Effect of caffeine as an ergogenic aid to prevent muscle fatigue

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Summary

Caffeine, one of the most widely used psychoactive substances worldwide, has been linked to the delay in the appearance of neuromuscular fatigue and the reduction in the effort perception during physical activity. As a result of a progressive increase in the consumption of food supplements to improve the sports performance, we decided to review the ergogenic effect of caffeine on muscle fatigue at central and peripheral levels. A bibliographic search was conducted between january 2008 and may 2018, identifying studies published in electronic databases (PubMed, SciELO, Dialnet) and documents from national and international organizations (EFSA, AECOSAN, SEMED/FEMEDE, AIS, EUFIC, WADA) about caffeine and its effect on muscle fatigue. The mechanism of action of caffeine in strength and endurance sports is analyzed, as well as the optimal dosage, routes of administration and posology guidelines. We also review other aspects such as toxicity, doping and the current legislation that regulates the labeling of food supplements containing caffeine.

Key words:
Caffeine. Ergogenic effect. Muscle fatigue. Muscle strength. Performance-enhancing effect.

Efecto de la cafeína como ayuda ergogénica para evitar y prevenir la fatiga muscular

Resumen

La cafeína, una de las sustancias psicoactivas de mayor consumo a nivel mundial, se ha relacionado con el retraso en la aparición de la fatiga muscular y la disminución en la percepción del esfuerzo durante la actividad física. Debido al aumento progresivo en el consumo de complementos alimenticios para mejorar el rendimiento deportivo, decidimos realizar esta revisión con el objetivo de sintetizar la evidencia disponible sobre el efecto de la cafeína como ayuda ergogénica en la fatiga central y periférica, examinando los mecanismos de acción y especificando las dosis y la forma de administración idóneas para obtener el efecto ergogénico deseado. Para ello se realizó una búsqueda bibliográfica entre enero de 2008 y mayo de 2018, identificando estudios publicados en bases de datos electrónicas (PubMed, SciELO, Dialnet) y documentos de organismos nacionales e internacionales (EFSA, AECOSAN, SEMED/FEMEDE, AIS, EUFIC, WADA) sobre la cafeína y su efecto sobre la fatiga muscular. Se analiza el mecanismo de acción de la cafeína en deportes de fuerza y resistencia, así como las dosis, vías y pautas de administración óptimas. Se revisan además otros aspectos como la toxicidad, el dopaje y la normativa actual que regula el etiquetado de los complementos alimenticios que contienen cafeína.

Palabras clave:
Cafeína. Efecto ergogénico. Fatiga muscular. Fuerza muscular. Mejora del rendimiento.

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Introduction

Physical activity is an essential strategy to maintain a healthy lifestyle, and it is also recommended for the prevention and treatment of numerous pathologies.

The importance of nutrition on physical performance has long been recognised, not only at competition level but also among those who engage in leisure sports and weight training activities. In order to achieve sporting success, training must be accompanied by the best and most suitable diet for each sports activity. However, given that muscle fatigue is one of the most important causes of the appearance of sports injuries, studies have found a progressive increase in the consumption of ergogenic aids by athletes at different levels and disciplines[1,2] for the purpose of minimising central and peripheral fatigue alike[3,4].

The "Australian Institute of Sport", based on scientific evidence and on criteria considering the safety, legality and effectiveness of sports performance, classifies caffeine (together with ß-alanine, sodium bicarbonate, creatine, beetroot juice and glycerol) within the group: *Ergogenic Aid Supplements / Ingredients with evidence level A*[5].

In chemical terms, caffeine (1,3,7-trimethylxanthine) is an alkaloid of the group of xanthenes, which are substances derived from the purines that are naturally found in tea plants, coffee, mate, cacao, chocolate, guarana and cola nut. Together with the theobromine from the cacao plant and theophylline from black and green tea, caffeine is one of the most consumed psychoactive substances in the world[6]. Products are also available (energy drinks, gels, chewing gums, some medicines) that offer additional concentrations of caffeine to increase physical or psychological performance, also producing effects on other physiological functions such as emotional state, mood, sleep or pain[4].

The capacity of caffeine to improve muscle work has been widely studied over the years, with investigations even dating back to the early 20th century. However the use of caffeine by athletes as an ergogenic aid did not become apparent until the 1970s -1980s[4]. Given that this is an almost ubiquitous substance in the normal human diet, the study of its effect on the human body is of great interest. In this regard, one of the aspects that has generated the most curiosity is its influence on the appearance of fatigue when engaged in sports activities.

This review aims to summarise the evidence available on the effect of caffeine as an ergogenic aid for central and peripheral fatigue, by examining the action mechanisms and specifying the ideal doses and route of administration in order to obtain the desired ergogenic effect.

Methodology

A literature search was conducted on the ergogenic effect of caffeine on muscle fatigue, by consulting electronic databases (PubMed, SciELO, Dialnet), basically selecting systematic reviews, meta-analyses and specific articles by experts, published between January 2008 and May 2018 and following the "snowball" strategy in order to obtain as much information as possible. A review was also made of documents from national and international organisations: EFSA, AECOSAN, SEMED/FEMEDE, AIS, EUFIC, WADA (Table 1).

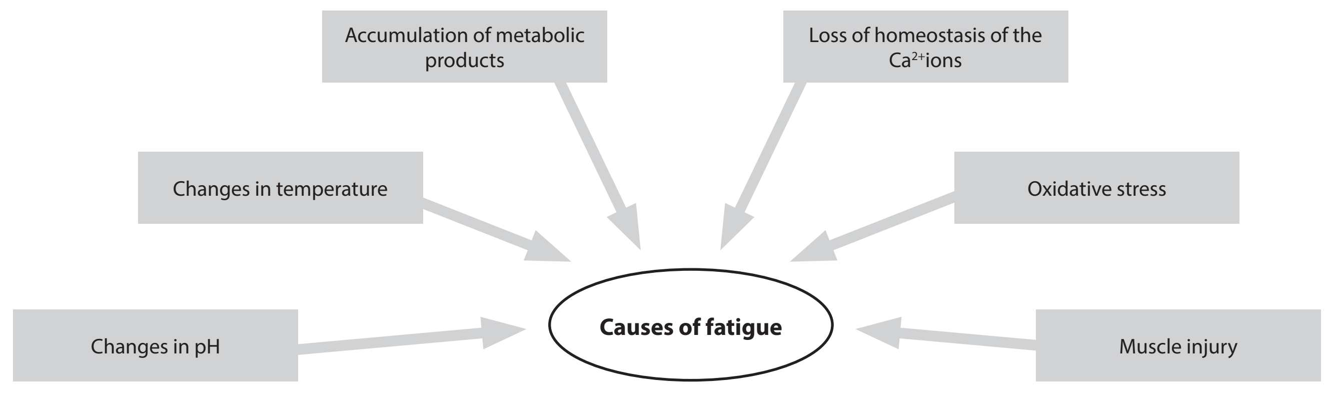
Considerations on muscle fatigue

Muscle fatigue, a phenomenon that generally limits sporting activity and the performance of prolonged, strenuous exercise, is defined as a reduction in the maximal strength or power in response to contractile

Table 1. Inclusion / exclusion criteria, key words, databases consulted.

Inclusion criteria	**Exclusion criteria**
- Relevant information on the ergogenic effect of caffeine and muscle fatigue. - Consensus documents based on scientific evidence - Languages: Spanish, English and French. - Articles with access to the full text - Publication period: January 2008 - May 2018 - Study design: original articles, literature reviews, systematic reviews and meta-analyses.	- Articles not related to the purpose of the study. - Studies not conducted on humans - Articles with no scientific relevance
Keywords	
- caffeine - ergogenic effect - muscle fatigue - muscle strength - performance-enhancing effect	
Electronic databases	**National and international scientific organisations and societies:**
- PubMed - Scielo - Dialnet	- EFSA: European Food Safety Authority - AECOSAN: Spanish Agency for Nutrition and Food Safety - SEMED/FEMEDE: Spanish Society of Sports Medicine - AIS: Australian Institute of Sport - EUFIC: European Food Information Council - WADA: World Anti-Doping Agency

Figure 1. Suggested causes of fatigue



Source: Gómez-Campos, *et al.* 2010[10].

activity. Despite the fact that the causes of exercise-related fatigue are complex, it is generally accepted that fatigue depends on a person's level of training and nutritional condition, on the type of muscle fibres, as well as the intensity, duration and type of exercise performed. It should be underscored that muscle fatigue is different from muscle injury, since the former is reversible after a few hours' rest, while complete recovery following an injury may take days or weeks[7].

Alterations at different motor levels may contribute to the appearance of muscle fatigue, allowing us to classify fatigue into *central* when it results from alterations in the central nervous system (CNS), at the brain stem or spinal cord, decreasing the output of nervous impulses to the muscles, and *peripheral*, when it is caused by the dysfunction of the peripheral nervous system (PNS) or by a musculoskeletal pathology, due to changes at the neuromuscular junction or else at the nerve endings[7-9].

The hypothesis on the origin of *central fatigue* is based on the exercise-induced changes in the concentration of neurotransmitters within the CNS (serotonin, dopamine, noradrenaline) which produce stimuli at the spinal cord motor neuron level, finally activating the motor units to generate power. The slowing down or termination of this activation, contributes to the loss of strength inherent in fatigue[7,9]. Other factors that may influence the genesis of central fatigue are the brain levels of glycogen and ammonium. Hyperthermia, which is frequently associated with exercise, may also reduce the activity of the CNS[9].

On the other hand, *peripheral fatigue* is considered to result from homoeostasis alterations in the skeletal muscle, due to a limitation of one or more processes in the motor unit[10].

The production of skeletal muscle strength depends on contractile mechanisms and some of the changes at a neural, mechanical or energy level that could cause fatigue are as follows[7]:

The accumulation of intracellular metabolites (hydrogen ions, lactate, inorganic phosphate, reactive oxygen species) that modify the muscle contractile activity through interference in the release of calcium from the sarcoplasmic reticulum, reduction in muscle fiber calcium sensitivity and direct motor neuron inhibition. However, the appearance of muscle fatigue attributed to a decrease in pH due to the accumulation of hydrogen ions is currently being questioned, given that, at physiological temperatures, it does not appear to be a limiting mechanism[7,11].

Reduction in the blood supply and, therefore, in the oxygen supply to the active muscle groups during voluntary muscle contraction due to an increase in the mean blood pressure[7].

Imbalance between the consumption and production of adenosine triphosphate (ATP) at a muscle level due to a decrease in glycogen reserves during exercise[9]. The mechanism by which glycogen depletion in the muscle leads to muscle fatigue is still under study[7].

Effect of caffeine

Caffeine exerts its ergogenic effect through a number of mechanisms, with particular mention of the competitive inhibition of adenosine receptors in the CNS at the presynaptic terminals and which govern the release of other neurotransmitters such as acetylcholine, glutamate and dopamine, thereby enhancing the attention, concentration and alertness in mental and physical exercises, and reducing the perception of fatigue during exercise[4,12,13].

Changes in perceived pain with the intake of caffeine have also been observed. This is due to an increase in the secretion of ß-endorphins[14], which favours increased endurance.

This central model is the one that would best explain the ergogenic effect of caffeine on high-intensity exercises, in contrast to the widely accepted theory of the stimulation of fatty acids and subsequent saving in muscle glycogen[15,16].

With reference to the factors related to peripheral fatigue, there is evidence of possible mechanisms that would explain the ergogenic effect of caffeine on muscle strength sports, with particular mention of the loss of potassium during contractions and the potentiation of sarcoplasmic reticulum calcium release, all of this generating an overall improvement of the neuromuscular function[9,16].

Results and discussion

Caffeine in strength sports

With regard to the effect of caffeine on muscle power and strength, the results are misleading. Pioneering authors such as Astorino *et al*.[17] or Williams *et al*.[18], both in 2008, and other subsequent authors such as Ali *et al*.[19] in 2016 did not demonstrate significant ergogenic effects on strength sports, while Goldstein *et al*.[20] in 2010 and Grgic and Mikulic[21] in 2017 supported the effectiveness of caffeine at a dose level of 6 mg/kg of body mass to increase the strength of muscle groups in the upper and lower body, respectively.

Individual studies report inconsistent findings for different reasons: total number of participants and their specific characteristics (training level, gender, level of caffeine habituation, etc.), type of exercise studied, intake method, etc. It is therefore not possible to draw sound conclusions on the ergogenic potential of caffeine for the findings of maximal muscle strength.

For this reason, in 2018, Grgic *et al*.[22] published a systematic review and meta-analysis of the findings of individual studies on the acute effects of caffeine intake on maximal muscle strength, concluding that a dose of 3-6 mg/kg of body mass could induce significant improvements in the production of muscle strength and power expressed as vertical jump height, which would be applicable to a wide variety of sports in which jumping is a predominant activity that affects the sports performance. Despite reporting small and medium ergogenic effects, it should be pointed out that, in some sports, small improvements in performance represent significant differences in the results.

Caffeine in endurance sports

There is extensive scientific literature on the utility of caffeine to improve performance in aerobic exercise, observed through diverse parameters such as an increase in work time and time-to-exhaustion, improved peak oxygen consumption in submaximal exercise and improved perceived effort, among others[23,24].

Already in 2009, a systematic review by Ganio *et al*.[25] on 33 clinical trials evidenced a mean improvement in performance of 3.2-4.3% with caffeine ingestion in quantities of 3-6 mg/kg of body mass before and/or during time-trial endurance activities of varied duration (5-150 min) and in different modes of exercise (cycling, running, rowing, cross-country skiing and swimming). These authors concluded, moreover, that abstaining from caffeine intake for at least 7 days before competition improved its ergogenic effect. However, although Irwin *et al.*[26] show an ergogenic improvement in high-intensity endurance exercises with a dose of 3mg/kg regardless of the prior period of abstention, the review in 2016 by Naderi *et al*.[27] supports the conclusions obtained by Ganio *et al*.[25], attributing the said effect to the enzymatic regulation secondary to chronic caffeine intake.

There are fewer studies on the effects of caffeine on *anaerobic exertion*, such as intense, short duration activities, supramaximal activities and repeat sprints[28]. Systematic reviews have been made, such as that by Astorino and Roberson[29] in 2010 on short-term high-intensity exercise performance (≤5 min), where approximately 65% of the studies showed an average benefit of 6.5% in performance, with variations according to the training level and caffeine intake of participants, total ingested dose and type of tests, in addition to the genetic differences among athletes.

A double blind test with placebo in 2013[30] showed how a caffeine dose of 5 mg/kg of body mass, not only improved performance but also the perception of fatigue and muscle pain in endurance exercises undertaken by trained athletes. In 2017, Wellington *et al*.[31] showed a 1% improvement in a repeated sprint test on rugby players with a does of 300 mg of caffeine 60 minutes before exercise while, in a meta-analysis, Christensen *et al.*[12] demonstrated a 1% improvement in the average velocity, also in resistance tests. Likewise, the results of the meta-analysis by Grgic *et al*.[22] in 2018 are in addition to the investigations suggesting improved anaerobic performance of caffeine, demonstrating a significant difference compared to placebo in the production of mean and maximal power on a cycle ergometer.

Pharmacokinetics and timing

Due to its pharmacokinetic characteristics, orally administered caffeine is quickly absorbed from the gastrointestinal system into the blood flow, observing high plasma concentrations 15 minutes after intake, reaching a maximum after 30-60 minutes, with a mean life of 3 to 10 hours. Absorption through the oral mucosa reaches maximum levels far more quickly. Caffeine offers complete bioavailability and high solubility, so that it is rapidly distributed throughout the body, easily passing through cell membranes as well as the placental and blood-brain barriers, reaching high concentrations throughout the body, even in the brain[32].

The metabolism primarily takes place at a hepatic level (in a much lower proportion at brain and kidney level) through the P450 cytochrome enzymes, giving rise to metabolites that are excreted through the kidney and that could mediate some of caffeine's performance enhancing effects[13].

The different genetic polymorphisms of cytochrome P450 are among the intrinsic factors that could explain the modifications in the caffeine pharmacokinetics. Moreover, the chronic intake of caffeine accelerates its metabolic clearance, giving rise to habituation in most consumers. Therefore, abstaining from food and drink containing caffeine in the days prior to a competition could promote an ergogenic effect. Studies have also demonstrated a greater neuromuscular response to morning consumption of caffeine compared to evening consumption, due to greater enzyme activity during the first hours of the day[27]. Notable exogenous factors that affect caffeine clearance include co-medication or smoking, which could even duplicate the caffeine elimination rate[4,23].

Despite the fact that high concentrations of caffeine can be found in a number of foods, this intake may not be sufficient to achieve the desired ergogenic effect due to the variable amounts of caffeine that they contain (depending on processing or preparation) or to the presence of antagonistic substances or absorption modifiers. Therefore the consumption of specific preparations is supported[23,33] (Table 2).

In athletic environments, caffeine is generally administered in an anhydrous form (dried), either in tablets or powder solutions. Other forms of presentation may have a different degree of absorption, as in the case of administration through the oral or nasal mucosa which constitutes a direct route to the CNS, making it possible to detect high plasma levels in just 5-15 minutes[34].

In different studies reporting the ergogenic benefits of caffeine, it was observed that the normal dose in adults (see Figure 2 for children-teenagers) ranges between 3-6 mg/kg of body mass, administered 30-60 minutes before exercise, obtaining improvements in time-to-exhaustion, work capacity and perceived effort in resistance sports[13,16].

Investigating the use of caffeine delivered in low doses (<3 mg/kg of body mass, ~200 mg) before or during exercise, improved performance is also observed, particularly at a cognitive level, with the subsequent improvement in wakefulness, alertness and mood during and after strenuous exercise due to the effect of caffeine on the CNS[27,35].

On the other hand, high doses of caffeine (≥9 mg/kg of body mass) do not appear to provide greater benefits, and may instead increase the risk of adverse effects (sickness, diarrhoea, dehydration, anxiety, insomnia, anxiety)[16,27] which will condition sports performance[28].

Thus, taking into account the wide range of doses with an ergogenic effect due to the considerable inter-individual variation[13], it is advisable to try out different strategies during training sessions in order to obtain individualised protocols that provide the maximum benefits with the least possible risk[28].

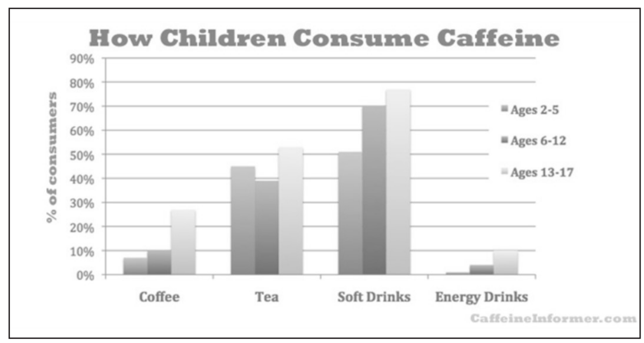
Table 2. Caffeine in foods and drinks.

Food or drink	Caffeine content (mg)
Espresso coffee (60 ml)	80
Filtered coffee (250 ml)	95-165
Decaffeinated coffee	1-2
"Starbucks" coffee (short/Venti)	160 / 400
Black tea (220 ml)	50
Green tea (220 ml)	25-30
Cola drink (330 ml)	40
Energising drink (250 ml)	80
Dark chocolate (50 g)	25
Milk chocolate (50 g)	10
Caffeinated energy bar (65 g)	50
Sports gel with caffeine (40-60 ml)	25-150
"Shot" energy gel (33 ml)	200-300
Caffeine in capsules (1 g)	100
Guarana drink (330 ml)	30

Source: Prepared by the author, based on:
- EUFIC (2016): Caffeine (Q&A): How much caffeine is found in different foods and drinks? (https://www.eufic.org/en/whats-in-food/article/caffeine-qas)
- Mayo Clinic (2018): Contenido de cafeína del café, el té, las gaseosas y más (Caffeine content of coffee, tea, carbonated & others) (https://www.mayoclinic.org/es-es/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20049372)
- Botanical on-line (2019): Cantidad de cafeína de los alimentos, plantas y bebidas. (Amount of caffeine in foods, plants and drinks) (https://www.botanical-online.com/alimentos/cafeina-alimentos-ricos)
- Verster & Koenig (2018): Caffeine intake and its sources: A review of national representative studies. Crit Rev Food Sci Nutr. 2018;58(8):1250-59 (https://doi.org/10.1080/10408398.2016.1247252)

Figure 2. Caffeine consumption in children and adolescents.

- Stable daily consumption over the last decade, despite the introduction of new drinks with caffeine[1]
- Prevalence: ~ 75 % children and adolescents aged 6-17 years[2]
- Mean total daily intake below the caffeine consumption recommendations (EFSA: 3 mg/kg/day for children and adolescents)[1,2,3]:
  - 6-11 years: 25 mg/day
  - 12-17 years: 50 mg/day
- Principal sources (variable according to country)[4]:
  - Coffee and tea (consumption rising)
  - Cola drinks (consumption falling) and
  - Energy drinks (consumption increasing with age, particularly in males)
- Metabolism slower than for adults due to the lower efficiency of enzyme CYP1A2[3]
- Doses of 1.5 mg/kg/day can already produce sleep disturbances[3]
- Energy drinks[1,5]:
  - Account for a low percentage of total caffeine consumption (5-12 %)
  - Can involve a greater risk of adverse effects due to their high caffeine content (80-250 mg)
  - Consumption among adolescents is associated with a greater prevalence of risk conducts (smoking, alcoholism, drug addiction, etc.)



Source:
1. Verster & Koenig, 2018 (https://doi.org/10.1080/10408398.2016.1247252)
2. Ahluwalia, *et al*., 2015 (https://doi.org/10.3945/an.114.007401)
3. EFSA, 2015 (https://www.efsa.europa.eu/en/efsajournal/pub/4102)
4. Tran, *et al*., 2016 (https://doi.org/10.1016/j.fct.2016.06.007)
5. Temple *et al*., 2017 (https://doi.org/10.3389/fpsyt.2017.00080)

Toxicity of caffeine

The progressive increase in the consumption of energy drinks containing high concentrations of caffeine and other substances such as taurine, guarana, L-carnitine, ginseng, has led to an increased number of cases of toxicity[36] , occurring at both a cardiac level (atrial fibrillation) and at the CNS level (convulsions). However, recent investigations report that the said components consumed separately could have a neutral or even positive effect on health, provided that they do not exceed the toxic doses37.

Acute consumption of caffeine could produce a slight increase in blood pressure and the heart rate, associated with decreased myocardial blood flow, as well as an increase in plasma catecholamine, rennin and free fatty acid levels38 and although a prospective study published by Klatsky et al.39 in 2011 shows an independent inverse relationship of gender, race and age between coffee consumption and the risk of hospital admittance due to cardiac arrhythmias, there is evidence of possible adverse effects of caffeine when consumed at high doses (>500-600 mg/day), producing nervousness, anxiety, irritability, insomnia, headaches and gastrointestinal problems, in addition to increased sympathetic nerve activity at a cardiac level, estimating an average lethal dose of 10 g of caffeine for adults[40].

In 2015, Yamamoto *et al*.[41] reviewed different cases of caffeine intoxication, especially those resulting in death. The majority of the cases were associated with the consumption of other types of drugs, alcohol in particular, reporting that the caffeine concentration in individuals who had not consumed alcohol was higher than for those who had combined both substances. Hypotheses have been established with regard to the lethal mechanism of caffeine, associating it with ventricular arrhythmias, however other studies suggest other mechanisms such as convulsions, rhabdomyolysis and acute kidney failure[42] or respiratory arrest due to functional brain damage[41]. Studies on animals[43] and humans[41] show that, in lethal cases of intoxication, caffeine is distributed in different organs, primarily in the kidney, brain and liver. Therefore, the cause of death may not solely be associated with the ventricular arrhythmia mechanism but also with general organ damage.

Doping

Caffeine was included in the list of substances banned by the *World Anti-Doping Agency* (WADA) from 1984 until 2004, when it was removed. The permitted concentration in urine was <12 µgr/ml, (~6-8 cups of coffee). Due to the fact that the ergogenic doses of caffeine were found to be almost indistinguishable from normal consumption, the WADA removed its restriction in order to prevent penalizing athletes unfairly. However, considering the growing use of caffeine since the restrictions were lifted, and in order to clarify whether the said consumption was for performance-enhancing purposes, in 2017 experts considered that it ought to be included on the WADA watch list, where it is still today. Therefore, its levels are currently still being monitored[44,45].

Labelling / Regulations

The European Union strengthens the obligations to inform consumers about those drinks and foods (including food supplements) that have a high caffeine content through (EU) Regulation No. 1169/2011 on the provision of food information to consumers[46]. Although the European legislation on food supplements does not specify the maximum permitted level, it does regulate the information that must appear on the label with regard to caffeine[46]:

- Beverages in which the name of the food includes the term 'coffee' or 'tea' (except those based on coffee, tea or coffee or tea extract) and are either intended for consumption without modification or are in concentrated or dried form, and contain caffeine in a proportion in excess of 150 mg/l must indicate:
  - *"High caffeine content. Not recommended for children or pregnant or breast-feeding women"* in the same field of vision as the name of the beverage, followed by a reference to the caffeine content expressed in mg per 100 ml.
- Foods other than beverages, to which caffeine is added with a physiological purpose, must indicate:
  - *"Contains caffeine. Not recommended for children or pregnant women"* in the same field of vision as the name of the food, followed by a reference to the caffeine content expressed in mg per 100 g/ml. In the case of food supplements, the caffeine content shall be expressed per portion as recommended for daily consumption on the labelling.

With regard to the caffeine used as a flavouring in the production or preparation of a food, such as cola beverages, it shall be mentioned by its specific name in the list of ingredients immediately after the term "flavouring". In this case, however, there is no obligation to specify on the label the dose content or the aforementioned restriction on special populations, although the maximum permitted quantities of flavouring are set out in Regulation 1334/2008 on flavourings[47].

On the other hand, with regard to medicinal products containing caffeine, these are not governed by these regulations but by Directive 2001/83/EC, given that they are not classified as "foods" but as medicinal products[48].

Despite the fact that EFSA issued a favourable ruling in 2011[49] for six health claims of article 13.1 of Regulation 1924/2006 (four with specific conditions/restrictions on use and two related to sport/physical activity), there are no health claims relating to caffeine, given that the European Commission overruled the approval of the said claims, in order to protect consumers.

Conclusions

- Caffeine improves physical performance in resistance sports (aerobic exercise) and also in high-intensity activities and team sports (anaerobic exercise).
- At a central level, the effect of caffeine on fatigue is due to neurochemical changes that modify the rating of perceived exertion during exercise and reduce the sensation of pain while, at a peripheral level, it is due to the stimulation of Na^+-K^+-AT Pase that promotes the release of calcium from the sarcoplasmic reticulum, improving the neuromuscular function.
- Low-moderate doses of 3-6 mg/kg of body mass in the form of anhydrous caffeine administered 30-60 minutes before exercise appear to have the most consistent positive results on sport performance, although doses of less than 3 mg/kg of body mass (~200 mg) administered before or during prolonged activities appear to be equally beneficial, particularly at a cognitive level. On the other hand, doses of more than 9 mg/kg of body mass do not appear to increase the ergogenic benefit, and can increase the risk of adverse effects which will condition sport performance.
- Due to the variability in response based on the time of administration, interacting with other ergogenic ingredients, sporting discipline, genotype and gender, it is advisable to personalise the usage protocols in order to maximise the benefit and minimise the side effects.
- The lethal mechanism in the case of caffeine intoxication is associated with alterations not only at a cardiac level but also with the overall systemic affectation (kidney, brain, liver).

– Aspects to explore in future studies on the ergogenic response of caffeine:
  - Influence of habitual consumption of coffee/caffeine.
  - Optimal administration time / influence on circadian rhythm.
  - Variation of the ergogenic effect according to the caffeine source.
  - Influence of the athlete's prior training level.
  - Influence of the chronic administration of caffeine in the adaptation to training.
  - Influence of gender difference.

Conflict of interest

The authors have no conflict of interest at all.

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