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Review

Caffeine and the anticonvulsant potency of antiepileptic drugs: experimental and clinical data

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Abstract:
Caffeine (1,3,7-trimethylxanthine) is the most commonly ingested stimulant in the world. The daily consumption of this methylxanthine in coffee, tea and soft drinks is approximately 200 mg per person, which yields a pharmacologically active blood concentration. Experimental data indicate that caffeine may either lower the convulsive threshold in experimental models of epilepsy or induce seizure activity in doses over 400 mg/kg in rodents. Interestingly, animal data have demonstrated that caffeine, at doses far below its convulsive potential, diminishes the protective effects of conventional antiepileptic drugs (AEDs – carbamazepine, phenobarbital, phenytoin, valproate) and the newer AED, topiramate against electroconvulsions in mice. However, in contrast to these AEDs, caffeine did not impair the anticonvulsant efficacy of other newer AEDs, lamotrigine, tiagabine, and oxcarbazepine in this experimental model of epileptic seizure. Although limited, the clinical data generally confirm the experimental findings, suggesting increased seizure frequency in epileptic patients who began ingesting caffeine in high quantities. Thus far, no analysis has been performed in epileptic patients to determine whether the hazardous effects of caffeine are dependent upon individual antiepileptic treatments. These data clearly indicate that methylxanthines should be avoided in epileptic patients.

Key words:
antiepileptic drugs, caffeine, seizures, methylxanthines, epilepsy

Abbreviations: AEDs – antiepileptic drugs, CBZ – carbamazepine, CGS 15943A – 5-amino-9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-c]quinazoline, CGS 21680 – 2-[4-(2-carboxyethyl)-phenylamino]-5'-N-ethylcarboxamidoadenosine, CNS – central nervous system, GBP – gabapentin, GPCR – G-protein coupled receptor, IB-MECA – N^6-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine, LTG – lamotrigine, MES – maximal electroshock, MX(s) – methylxanthine(s), OXC – oxcarbazepine, PB – phenobarbital, PHT– phenytoin, TGB – tiagabine, TPM – topiramate, VPA – valproate

Introduction

Caffeine (1,3,7-trimethylxanthine), which belongs to the group of purine alkaloids, is the most commonly and widely ingested stimulant. Caffeine is found in beverages such as coffee, tea, and many soft drinks as well as in chocolate products and desiccated coconut. It is also present in a variety of analgesics, appetite

stimulants, and some antiviral drugs [2, 28, 31, 44]. Estimates in North America show that 90% of the population consumes caffeine-containing beverages. The daily consumption of this methylxanthine (MX) is, on average, 200 mg per person, which produces pharmacologically active blood concentrations [2].

The history of caffeine is closely associated with the history of coffee. Its name was derived from the Arabian word "gahwa", which means "excising tiredness". The stimulatory effects of coffee on the central nervous system were discovered in the XVII century [47]. The first chemical analysis of coffee was made in 1685 by P.S. Dufour, who discovered that coffee contained the bitter alkaloid caffeine [47]. The content of caffeine in a cup of coffee varies from 75 to 150 mg, depending on how the coffee is prepared and brewed [50].

Chronic caffeine ingestion may result in physical dependence and tolerance to its central effects [2, 44]. One of the most dangerous complications of caffeine overdose is seizure activity. Caffeine may either lower the convulsive threshold in experimental models of epilepsy or induce seizures in rodents when administered in doses over 400 mg/kg [10, 11, 13, 16].

The inhibitory role of adenosine in the control of seizure activity has also been well characterized [18, 41]. Among adenosine receptors, four types have already been distinguished: A_1, A_{2A}, A_{2B}, and A_3. All of them are coupled to G-proteins, and adenosine is their endogenous ligand [30, 35]. A_1 receptors are found in many tissues and organs. The greatest concentrations of A_1 receptors are found in the central nervous system (CNS), especially in the human cortex, hippocampus, cerebellum, brain stem, and spinal cord [51]. They are also widely distributed in the immune system [35]. The A_1 receptor is a $G_{i/o}$-coupled G-protein coupled receptor (GPCR); its activation suppresses adenylyl cyclase causing a decrease in cAMP (a secondary messenger). The consequences of central A_1 receptor activation are sedation, motor activity depression, anxiolytic, and anticonvulsant effects [36].

In contrast, the A_2 receptor is a G_s-coupled GPCR; its stimulation results in the activation of adenylyl cyclase and causes the release of the neurotransmitters acetylcholine, noradrenaline, dopamine, and glutamate [20, 49]. Therefore, these receptors mediate excitatory neurotransmission in the CNS. Brain distribution of A_{2A} receptors, which have a high affinity for adenosine, is mainly restricted to the dopamine-rich areas of the brain, such as the striatum [24]. A_3 adenosine receptors are $G_{li/o}$-coupled GPCRs. These receptors have a significantly lower affinity for adenosine that the A_1 and A_{2A} subtypes [6].

Although A_1 adenosine receptor-mediated events are associated with the anticonvulsant effects of their respective ligands, which may be injected peripherally or locally into the brain, the role of the remaining receptor subtypes in many experimental models of epileptic seizure remains unclear [21, 46, 53–55]. Some data indicate that A_{2A} adenosine receptor agonists or antagonists, given locally into the piriform cortex, did not significantly modulate .amygdala-kindled seizures in rats [46]. In contrast, results reported by Zeraati et al. [55] provide evidence that an A_{2A} receptor agonist, administered into the CA_1 hippocampal field, produced a clear proconvulsive effect, prolonging afterdischarge in piriform cortex-kindled rats. However, in audiogenic seizures in DBA/2 mice, the A_2 receptor agonist 2-[4-(2-carboxyethyl)-phenylamino]-5'-N-ethylcarboxamidoadenosine (CGS 21680) suppressed seizure activity following its peripheral administration [22]. In the same experimental model, N^6-(3-iodobenzyl)-5'-N-methylcarboxamidoadenosine (IB-MECA; an A_3 adenosine receptor agonist) was ineffective; in contrast, Von Lubitz et al. [54] have shown that this agonist protected mice against pentetrazole- or N-methyl-D-aspartate-induced convulsions. However, these authors consider IB-MECA-produced arteriolar constriction and hypotension as probable factors contributing to the final anticonvulsant effect, which may be of a pharmacokinetic nature.

Caffeine, a nonselective antagonist of adenosine receptors [48], has been documented to produce seizures *per se* [10, 11, 13] and exert proconvulsive effects *in vitro* [33]. Specifically, caffeine significantly prolonged afterdischarges following cortical stimulation in rats [33]. Also, when given at 10–20 mg/kg for postnatal days 7–11, caffeine shortened the latency to pentetrazole (40 mg/kg)-induced rhythmic EEG activity and extended its duration in 18-day-old rats. However, some anticonvulsant effects of caffeine were noted when pentetrazole was given at 20 mg/kg [52]. When analyzing the epileptogenic effects of caffeine and other MXs in hippocampal slices, Moraidis and Bingman [40] have determined that this specific effect of MXs is correlated with their affinities to A_1 adenosine receptors. Other data also support the conclusion that the proconvulsive effects of MXs are mainly due to their antagonism of adenosine A_1 receptors [1, 22]. Caffeine is a convulsant agent in mice, and its CD_{50} (50% convulsant dose) is approximately 400 mg/kg [13]. The convulsive potential of another MX, theophylline, has also been confirmed in asth-

matic patients who were administered high doses of this drug during intensive treatment of status asthmaticus [56]. It seems clear that proconvulsive and/or convulsive agents are capable of reducing the anticonvulsant potential of antiepileptic drugs (AEDs); however, the problem is not that simple. For instance, the $GABA_A$ receptor antagonist, bicuculline, is a potent convulsant, but it is completely incapable of affecting the protective effects of AEDs against maximal electroshock (MES)-induced seizures in mice [14]. This indicates that a hazardous interaction of a drug with antiepileptic treatment cannot be predicted from its convulsant potential. Consequently, a series of experiments were conducted to determine whether caffeine bears an untoward capacity to reduce the protective potential of AEDs. Certainly, any negative outcomes derived from combinations of caffeine with antiepileptic drugs would be of utmost clinical importance.

Influence of caffeine on the protective activity of AEDs

Numerous studies have demonstrated that caffeine, in relatively low doses, diminished the protective effects of classic AEDs in two models of experimental epilepsy: electroshock- and pentylenetetrazole-induced convulsions [13, 18, 25, 26, 31, 38]. Another MX, aminophylline (theophylline$_2$ × ethylenediamine) also considerably reduced the convulsive potential of phenobarbital (PB) against amygdala-kindled seizures [17]. According to Löscher and Schmidt [37], these models mimic human generalized tonic-clonic, myoclonic, and partial complex seizures. The effects of caffeine on the anticonvulsant activity of classic AEDs [phenytoin (PHT), PB, carbamazepine (CBZ), and valproate (VPA)] against MES-induced convulsions in mice were studied, both after acute and chronic exposure to caffeine, to determine whether the possible hazardous influence of caffeine was subject to tolerance. The data have clearly shown that acute caffeine administration (in doses of 23.1 and 46.2 mg/kg, equivalent to 25 and 50 mg/kg of aminophylline, respectively) produced a significant decrease in the protective potency of these AEDs [13, 25, 26]. The most sensitive AED to caffeine was PB; its protective activity was significantly reduced by caffeine at 11.55 mg/kg. Moreover, no tolerance to this untoward effect of caffeine has been observed. In fact, following 15 days of caffeine administration to mice in the previously specified doses, the protective efficacy of PHT was reduced similarly to acute caffeine. However, this was not the case with CBZ, PB, or VPA, whose protection was even more significantly reduced when compared with acute caffeine administration [25, 26].

The influence of caffeine upon the anticonvulsant activity of classic AEDs has also been studied in rats in the MES test. The results indicate that caffeine, at a relatively high dose of 200 mg/kg, reduced the protective potency of PHT, PB, and diazepam while the potency of VPA remained unchanged [34]. These authors, however, measured the final effects of the ED_{100} of the tested AEDs in combination with caffeine. Also, there were no pharmacokinetic studies evaluating possible pharmacokinetic interactions between caffeine and AEDs [34].

In addition to the chronic administration of caffeine, another set of experiments were conducted. After two weeks of daily injections, caffeine was withdrawn for 24 h, and a challenge dose of caffeine was given. This procedure resulted in the most prominent hazardous effects of caffeine toward classic AEDs [25, 26].

At present, a number of newer AEDs, sharing similar anticonvulsant efficacy with classical drugs but inducing fewer adverse effects and possessing more predictable pharmacokinetics [12], are available. It would be interesting to know whether caffeine is able to affect their protective activity as in the case of classic AEDs. The newer AED, topiramate (TPM), was also sensitive to caffeine administered acutely at doses of 23.1 and 46.2 mg/kg. Caffeine produced significant increases in its respective ED_{50} values against MES-induced convulsions in mice [8]. The same was true for gabapentin (200 mg/kg), whose anticonvulsant activity (an increased electroconvulsive threshold in mice) was reduced by both acute and chronic caffeine at 46.2 mg/kg [8]. Low interaction potential has been shown by felbamate, a newer AED used rarely due to its considerable adverse potential, resulting from an increased risk of inducing aplastic anemia [12]. Its anticonvulsant activity was significantly reduced by caffeine at a high dose of 161.7 mg/kg [27]. Strikingly, neither acute nor chronic caffeine (up to 46.2 mg/kg) affected the protection offered by lamotrigine (LTG) or oxcarbazepine (OXC) against MES-induced convulsions in mice [9]. A summary of the interactions of selected AEDs with caffeine in the

Tab. 1. Influence of acute or chronic caffeine upon the anticonvulsant activity of selected antiepileptic drugs against maximal electroshock-induced convulsions in mice [9, 13, 24, 26]

Antiepileptic drug	Caffeine (mg/kg)		
	11.55	23.1	46.2
Phenobarbital	↑ (↑↑)	↑↑ (↑↑)	↑↑↑ (NT)
Phenytoin	↑ (0)	↑ (0)	↑↑ (↑↑)
Carbamazepine	0 (↑)	↑ (↑↑)	↑↑ (NT)
Valproate	0 (0)	↑ (↑)	↑ (↑)
Lamotrigine	NT	0 (0)	0 (0)
Topiramate	0 (0)	↑↑ (↑↑)	↑↑↑ (↑↑↑)
Oxcarbazepine	NT	0 (0)	0 (0)

Caffeine and antiepileptic drugs were injected intraperitoneally: caffeine 30 min, phenytoin and phenobarbital 120 min, carbamazepine and topiramate 60 min, and valproate 30 min before maximal electroshock test. 0 – no significant increase in the respective ED_{50} (the dose necessary to block the hindlimb tonic-extensor component of the maximal electroshock-induced seizures in 50% of the examined animals) value *vs.* the control group; ↑ – at least a 25% increase reflecting a reduction in the protective activity of antiepileptic drugs; ↑↑ – at least a 50% increase; ↑↑↑ – at least a 90% increase; (...) – chronic caffeine; NT – not tested

MES test may be found in Table 1. Also, acute or chronic caffeine administered in the previously described dose range did not significantly affect the electroconvulsive threshold associated with tiagabine (TGB; 4 and 6 mg/kg) [9]. Caffeine (up to 46.2 mg/kg), given acutely or chronically, did not significantly modify neurotoxicity of LTG, OXC, or TGB evaluated in the chimney test (quantifying an impairment of motor coordination) [9]. Only in the case of TGB (4 mg/kg) was a pharmacokinetic interaction observed; chronic caffeine was found to raise its total plasma concentration [9].

The question arises whether this undesired interaction of caffeine with classic AEDs is restricted to models of electroconvulsion in rodents. The available experimental data seem to extend the observations derived from electroconvulsions to those observed in pentetrazole-induced clonic seizures in rodents. Caffeine (200 mg/kg) has been found to reverse the anticonvulsant action of diazepam (0.5 mg/kg) in mice. However, no pharmacokinetic verification of this effect was conducted [29]. The same high dose of caffeine has also been able to reduce the protection by diazepam and PB although it was ineffective with respect to VPA and ethosuximide in rats. Again, no pharmacokinetic studies were performed [34]. According to Łuszczki et al. [38], acute caffeine at 46.2 and 69.3 mg/kg did weaken the anticonvulsant potency of ethosuximide; however, a dose of 92.4 mg/kg was unable to exert a significant influence upon the protection by clonazepam, PB, and VPA.

Clinical evidence

Clinical data are scant and primarily limited to case reports. Kaufman and Sachdeo [32] provide evidence from a patient with a 36-year duration of mixed epilepsy consisting of tonic-clonic, absence, atonic and myoclonic seizures satisfactorily controlled with two AEDs. In spite of therapeutic serum AED concentrations and no concurrent diseases, there was a sudden increase in seizure frequency and a change to newer AEDs was considered. After approximately 2 months, it was discovered that the patient had started drinking caffeinated beverages, and a change to decaffeinated soft drinks would have almost immediately returned his seizure frequency to baseline without having to switch to other AEDs [32]. Another example describes a patient who had never achieved a seizure-free status and experienced approximately five simple seizures per day and one complex partial seizure a week [4]. The patient used to drink a large amount of coffee, up to 10 cups (0.25 l each) daily, but due to nervousness, he quit this habit. Strikingly, within a week there was a considerable reduction in his seizure frequency to one partial seizure a day without complex partial seizures [4]. Out of 78 coffee drinkers with epilepsy, 71 found no association between their drinking habit and seizure frequency [3]. However, in 7 heavy coffee users (more than 4 cups of coffee daily) quitting this habit restored their seizure frequency to baseline without any modification of the antiepileptic treatment [3].

Conclusions

The experiments listed above clearly demonstrate a close association between caffeine and seizure activity. The data show a caffeine-induced decrease in the convulsive threshold, especially in chemically in-

duced seizures [10, 11]. The threshold for electroconvulsions is unaffected by caffeine [13]. Caffeine has been also documented to reduce the protective activity of a considerable number of classic and newer AEDs against MES- or pentetrazole-induced convulsions in rodents. Because A_1 adenosine receptor-mediated events are involved in the modulation of seizures, the question arises whether the hazardous influence of caffeine on the anticonvulsant effects of various AEDs is due to its mechanism of action at A_1 adenosine receptors. This seems unlikely, especially with respect to electroconvulsions. This assumption is based on a study evaluating the effect of the nonxanthine adenosine antagonist, 5-amino-9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-c]quinazoline (CGS 15943A), on the protection offered by classic AEDs against MES-induced convulsions in mice [15]. CGS 15943A had no effect on the anticonvulsant activity of classic AEDs except for PHT; therefore, in this particular case, the involvement of A_1 adenosine receptors is likely. However, the involvement of A_1 adenosine receptors may be taken into consideration with respect to the newer AED, TPM and its interaction with caffeine. Nevertheless, the interaction between AEDs and caffeine is of CNS origin because 8-(p-sulfophenyl)-theophylline (a theophylline derivative unable to cross the blood-brain barrier), in doses equivalent to aminophylline (50 mg/kg), did not modify the protective action of PB, PHT, or VPA against MES [5].

If A_1 adenosine receptors are not generally associated with the hazardous interaction between caffeine and AEDs, other possible mechanisms of action must be considered. For example, one possible mechanism may involve the caffeine-dependent release of calcium ions from the endoplasmic reticulum [27, 39, 43], an effect mediated by ryanodine receptors [7]. Interestingly, clonazepam, CBZ, and VPA antagonized caffeine-induced epileptiform activity in rat hippocampal slices due to the effect of caffeine on the ryanodine receptors [39]. This finding excludes the release of calcium ions from the endoplasmic reticulum as a key factor for the untoward interaction of caffeine with AEDs in the MES test. However, this mechanism may be of importance when caffeine is given in combination with either VPA or clonazepam, whose protective activities were not affected by caffeine in the pentetrazole test [38].

MXs are also inhibitors of phosphodiesterases at high doses [44], and this may be a possible mechanism of action for the interaction of caffeine with AEDs. However, similar to A_1 adenosine receptors, this mechanism appears unlikely because pentoxifylline, in doses equivalent to caffeine, only moderately reduced the anticonvulsant activity of PHT against MES in mice and was completely ineffective against other classic AEDs [13].

The resistance of some newer AEDs to caffeine in the MES test raises another question. The AEDs susceptible to caffeine display a number of anticonvulsant mechanisms of action: they are blockers of voltage-dependent sodium channels (CBZ, PHT, and VPA) or L- and T-type calcium channels (CBZ, TPM, and VPA), GABA enhancers (VPA, PB, TPM), and AMPA receptor blockers (PB or TPM) [12, 19, 45]. The drugs resistant to the hazardous influence of caffeine in the MES test differ in that they are inhibitors of other types of voltage-operated calcium channels. In fact, LTG and OXC inhibit N, P/Q, and R-calcium currents, and this particular feature is not shared by classic AEDs or TPM [45]. Moreover, while TGB resembles VPA in that both AEDs lead to a considerable increase in synaptic GABA, the effect of TGB is considerably more potent [45]. Although this difference may contribute to the resistance of TGB to acute caffeine, a pharmacokinetic factor may be involved in the interaction between TGB and caffeine because the free plasma concentration of TGB was significantly elevated [9].

Regardless of the particular mechanisms involved in the interaction between caffeine and certain AEDs, epileptic patients should be discouraged from ingesting caffeine or using drugs containing caffeine. Remarkably, caffeine may reach pharmacologically relevant plasma concentrations after 1–3 cups of coffee [44]; thus, coffee drinking habits may create real problems for epileptic patients, as highlighted in clinical reports [3, 4, 32]. To the degree that experimental data are transferable to clinical conditions, patients on LTG, OXC, or TGB therapy may be less susceptible to caffeine compared with patients taking classic AEDs or TPM. Caffeine may increase seizure frequency in epileptic patients through the untoward interaction with AEDs without being a risk factor for the development of seizures or epilepsy. In fact, Dworetzky et al. [23] have conducted a prospective study in 116,363 women evaluating caffeine as a risk factor. This study has shown that caffeine was not associated with an increased risk of epilepsy. Emotional stress or sleep deprivation may provoke seizures [42]. However, caffeine does not seem to be a seizure-

precipitating factor in epileptic patients [42]. Clinical data indicate that patients ingesting caffeine may experience increased seizure frequency [3, 4, 32], but it is not considered a seizure precipitant [42].

References:

1. Bahi N, Nehlig A, Evrard P, Gressens P: Caffeine does not affect excitotoxic brain lesions in newborn mice. Eur J Paediatr Neurol, 2001, 5, 161–165.
2. Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME: Caffeine dependence in teenagers. Drug Alcohol Depend, 2002, 66, 1–6.
3. Błaszczyk B: Caffeine and management of epilepsy – a clinical evidence. Pharmacol Rep, 2007, 59, 116.
4. Bonilha L, Li M: Heavy coffee drinking and epilepsy. Seizure, 2004, 13, 284–285.
5. Borowicz K, Kozicka M, Kleinrok Z, Czuczwar SJ: Influence of aminophylline and 8-(p-sulfophenyl)theophylline on the anticonvulsive action of diphenylhydantoin, phenobarbital, and valproate against maximal electroshock-induced convulsions in mice. J Neural Transm, 1991, 86, 127–134.
6. Brown RA, Spina D, Page CP: Adenosine receptors and asthma. Br J Pharmacol, 2008, 153, 446–456.
7. Butanda-Ochoa A, Höjer G, Morales-Tlalpan V, Diaz-Muñoz M: Recognition and activation of ryanodine receptors by purines. Curr Med Chem, 2006, 13, 647–657.
8. Chrościńska M, Jargiełło M, Czuczwar SJ: Influence of caffeine on the protective action of some conventional and novel antiepileptic drugs – an experimental evidence. Pharmacol Rep, 2007, 59, 118.
9. Chrościńska-Krawczyk M, Ratnaraj N, Patsalos PN, Czuczwar SJ: Effect of caffeine on the anticonvulsant effects of oxcarbazepine, lamotrigine, and tiagabine in a mouse model of generalized tonic-clonic seizures. Pharmacol Rep, 2009, 61, 819–826.
10. Chu NS: Caffeine- and aminophylline-induced seizures. Epilepsia, 1981, 22, 85–94.
11. Cutrufo C, Bortot L, Giachetti A, Manzini S: Different effects of various xanthines on pentylenetetrazole-induced seizures in rats: An EEG and behavioural study. Eur J Pharmacol, 1992, 222, 1–6.
12. Czapiński P, Błaszczyk B, Czuczwar SJ: Mechanisms of action of antiepileptic drugs. Curr Top Med Chem, 2005, 5, 3–14.
13. Czuczwar SJ, Gąsior M, Janusz W, Szczepanik B, Włodarczyk D, Kleinrok Z: Influence of different methylxanthines on the anticonvulsant action of common antiepileptic drugs in mice. Epilepsia, 1990, 31, 318–323.
14. Czuczwar SJ, Ikonomidou C, Kleinrok Z, Turski L, Turski W: Effect of aminophylline on the protective action of common antiepileptic drugs against electroconvulsions in mice. Epilepsia, 1986, 27, 204–208.
15. Czuczwar SJ, Janusz W, Szczepanik B, Kleinrok Z: Influence of CGS 15943A (a nonxanthine adenosine antagonist) on the protection offered by a variety of antiepileptic drugs against maximal electroshock-induced seizures in mice. J Neural Transm, 1991, 86, 127–134.
16. Czuczwar SJ, Janusz W, Wamil A, Kleinrok Z: Inhibition of aminophylline-induced convulsions in mice by antiepileptic drugs and other agents. Eur J Pharmacol, 1987, 144, 309–315.
17. Czuczwar SJ, Jäckel R, Löscher W: Effects of aminophylline and enprofylline on the protective activity of phenobarbital against amygdale-kindled seizures in rats. Epilepsy Res, 1987, 1, 234–238.
18. Czuczwar SJ, Kleinrok Z: Modulation of the protective efficacy of common antiepileptic drugs by xanthine derivatives: implications for the clinical use of xanthines in epileptic patients. Pharmacol Res, 1990, 22, 661–665.
19. Czuczwar SJ, Patsalos PN: The new generation of GABA enhancers. Potential in the treatment of epilepsy. CNS Drugs, 2001, 15, 339–350.
20. Daly JW, Butts-Lamb P, Padgett W: Subclasses of adenosine receptors in the central nervous system: Interactions with caffeine and related methylxanthines. Cell Moll Neurobiol, 1983, 3, 69–80.
21. De Sarro G, De Sarro A, Di Paola ED, Bertorelli R: Effects of adenosine receptor agonists and antagonists on audiogenic seizure-sensible DBA/2 mice. Eur J Pharmacol, 1999, 371, 137–145.
22. Dingledine R, McBain C, McNamara JO: Excitatory amino acid receptors in epilepsy. Trends Pharmacol Sci, 1990, 11, 334–338.
23. Dworetzky BA, Bromfield EB, Townsend MK, Kang JH: A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses ' Health Study II. Epilepsia, 2010, 51, 198–205.
24. Fredholm BB, Lizerman AP, Jacobson KA, Klotz K-N, Linden J: International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacol Rev, 2001, 53, 527–552.
25. Gąsior M, Borowicz KK, Buszewicz G, Kleinrok Z, Czuczwar SJ: Anticonvulsant activity of phenobarbital and valproate against maximal electroshock in mice during chronic treatment with caffeine and caffeine discontinuation. Epilepsia, 1996, 37, 262–268.
26. Gąsior M, Borowicz KK, Kleinrok Z, Czuczwar SJ: Chronic caffeine and the anticonvulsant potency of antiepileptic drugs against maximal electroshock. Pharmacol Biochem Behav, 1996, 54, 639–644.
27. Gąsior M, Świąder M, Przybyłko M, Borowicz K, Turski WA, Kleinrok Z, Czuczwar SJ: Felbamate demonstrates low propensity for interaction with methylxanthines and Ca^{2+} channel modulators against experimental seizures in mice. Eur J Pharmacol, 1998, 352, 207–214.
28. Gilbert RM, Marshman JA, Schwieder M, Berg R: Caffeine content of beverages as consumed. Can Med Assoc J, 1976, 114, 205–207.
29. Goto M, Morishita S, Fukuda H: Anticonvulsant action of diazepam in mice pretreated with caffeine. J Pharmacobiodyn, 1983, 6, 654–659.
30. Huber A, Güttinger M, Möhler H, Boison D: Seizure suppression by adenosine A_{2A} receptor activation in a rat

model of audiogenic brainstem epilepsy. Neurosci Lett, 2002, 329, 289–292.
31. Jankiewicz K, Chrościńska-Krawczyk M, Błaszczyk B, Czuczwar SJ: Caffeine and antiepileptic drugs: experimental and clinical data (Polish). Przegl Lek, 2007, 64, 965–967.
32. Kaufman K, Sachdeo R: Caffeinated beverages and decreased seizure control. Seizure, 2003, 12, 519–521.
33. Koryntová H, Kubová H, Tutka P, Mares P: Changes of cortical epileptic afterdischarges under the influence of convulsant drugs. Brain Res Bull, 2002, 58, 49–54.
34. Kulkarni C, Joseph T, David J: Influence of adenosine receptor antagonists, aminophylline and caffeine, on seizure protective ability of antiepileptic drugs in rats. Indian J Exp Biol, 1991, 29, 751–754.
35. Kumar V, Sharma A: Adenosine: an endogenous modulator of innate immune system with therapeutic potential. Eur J Pharmacol, 2009, 616, 7–15.
36. Londos C, Cooper D, Wolff J: Subclasses of external adenosine receptors. Proc Natl Acad Sci USA, 1980, 77, 2551–2554.
37. Löscher W, Schimdt D: Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. Epilepsy Res, 1988, 2, 145–181.
38. Łuszczki JJ, Zuchora M, Sawicka KM, Kozińska J, Czuczwar SJ: Acute exposure to caffeine decreases the anticonvulsant action of ethosuximide, but not clonazepam, phenobarbital and valproate against pentetrazole-induced seizures in mice. Pharmacol Rep, 2006, 58, 652–659.
39. Margineau DG, Klitgaard H: Caffeine-induced epileptiform field potentials in rat hippocampal slices: a pharmacological characterization. Neuropharmacology, 2004, 47, 926–934.
40. Moraidis I, Bingman D: Epileptogenic actions of xanthines in relation to their activities for adenosine A_1 receptors in CA_3 neurons of hippocampal slices (guinea pig). Brain Res, 1994, 640, 140–145.
41. Murray TF, Zhang G, Franklin PH: Manipulation of endogenous adenosine affects seizure susceptibility. Drug Dev Res, 1992, 28, 410–415.
42. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA: Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav, 2005, 6, 85–89.
43. Neering IR, McBurney RN: Role for microsomal Ca storage in mammalian neurons? Nature, 1984, 309, 158–160.
44. Nehlig A, Daval JL, Debry G: Caffeine and the central nervous system: Mechanism of action, biochemical, metabolic and psychostimulant effects. Brain Res Rev, 1992, 17, 139–170.
45. Perucca E: An introduction to antiepileptic drugs. Epilepsia, 2005, 46, Suppl 4, 31–37.
46. Rezvani ME, Mirnajafi-Zadeh J, Fathollahi Y, Palizvan MR: Anticonvulsant effect of A_1 but not of A_{2A} adenosine receptors of piriform cortex in amygdala-kindled rats. Can J Physiol Pharmacol, 2007, 85, 606–612.
47. Rum L: Coffee – Legend, History (Polish), W Kolorach Tęczy Publisher, Wrocław, 2000.
48. Schwabe U, Ukena D, Lohse MJ: Xanthine derivatives as antagonists at A_1 and A_2 adenosine receptors. Naunyn-Schmiedeberg's Arch Pharmacol, 1985, 330, 212–221.
49. Sebastiao AM, Ribeiro JA: Adenosine A_2 receptor mediated excitatory action on the nervous system. Prog Neurobiol, 1996, 48, 167–189.
50. Shi D, Nikodijevic O, Jacobson KA, Daly J: Chronic caffeine alters the density of adenosine, adrenergic, cholinergic, GABA, and serotonin receptors and calcium channels in mouse brain. Cell Mol Neurobiol, 1993, 13, 247–261.
51. Svennigsson P, Hall H, Sedval G, Fredholm BB: Distribution of adenosine receptors in the postmortem human brain: an extended autoradiographic study. Synapse, 1997, 27, 322–335.
52. Tchekalarova J, Kubova H, Mares P: Postanatal caffeine treatment affects differently two pentylenetetrazol seizure models in rats. Seizure, 2009, 18, 463–469.
53. Vianna EP, Ferreira AT, Dona F, Cavalheiro EA, da Silva Fernandes MJ: Modulation of seizures and synaptic plasticity by adenosinergic receptors in an experimental model of temporal lobe epilepsy induced by pilocarpine in rats. Epilepsia, 2005, 46, Suppl 5, 166–173.
54. Von Lubitz DK, Carter MF, Deutsch SI, Lin RC, Mastropaolo J, Meshulam Y, Jacobson KA: The effects of adenosine A_3 receptors stimulation on seizures in mice. Eur J Pharmacol, 1995, 275, 23–29.
55. Zeraati M, Mirnajafi-Zadeh J, Fathollahi Y, Namvar S, Rezvani ME: Adenosine A_1 and A_{2A} receptors of hippocampal CA_1 region have opposite effects on piriform cortex kindled seizures in rats. Seizure, 2006, 15, 41–48.
56. Zwillich CW, Sutton FD, Neff TA, Cohn WM, Matthay RA, Weinberger MM: Theophylline-induced seizures in adults. Correlation with serum concentrations. Ann Intern Med, 1975, 82, 784–787.

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