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Review

Caffeine and seizures: A systematic review and quantitative analysis

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ABSTRACT

Purpose: Caffeine is the most commonly used central nervous system (CNS) stimulant. The relationship between caffeine, seizures, epilepsy, and antiepileptic drugs (AEDs) is complex and not fully understood. Case reports suggest that caffeine triggers seizures in susceptible people. Our systematic review reports on the relationship between caffeine, seizures, and drugs in animal and human studies. Quantitative analyses were also done on animal studies regarding the effects of caffeine on AEDs.
Methods: PubMed was searched for studies assessing the effects of caffeine on seizure susceptibility, epilepsy, and drug interactions in people and in animal models. To quantify the interaction between AEDs and caffeine, the data of six animal studies were pooled and analyzed using a general linear model univariate analysis or One-way Analysis of Variance (ANOVA).
Results: In total, 442 items were identified from which we included 105 studies. Caffeine can increase seizure susceptibility and protect from seizures, depending on the dose, administration type (chronic or acute), and the developmental stage at which caffeine exposure started. In animal studies, caffeine decreased the antiepileptic potency of some drugs; this effect was strongest in topiramate.
Conclusion: Preclinical studies suggest that caffeine increases seizure susceptibility. In some cases, chronic use of caffeine may protect against seizures. Caffeine lowers the efficacy of several drugs, especially topiramate. It is unclear how these findings in models can be translated to the clinical condition. Until clinical studies suggest otherwise, caffeine intake should be considered as a factor in achieving and maintaining seizure control in epilepsy.

1. Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed central nervous system (CNS) stimulant [1]. Globally, the average intake is around 300 mg/day, mostly as coffee, tea, soft drinks, and energy drinks [2,3]. An average cup of coffee (200 mL) contains ca. 74 mg caffeine [2]. Chocolate, certain plants, and a wide variety of drugs also contain caffeine [4].

Caffeine counters fatigue and enhances vigilance, reaction speed, information processing, arousal, and motor activity [1]. These effects are probably mediated by neuronal adenosine-receptors [5]. When firing, neurons produce the inhibitory neuromodulator adenosine as a byproduct [6]. Adenosine promotes sleep through adenosine receptors and reduces cortical excitability [7]. The molecular structure of caffeine is similar to adenosine, and it is a mixed competitive adenosine A1 and A2A receptor antagonist. Caffeine affects the responsiveness to gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter, by modulating GABA-A receptors [8–10]. Adenosine A1-receptor activation is also involved in the inhibition of dopamine, a neurotransmitter which plays a role in focus and motivation, and release of glutamate, an important excitatory neurotransmitter. Caffeine increases dopamine and glutamate release and inhibits GABA, resulting in a "pepping" effect [11,12].

Epilepsy is a paroxysmal neurological condition characterized by recurrent seizures, with a prevalence of up to 0.7% in the general population [13–15]. There are several case studies in which caffeine seemed to trigger seizures in people with and without epilepsy (summarized in Table 1). Seizures occurred after toxic doses of caffeine intake [16–23] or prolonged periods of caffeine intake [3,24–27]. In one case, a man had at least six focal seizures each week [25]. Treatment with several antiepileptic drugs (AEDs) failed. Six months after he stopped drinking coffee (>2 L/day), he became seizure-free. Another report described a

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Table 1
Case reports: overview of case studies describing potential seizure-inducing effects of caffeine. Cases are discussed in the introduction.

Reference	Gender (M/F)	Age (in years)	Epilepsy (+/−)	Type of seizure (focal, tonic–clonic, absence)	Caffeine dose (mg)	Caffeine intake through	AED (other relevant drugs)	Comments
3	M	49	+	Focal, tonic–clonic and absence	168 (in 3 h)	Snapple Iced Tea (4 pints)	Phenytoin & primidone (unchanged)	Consumed in 3 h on an empty stomach. After switching to decaffeinated Snapple Iced Tea, no more seizures.
16	F	Neonate	−	Equivalent of tonic–clonic seizures in neonate	250.04 (94 mg/kg)	*im* injection of CSB	Phenobarbital + (dexamethasone)	Hypoxia causes CNS irritability
16	M	Neonate	−	Equivalent of tonic–clonic seizures in neonate	511.36 (two times 68 mg/kg)	*im* injection of CSB	(Dexamethasone + atropine)	Two injections of 255.68 mg caffeine. Hypoxia causes CNS irritability
16	M	Neonate	−	Equivalent of tonic–clonic seizures in neonate	248.64 (84 mg/kg)	*im* injection of CSB	(Naloxone hydrochloride)	Hypoxia causes CNS irritability
16	F	Neonate	−	Equivalent of tonic–clonic seizures in neonate	62.280 (36 mg/kg)	*im* injection of CSB	–	Hypoxia causes CNS irritability
17	F	17	−	Tonic–clonic	Unknown	"Pick-me-up-pill" (Caffeine + phenylpropanolamine + pseudoephedrine)	–	Seizures after taking "pick-me-up-pill".
18	F	24	−	Tonic–clonic	1000 (in 3 h)	*iv* injection of CSB	(Analgesia + anesthesia for C-section)	CSB + epidural blood patch to treat persisting postpartum headache.
19	F	27	− (migraine)	Tonic–clonic	500	*iv* injection of CSB	–	–
20	F	45	− (migraine)	Tonic–clonic	250 per day	Coffee	(Aspirin, 5 g/day)	Withdrawal of caffeine and aspirin caused seizures and headaches.
21	F	21	−	Tonic–clonic	1000 (in 23 h)	Pills (250 mg each)	–	After complicated delivery of a healthy child, caffeine pills to treat headaches.
22	M	40	+	Focal, tonic–clonic	~800	Coffee	Carbamazepine (unchanged)	Stopped drinking coffee, no more seizures.
23	F	18	−	Presumed seizure	Unknown (1 energydrink)	Energydrink (unknown label)	(Aspirin 1000 mg)	Collapsed in a nightclub setting, flashing lights.
24	M	25	−	Tonic–clonic	480	Energydrink (Rockstar)	–	Twice seizures 30–60 min after drinking large amounts of energydrink.
24	F	28	− (migraine)	Tonic–clonic	Unknown	Energydrink (Monster) + diet pills with caffeine	–	Only seizures (twice) when energydrink + diet pills containing caffeine
24	M	19	− (migraine)	Tonic–clonic	>480	Energydrink (unknown label)	–	Subject could not remember the amount or label: "couple of 24-oz cans".
24	M	26	−	Tonic–clonic	>480	Energydrink (Monster)	–	Two or more 24-oz cans Monster energydrink caused seizures
25	M	15	−	Tonic–clonic	~480	Coffee + energydrink (5-hour ENERGY)	–	–
26	Unknown	25	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 2400 mg)	Tramadol abuse
26	Unknown	21	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 720 mg)	Tramadol abuse
26	Unknown	17	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse
26	Unknown	20	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse
26	Unknown	15	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 840 mg)	Tramadol abuse
26	Unknown	17	−	"Convulsive crisis"	Unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse
27	F	33	+	Seizures and status epilepticus	Unknown (24 oz coffee on weekdays; 60 on Fr, Sa, Su)	Coffee	Levetiracetam, carbamazepine, and zonisamide	Underwent left temporal lobectomy and responsive neurostimulation therapy for medically refractory epilepsy.

AED = antiepileptic drug; CSB = Caffeine Sodium Benzoate; CNS = central nervous system.

man with generalized epilepsy who had been seizure-free on AEDs [3]. His seizures suddenly recurred when he started drinking large quantities of caffeinated iced tea. After he switched to decaffeinated iced tea, the seizure frequency decreased. A woman who drank around half a liter of coffee on weekdays, and almost 2 L on Fridays, Saturdays, and Sundays had several episodes of status epilepticus (SEs) at the weekends. When she stopped drinking coffee on these days, she had fewer seizures and no SEs [27]. In Electroconvulsive Therapy (ECT), a treatment for severe depression, caffeine has been used to prolong seizures [28].

The question, thus, arises as to how caffeine affects seizure susceptibility. We conducted a systematic review aiming to answer three questions: Firstly, what information do preclinical studies provide about the effects of caffeine on seizures? Secondly, do preclinical and/or clinical studies point to interactions between caffeine and AEDs? Given the large body of data on this topic, we performed a quantitative analysis of available data [29–42]. Lastly, we reviewed the literature on pathophysiological mechanisms that may link seizures to caffeine exposure.