone or if the combination of celecoxib with caffeine has an anti-inflammatory effect too.

Conclusions

After single dose administration, both caffeine and celecoxib determined an increase in the analgesic effect compared to the control group under the testing conditions. No dose-effect relationship could be observed for caffeine. In the combination study, caffeine slightly decreased the effects of celecoxib. Following multiple dose administration, only the higher doses (10 mg/kg and 25 mg/kg) of caffeine tested had analgesic effects while celecoxib showed analgesic effects only in the hot plate test. Caffeine had no influence on analgesic effects of celecoxib following multiple dose administration. IL-6 and CPR determinations showed that analgesic effects of celecoxib might be mediated by pro-inflammatory cytokines. Caffeine did not affect the IL-6 and CRP levels.

Conflict of interest

The authors declare no conflict of interest.

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