The use of Caffeine by people with Epilepsy: the myths and the evidence

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Abstract [148/150 words]

Purpose of review: Caffeine is the most widely consumed central nervous stimulant. For people with epilepsy, it is often unclear whether drinking coffee carries a risk of triggering seizures.

Recent findings: The relationship between caffeine, seizures, epilepsy and anti-seizure drugs is not fully understood. Clinical studies are scarce. In animal models, caffeine can increase seizure susceptibility but can also protect from seizures. Effects seem dose-dependent and, influenced but the duration of intake and the developmental stage at which caffeine exposure started. Caffeine lowers the efficacy of several anti-seizure medication, especially topiramate.

Summary: It is unclear how these findings, mainly from animal studies can be translated to the clinical condition. At present, there is no evidence to advice people with epilepsy against the use or overuse of caffeine. Until clinical studies suggest otherwise, caffeine intake should be considered as a factor in achieving and maintaining seizure control in epilepsy.

1 Introduction

Epilepsy is a complex paroxysmal neurological condition characterized by recurrent seizures. The condition is relatively common with a prevalence of up to 0.7% in the general population [1–3]. Caffeine is the most consumed Central Nervous System (CNS) stimulant worldwide [4]. Given its stimulative effects, it is not surprising that people with epilepsy and health providers question whether caffeine is a trigger for seizures [5]. There are currently no guidelines that unequivocally answer this question. We review current evidence on the effect of caffeine on seizures which was also covered in a recent systematic review [6]. We attempt to provide some practical advice on whether people with epilepsy should be advised to reduce their caffeine intake.

Caffeine (1,3,7-trimethylxanthine) has been found to offset fatigue and enhance vigilance, reaction speed, information processing, arousal and motor activity. The effects of caffeine are likely due to its interaction with various neurotransmitters, most importantly adenosine [7]. Adenosine is produced as a by-product of neuronal firing. [8] It promotes sleep and reduces cortical excitability through binding to the adenosine receptors [9]. As the molecular structure of caffeine is similar to adenosine, caffeine can also bind to the adenosine A1 and A2A receptors and in doing so prevents adenosine from binding, thus acting as an adenosine-antagonist. Caffeine also interacts with another important inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), by modulating GABA-A receptors [10–12]. The activation of the adenosine A1-receptor inhibits dopamine, a neurotransmitter involved in focus and motivation, and release of glutamate, an important excitatory neurotransmitter. Caffeine thus increases dopamine and glutamate release and inhibits GABA, resulting in a stimulating net effect [13, 14].

2. Clinical studies

2.1 Case reports

Several case reports have suggested in that caffeine can trigger seizures in people with epilepsy. Seizures were either found to occur after the intake of unusually high (toxic) caffeine doses [15–22], or after prolonged periods of caffeine intake [23–27]. One case report describes a woman with several episodes of status epilepticus (SEs) occurring at weekends [27]. She regularly drank almost 2 liters of coffee on Fridays, Saturdays and Sundays, and around half a liter of coffee on weekdays. When she stopped drinking coffee at the weekends, she had fewer seizures and no episodes of SEs [27]. In another case, a man with at least six focal pharmaco-resistant seizures weekly, became seizure-free after stopping drinking more than 2 liters of coffee per day [25]. Conversely, there is a report of a man with generalized epilepsy who had been seizure-free on anti-seizure medication, but his seizures recurred when he started drinking large quantities of caffeinated iced tea [23]. The seizures decreased again when he started to drink decaffeinated iced tea. There are also anecdotal reports of seizures after the intake of energy drinks [28]. Caffeine was also found to prolong seizures after electroconvulsive therapy, a treatment for severe depression [29].

2.2 Clinical studies on the effect of caffeine on seizures

There are only a few clinical studies on the effect of caffeine on seizures. One was an observational study of people attending hospital after a seizure. They were asked about their usual caffeine intake [30]. On average, the coffee consumption on the day preceding the seizure was not higher than their average consumption, or than the consumption on a seizure-free day. About two thirds of them were diagnosed with epilepsy. In this subgroup, there was a trend towards less caffeine consumption prior to the seizure compared to the habitual intake, which was statistically significant in those with generalized epilepsy

[30]. This may suggest that caffeine withdrawal plays a role in triggering seizures in some forms of epilepsy.
Two other studies were large questionnaire studies, examining the effect of prolonged caffeine intake on seizures and epilepsy. The first study assessed several health and lifestyle parameters in over 100,000 nurses, including epilepsy, seizures and caffeine intake [31]. Those reporting seizures or epilepsy did not have a different caffeine intake than the total cohort. A second study assessed whether caffeine exposure in the womb influenced the development of febrile seizures, using a questionnaire on lifestyle during pregnancy of over 35,000 women receiving antenatal care in Denmark [32]. Maternal caffeine intake during pregnancy did not influence the risk of febrile seizures in the first three months of life. This study did not provide a long-term follow-up or information on seizures other than febrile seizures.
In pre-term infants, caffeine citrate can be used to improve the microstructural development of white matter. In a randomized controlled trial, infants were given either the standard dose of 30 mg/kg or a high dose of 80 mg/kg of caffeine citrate [33]. In the group receiving the high dose there was a non-significant trend for more numerous and longer seizures compared to children that had received the standard dose.

The anti-seizure drugs phenytoin enhanced caffeine clearance and reduced the mean half-life of caffeine was reduced by almost 50%. Carbamazepine and valproic acid did not affect caffeine metabolism [34].

3 Animal studies on the effects of caffeine on seizures

3.1 Seizures after caffeine exposure

In studies with rats, mice, rabbits, guinea pigs, cats and dogs it has been found that extremely high doses of caffeine increase brain excitability and trigger seizures and encephalopathy. Caffeine is therefore used as an animal model of seizures [35]. When seizures are triggered by other agents such as pentylenetetrazol (PTZ), another animal model for epilepsy, caffeine also lowers the seizure threshold [36–39].

3.2 Seizures after maternal caffeine exposure

The offspring of rat dams that received caffeine during pregnancy in doses that would be equivalent to about three to four cups of coffee a day in humans were shown to be more susceptible to seizures induced by hyperthermia or flurothyl than controls that received only water [40, 41]. In the pups that had been exposed to caffeine, there was a delayed migration of GABAergic neurons into the hippocampus which was not found in controls. This delayed migration was associated with a general increase in neuronal network excitability [40]. Another study, reported no difference in adenosine A1, A2A and GABA-A receptor mRNA expression in rat pups that had been exposed to caffeine in utero compared to a control group that had not [42].

3.3 Protective effects of caffeine

It may come as a surprise that there are studies in animals suggesting that caffeine may have protective effects against epilepsy and seizures. In young rodents for example, prolonged, low-dose caffeine exposure was shown to decrease seizure susceptibility. One study administered caffeine to rats in the first week after birth [43]. They were also infused with one of five pro-convulsants: PTZ, picrotoxin, bicuculline, strychnine or kainic acid until the first myoclonic jerk appeared. Compared to controls, rat pups that had been exposed to caffeine had a 20-40% higher seizure threshold to PTZ at 28 days after birth. There was a further increase in seizure threshold (40-50% elevation) to PTZ and picrotoxin in rats of 42 days old that had been given caffeine compared to controls. In adulthood (70-90 days) the caffeine group showed a significant increase of seizure threshold for PTZ and kainic acid compared to controls.

In another study, chronic low doses of caffeine 7-11 days after birth significantly elevated the seizure threshold for generalized tonic clonic seizures (GCTS) but not for myoclonic jerks or minimal clonic seizures [44]. The seizure threshold in response to electrical stimulation was not altered in rats that received caffeine repeatedly for 7 to 11 days, or for 13 to 17 days after birth [45], nor when electrical seizures were induced at 67 days [46]. In a PTZ model of absence and myoclonic seizures, low-dose exposure to caffeine reduced the frequency of seizure-like episodes and shortened their duration in a dose-dependent fashion [47]. The anti-seizure medication phenobarbital is commonly used to treat neonatal seizures but carries the risk of inducing neurodegeneration [48]. A study was carried out to assess the neuroprotective properties of caffeine to counter the degeneration caused by phenobarbital. On day 4 after birth, the rat pups received phenobarbital with or without caffeine for three consecutive days. In the brains of rats that received phenobarbital only, there was an increase of cell death, not seen in pups which had received caffeine co-treatment. Caffeine appeared to reduce inflammatory cytokines and neurotoxicity and to counter the reduction of A1- and A2A receptors induced by phenobarbital [48]. In juvenile rats, caffeine combined with ethanol increased the vulnerability to seizures triggered with PTZ, whereas caffeine alone had a protective effect [49].

Caffeine exposure in adult rodents

Studies on the potential protective effects of caffeine against seizures and epilepsy in adult animals have shown conflicting results. One study found no effect of chronic low-dose exposure to caffeine on seizures triggered with picrotoxin or kainic acid compared to the control (water) [50]. Another study, however, found that the duration of convulsions was significantly decreased in animals receiving caffeine over several days compared to an injection with saline [51]. The differences between these two studies may be explained by methodological differences, including the different methods of caffeine administration, and use of different pro-convulsive triggers.

In a rat model of genetic absence epilepsy, the number and duration of spike-and-wave discharges (SWDs) on intracranial EEG recordings were dose-dependently reduced after a single medium dose of caffeine, compared to the baseline. This study found no effect of a more chronic exposure to caffeine [52]. A more recent study also showed a decrease in SWD's after the administration of caffeine, linked to an increase of cytokine levels (IL-6 and NFkB) in the thalamus [53]. In a rat model of severe traumatic brain injury, a single dose of caffeine also reduced the duration of epileptic bursts [54]. Interestingly it was shown that a single dose of caffeine significantly reduced the incidence of seizure-induced respiratory arrest in mice, which may be involved in sudden death in epilepsy (SUDEP) [55]. Overall, it appears that caffeine has neuroprotective effects against seizures in animal models of absence epilepsy, after early-life convulsions and traumatic brain injury. This effect depends on age, pro-convulsant, seizure model, caffeine dose and administration method.

3.4 Interactions between caffeine and anti-seizure medication in animal models

Contrary to clinical studies, there is a relatively large number of studies on the interaction between caffeine and anti-seizure medication in animal models. In many, maximal electroshock (MES) was used to induce seizures to assess the effects of caffeine administration on the anticonvulsant properties of drugs [56–62]. Rats were injected with caffeine as well as one of following ASMs: carbamazepine, phenytoin, phenobarbital, valproic acid, felbamate, oxcarbazepine, lamotrigine, tiagabine, gabapentin and topiramate. Single-dose caffeine injections reduced the seizure threshold and increased the amount of phenobarbital, carbamazepine, phenytoin, topiramate, gabapentin, valproic acid and felbamate needed to protect 50% of the rats against electroconvulsions, whereas no changes were seen for

oxcarbazepine, lamotrigine and tiagabine [56–58, 60–62]. When caffeine was chronically administered, the amount of phenobarbital, carbamazepine, phenytoin, topiramate, gabapentin and valproic acid needed to protect 50% of the rats against seizures was also increased, but again unaltered for oxcarbazepine, lamotrigine and tiagabine [57, 59–62]. The results of studies using other animal models of epilepsy such as PTZ or rhythmic vestibular stimulation were also in line with these findings [63]. Caffeine significantly decreased the amount of PTZ needed to induce seizures compared to saline [38]. Diazepam, however, increased the threshold to PTZ-induced seizures. When diazepam and caffeine were given together, the anticonvulsant effect of diazepam was decreased. When inducing seizures with PTZ in mice and rats treated with ethosuximide, carbamazepine, clonazepam, phenobarbital or valproic acid [39, 64] the amount of ethosuximide needed to protect 50% of the mice [39] and the amount of carbamazepine needed to protect all the rats against seizures [64] was significantly elevated compared to the control group/condition. In mice, there were no effects for clonazepam, phenobarbital and valproic acid.

The interaction effects between caffeine and ASMs may occur on two different levels. First, as the concentrations of phenobarbital, clonazepam, phenobarbital, valproic acid, carbamazepine, gabapentin, topiramate and ethosuximide were unaffected in the presence of caffeine, caffeine may act as an antagonist of the anticonvulsant properties of these medications [39, 58, 61, 62]. The second, simpler explanation of the pharmacodynamic interaction between caffeine and ASMs is that caffeine increases seizure susceptibility, indirectly increasing the need for drugs, which makes it analogous to the interaction between any seizure precipitants.

Our quantitative analysis of previously published studies has shown that the interaction of caffeine and ASMs varies greatly between AEDs. While all ASMs seem to be affected by caffeine to some extent, topiramate has the strongest interaction with caffeine. Overall, there was no difference in the interaction with ASMs when comparing a single caffeine dose with repeated caffeine administration, except for carbamazepine, in which the interaction with caffeine was stronger when caffeine was administered chronically [6].

3.5 Pathophysiological mechanisms potentially underlying the effect of caffeine on seizures

What then may the pathophysiological mechanisms underlaying these different effects of caffeine on seizures? First, seizure susceptibility depends on brain excitability, which is influenced by genetics, structural anomalies, internal factors such as hormones and sleep and external factors such as diet. Genetics may influence (caffeine-related) seizure susceptibility in individuals, as suggested by a study in genetically mutated mice [65]. A more recent study suggests that caffeine can induce epigenetic changes that affect neuronal excitability, which may underlie epileptogenesis [66]. Sleep deficiency is an independent seizure trigger [67], as caffeine counters fatigue [4] and the sleep-promoting effects of adenosine [9], the effects of caffeine on seizure susceptibility may be related to its sleep-disrupting effects.

Early studies show that caffeine interferes with the processes that terminate the electrical seizure activity [68]. Results from in vitro studies show that caffeine causes an increase in intracellular Ca^2 release and Ca^2 influx, which is linked to increased seizure activity through elevated neuronal excitability and synchronous firing of neurons [69–71]. Similarly, caffeine may facilitate seizures by changing potassium currents leading to a less negative membrane potential [72], and by binding with the inhibitory A1-receptor subtype for endogenous extracellular adenosine [73, 74]. Recent findings suggest the involvement of the A2a-receptor for adenosine, which may explain the dose-dependent effects of

caffeine [75]. Interestingly, adenosine has a role in seizure termination and postictal depression [76, 77] potentially also through control of free radicals [78, 79] which were shown to play a role in epileptogenesis [79, 80]. Long-term exposure to low doses of caffeine may have neuroprotective influences by changing A1- [81–83] and A2-receptor [54, 84, 85] density and sensitivity to adenosine and caffeine [81]. These effects are area- [81] and age-dependent [81–83, 86]. Caffeine-exposure in early life may have more protective effects than in adulthood, most likely because there are more changes in A-receptor density at young ages [81–83, 86].

4. Discussion

Evidence mainly from animal studies seems to show that caffeine can either increase seizure susceptibility or protect against seizures. The effect depends on the dose, administration type (a single dose or long-term exposure) and the developmental stage at which exposure to caffeine started. In animal studies, caffeine interacted with some ASMs, particularly topiramate. Single-high doses of caffeine seem more likely to trigger seizures than repeated low doses of caffeine, suggesting the development of tolerance to A1- and A2A-receptor blockade by caffeine [43, 46, 47, 52, 83, 87, 88].

Some studies show conflicting results, which may have been produced by the use of different models pertaining to different epilepsy types [40, 42, 52, 68, 88], different ways of inducing seizures [39, 58], different methods for caffeine administration, and different doses of caffeine or chemical pro-convulsants [50–52, 68, 88]. Some sample sizes are small, limiting their reliability [38, 39].

Translating findings of animal studies to humans is a major challenge. There is a difference in caffeine metabolism between humans and animals. Caffeine doses used in many animal studies are much higher than the estimated equivalent average human caffeine consumption. So far, the findings from animal studies have not been replicated in clinical studies and provocative or protective effects of caffeine on seizure susceptibility have not been seen in humans [30–33].

Like animal studies, there are some limitations to previous clinical studies. Caffeine intake for example was measured as “units per day” [30–32, 67]. This method has limitations as the size of units (cups) and concentration of caffeine probably differed between studies and participants. These studies also relied on self-reports, which are sensitive to recall and response biases. Selection bias may have been present in studies in which only women were included [31, 32]. If it is true that caffeine does not significantly affect seizure susceptibility in humans, the lack of studies reporting such findings could be a result of publication bias, as negative results are notoriously hard to publish.

Future research

We highlight the scarcity of clinical data on the effects of caffeine on seizures and epilepsy. Findings from animal studies show that the relationship between seizures, AEDs and caffeine is complex. Translating these results to a human scenario is challenging, which makes it impossible to develop clear clinical recommendations regarding the consumption of caffeine in people with, or at risk of, epilepsy. Given the complex relationship between caffeine and seizures, the only reasonable recommendation that can be made to physicians who notice a change in seizure pattern, or pharmaco-resistant epilepsy, is that caffeine consumption should be included in history-taking.

To shed light on the influence of caffeine on seizures in humans, robust, prospective large-scale clinical studies will be paramount. Care will have to be taken to assess accurately caffeine intake and resulting

plasma concentrations. For the clinical management of people with epilepsy, it will also be important to investigate whether caffeine, in doses consumed by the average person, interferes with ASMs. The finding that caffeine may have a preventative role in SUDEP is exciting, but it will have to be replicated in animal studies first, before any clinical studies can be undertaken [55].

Conclusion

While animal studies suggest that caffeine can increase seizure susceptibility, it is unclear how these findings in animal models translate to humans. In animals, chronic exposure to caffeine may protect against seizures. Caffeine can interact with several ASMs, especially topiramate. Until there are robust clinical studies available, caffeine intake should be included in history-taking in people with epilepsy and considered as a factor that may play a role in achieving and maintaining seizure control.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose in relation to this work.

Ethical Publication Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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