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Chronic Caffeine and the Anticonvulsant Potency of Antiepileptic Drugs Against Maximal Electroshock

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GASIOR, M., K. BOROWICZ, Z. KLEINROK AND S. J. CZUCZWAR. *Chronic caffeine and the anticonvulsant potency of antiepileptic drugs against maximal electroshock.* PHARMACOL BIOCHEM BEHAV **54**(4) 639–644, 1996.—The anticonvulsant activities of intraperitoneally (IP) given carbamazepine (CBZ) or diphenylhydantoin (DPH), expressed as their respective ED_{50} values in mg/kg, were assessed after caffeine (CAFF) treatment against maximal electroshock-induced seizures in mice. CAFF was administered IP either in a single dose or every 12 h for 3 (subchronic CAFF) and 14 days (chronic CAFF). Moreover, the protective activity of the antiepileptics was determined in mice which, following chronic CAFF, received a challenge dose of CAFF after either 24 or 72 h since CAFF withdrawal. A significant reduction of the protective efficacy of CBZ was observed after chronic CAFF treatment (in a dose of 11.55 mg/kg), while a single dose and a 3-day treatment did not alter the action of CBZ. In case of CAFF (23.1 mg/kg), a significant elevation of CBZ's ED_{50} value was noted after 3- and 14-day treatments with CAFF. In contrast, chronic CAFF (23.1–46.2 mg/kg) decreased the anticonvulsive activity of DPH to the same extent as did acute CAFF. Moreover, the ED_{50} values for both, CBZ and DPH, evaluated 24 h after a 14-day treatment with CAFF (in doses of 23.1 and 46.2 mg/kg, respectively), were significantly elevated compared to respective control groups. A strong impairment of the anticon-vulsant action of CBZ and DPH was observed when a challenge dose of CAFF was injected following either 24 or 72 h injection-free time. Pharmacokinetic interactions do not seem to explain the obtained results in terms of total plasma levels of the antiepileptics after chronic treatment with CAFF. Our results may suggest that epileptic patients should avoid CAFF-containing beverages and medicines.

Chronic caffeine Antiepileptic drugs Electroshock Seizures

CAFFEINE (CAFF; 1,3,7-trimethylxanthine) is the most commonly self-administered substance in the world [for review see (21)]. Estimates in North America show that 90% of the population consume different forms of beverages containing behaviorally active doses of CAFF (17). The daily consumption of CAFF is, on average, 200 mg per person, although three- to fivefold higher ingestion is not unusual (17). Moreover, CAFF as well as other methylxanthines (MX), such as theophylline or theobromine, are often used as analgesics, appetite suppressants, myorelaxants, and stimulant adjuvants (21).

Interestingly, as early as 1601, William Parry described "a certain liquor which they call coffee . . . which will soon intoxicate the brain" (23). He was somewhat right because MX, indeed, may exhibit many side effects like nervousness, anxiety, cardiac arrhythmias in higher doses in man (26). Still, one of the most life-threatening complications of MX overdosing are seizures, clinically observed in cases with pulmonary disorders treated intensively with theophylline or aminophylline (theophylline$_2$ · ethylenediamine) (22,26,33,34). However, in animal studies, more evidences showing proconvulsant action of MX have been provided. For example, CAFF itself may either lower the convulsive threshold, or induce seizures in doses over 200 mg/kg (3,5,11). Francis and Fochtmann (14) demonstrated that pretreatment with CAFF in doses of 25–200 mg/kg significantly prolonged electroconvulsive seizure duration in rats. Administration of either CAFF or other MX prior to the electroconvulsive stimulus has been used in psychiatric practice to prolong seizure duration to ensure clinical efficacy of the electroconvulsive therapy in patients (4,29). This clinical application seems to be the only benefit of the proconvulsive

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properties of MX. Moreover, the proconvulsant activity of CAFF was also reported in the amygdaloid kindling model of partial seizures and pentylenetetrazol-induced convulsions (1,13). Further, CAFF and aminophylline diminished the protective activity of classical antiepileptic drugs against electroconvulsions, pentylenetetrazol-induced and amygdala-kindled seizures (6–8,10,12). But, in all above-mentioned experiments MX were used acutely. Practice shows that MX, and especially CAFF, are habitually consumed over longer periods of time and it may even lead to the development of physical dependence (18) and tolerance to their central effects (21). Previous studies demonstrated that a prolonged treatment with aminophylline did not result in the development of a tolerance to an aminophylline-induced reduction of the protective activity of classical antiepileptic drugs (30–32). If the experimental data could be extrapolated into clinical settings, these findings would point to hazards of aminophylline treatment in epileptic patients. It may be assumed that CAFF is also ingested by people suffering from epilepsy. The present study was undertaken to assess the anticonvulsant activity of two conventional antiepileptic drugs: carbamazepine (CBZ) and diphenylhydantoin (DPH) after acute, subchronic, and chronic CAFF treatments. In this aim, we used the maximal electroshock test (MES), representing a model of generalized human tonic–clonic epilepsy. Part of this study has already been published as an abstract (16).

METHOD

Animals

Experiments were carried out on male Swiss mice weighing 24–30 g. After 7 days of adaptation to laboratory conditions the animals were randomly collected to experimental groups (8–10 per group). Mice were kept in colony cages with free access to tap water and food (Murigran pellets; Bacutil, Motycz, Poland) under standard laboratory conditions with a natural light/dark cycle. The experiments were performed between 0800 and 1300 h.

Drugs and Administration Regimens

The following antiepileptic drugs were used throughout the experiments: carbamazepine (CBZ, Amizepin) and diphenylhydantoin (DPH, Phenytoinum), both obtained from Polfa Warsaw, Poland. The antiepileptics were suspended in a 1% solution of Tween 81 (Loba, Chemie, Vienna, Austria) and administered intraperitoneally (IP). The dose range of CBZ was 10–35 mg/kg and that of DPH, 5–30 mg/kg. Caffeine (Coffeinum Natrium benzoicum, Polfa, Łódź, Poland) was dissolved in sterile saline and given IP in doses referring to the pure methylxanthine.

Treatment Protocol (see also Fig. 1). Animals were injected twice a day (at 0800 and 2000 h) according to the following scheme: (a) saline for 14 days (control group); (b) saline for 14 days and then CAFF in a single dose (acute CAFF); (c) saline for 11 days and then CAFF for the next 3 days (subchronic CAFF); (d) CAFF for 14 days (chronic CAFF).

On day 15th mice from all groups received one of the antiepileptics in a single dose (CBZ, 60 min, or DPH, 120 min before the electroconvulsive test) and CAFF 30 min before the test [except for the control group (a), which was given saline instead of CAFF]. In addition, the protective activity of antiepileptic drugs was evaluated both 24 and 72 h after the last injection of chronic CAFF (washout period) in mice, which, on the test day received one of the antiepileptics combined with either saline or a challenging dose of CAFF.

The convulsive threshold was estimated in three additional

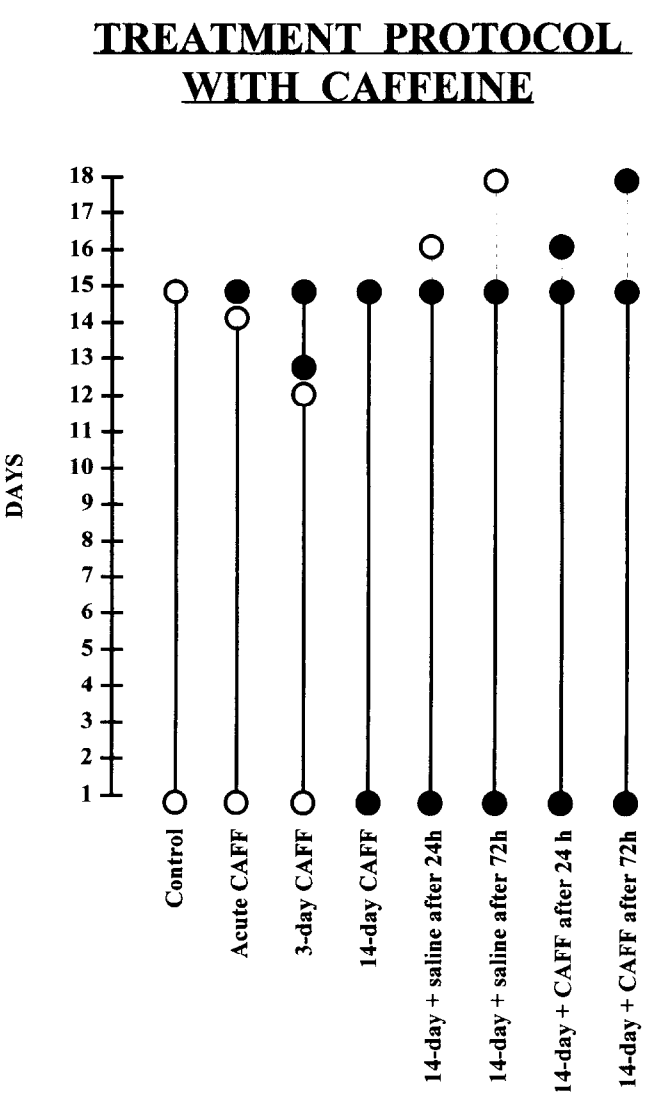

FIG. 1. Treatment protocol: solid lines mean continuous (twice a day) administration of either saline (open circles) or caffeine (solid circles). Dashed lines indicate 24 or 72 h injection free period (washout time) after 14-day treatment with caffeine followed by administration of either saline or a challenge dose of caffeine. On the last day of treatment mice from all groups received either saline or caffeine together with an antiepileptic drug and were challenged with the electroconvulsive shock.

groups of mice: (a) treated twice a day with saline for 14 days + saline on day 15th; (b) injected twice daily with saline + CAFF (92.4 mg/kg) on day 15th; (c) treated twice a day with CAFF (46.2 mg/kg) + CAFF (46.2 mg/kg) on day 15th. The threshold was evaluated 30 min after the last saline or CAFF injection.

The protective potency of CBZ was determined after treatment with CAFF in doses of 11.55 mg/kg (0.0595 mmol/kg) and 23.1 mg/kg (0.119 mmol/kg). DPH's anticonvulsive action was assessed after CAFF in doses of 23.1 and 46.2 mg/kg (0.238 mmol/kg). Doses of CAFF used throughout the study were based on the fact that CAFF and aminophylline were shown to reduce acutely, in doses of 46.2 mg/kg (0.238 mmol/kg) and 50 mg/kg (0.238 mmol/kg), respectively, the protective potency of various antiepileptic drugs against maximal electro-

shock-induced convulsions in mice (6,7,10,12). Moreover, the highest single dose of CAFF used in this study was 92.4 mg/kg (0.476 mmol/kg).

Electroconvulsions

Electroconvulsions were produced by means of an alternating current generator (Hugo Sachs Rodent Shocker, Type-221; Freiburg, Federal Republic of Germany), and delivered via ear-clip electrodes. The endpoint was the tonic extension of the hind limbs. To calculate the convulsive threshold, at least four groups of mice were shocked with electric stimuli of various intensities. On the basis of the percentage of animals responding with the endpoint, an intensity-effect curve was constructed and an individual CS_{50} (current $strength_{50}$) value (in mA) was calculated. Each CS_{50} value reflects the current strength required to induce tonic hindlimb extension in 50% of the mice tested. The protective efficacy of an antiepileptic drug, expressed as its effective $dose_{50}$ (ED_{50}) in mg/kg, was determined as an ability to protect 50% of mice tested against the tonic hindlimb extension. To evaluate each ED_{50} value, at least four groups of mice, after receiving progressive doses of an antiepileptic drug, were challenged with MES. Settings of the device were as follows: 25 mA current intensity and 0.2 s. stimulus duration. A dose–response curve was subsequently calculated on the basis of the percentage of animals protected against the endpoint.

Determination of Plasma Levels of Antiepileptic Drugs

Estimation of plasma levels of antiepileptic drugs was carried out in mice receiving either the treatment (a), which served as a control group, or treatment (d). Additional measurement was performed in mice receiving a challenge dose of CAFF after 24 h washout period from chronic CAFF together with an antiepileptic drug (see treatment protocol). The animals were killed by decapitation at times scheduled for MES and blood samples (about 1 ml) were collected into original Eppendorf tubes. Blood samples were centrifuged at 10,000 rev/min for 3 min and plasma samples of 70 μl were pipetted into the Abbott System cartridges. The plasma levels of antiepileptics were measured by immunofluorescence with an Abbott Tdx analyzer (Abbott, Irving, TX). The respective drug controls were placed at the beginning and end of each carousel for experimental samples. At least eight mice were used per an experimental group and the plasma levels (in μg/ml) were expressed as means ± SD.

Statistical Analysis

Both ED_{50} values (with 95% confidence limits) and their statistical analysis were estimated by fitting the data by computer probit analysis according to the method of Litchfield and Wilcoxon (19).

Plasma levels of antiepileptic drugs alone or combined with CAFF were statistically verified by Student's *t*-test.

A p value of at least < 0.05 was accepted as statistically significant.

RESULTS

Effect of CAFF Upon Electroconvulsive Threshold

Neither acute CAFF (92.4 mg/kg) nor chronic methylxanthine (46.2 mg/kg) affected the threshold which was 7.0 (6.5–7.5) mA in animals receiving saline for 14 days. Specifically, the threshold in the acute and chronic CAFF groups reached 6.9 (6.4–7.5) mA (results not shown).

Influence of CAFF Upon the Protective Effectiveness of CBZ

CAFF in a single dose of 92.4 mg/kg produced a significant decrease in the protective potency of CBZ. It was reflected by an elevation of its ED_{50} value from 15.0 (13.8–16.5) to 21.5 (18.3–25.3) mg/kg, respectively (results not shown).

However, CAFF (11.55 mg/kg) administered either acutely or for 3 days did not influence the protective activity of CBZ. In contrast, the 14-day treatment with CAFF resulted in an increase of the ED_{50} value for CBZ to 17.8 (16.3–19.5). It was statistically significant not only when compared with the control group, but with the acute CAFF group as well. A similar effect was observed when the challenge dose of CAFF was given to mice previously treated with CAFF for 14 days. In this case, the ED_{50} for CBZ was 20.3 (17–24.2) mg/kg (Fig. 2A).

When CAFF was used in a dose of 23.1 mg/kg, the protective potency of CBZ was reduced in groups receiving CAFF for 3 and 14 days. Moreover, a challenge dose of CAFF, administered either 24 or 72 h after the 14-day treatment with CAFF, again caused a significant lowering of the protective potency of CBZ. The ED_{50} values were 23.4 (20.5–26.8) and 17.7 (16.2–19.4) mg/kg, respectively (Fig. 2B).

The protective potency of CBZ evaluated 24 h after the last injection of CAFF (23.1 mg/kg) was diminished when compared to the control group (Fig. 2B). The remaining ED_{50} values, assessed either 24 or 72 h after the last administration of CAFF (11.55 mg/kg) or 72 h after the last injection of CAFF (23.1 mg/kg), did not differ from these of the control group (Fig. 2A and 2B).

Influence of CAFF Upon the Protection Provided by DPH

The control ED_{50} value for DPH was 10.2 (9.1–11.4) mg/kg and was significantly increased to 19.3 (16.1–23) after administration of CAFF in a single dose of 92.4 mg/kg (result not shown).

When CAFF was administered in a dose of 23.1 mg/kg, acutely, subchronically or chronically, the protective action of DPH was not influenced. However, it was impaired in groups of mice that were challenged with an additional dose of CAFF injected either 24 or 72 h after 14 days of treatment with the drug. The ED_{50}s were 15.2 (11.9–19.5) and 14.9 (12.4–17.9) mg/kg, respectively (Fig. 3A).

The protective activity of DPH was significantly decreased after acute, 3- and 14-day treatments with CAFF (46.2 mg/kg). The respective ED_{50} values for this antiepileptic drug were 15.9 (14–18.2), 15.5 (12.7–18.8), and 15.3 (12.6–18.6) mg/kg, respectively. There were apparently no differences in the protective efficacy of DPH after the acute, subchronic, and chronic treatments with CAFF (46.2 mg/kg). A further impairment of DPH's anticonvulsive action was observed when a challenge dose of CAFF was used either 24 or 72 h after the 14-day treatment with CAFF had been completed. The corresponding ED_{50}s for DPH were 21 (17.7–25) and 18.4 (14.9–22.8) mg/kg. Moreover, the ED_{50} value for DPH, assessed 24 h after 14 days of treatment with CAFF (46.2 mg/kg), was also significantly elevated (Fig. 3B).

Plasma Levels of CBZ and DPH After 14 Days of Treatment with CAFF and After a Challenge Dose of CAFF

Antiepileptic drugs were injected in equivalent doses to their ED_{50} values after the 14-day treatment with CAFF in a dose of 23.1 mg/kg (in case of CBZ) and 46.2 mg/kg (in case of DPH). Neither chronic CAFF nor its challenge dose affected the total plasma levels of CBZ and DPH (Table 1).

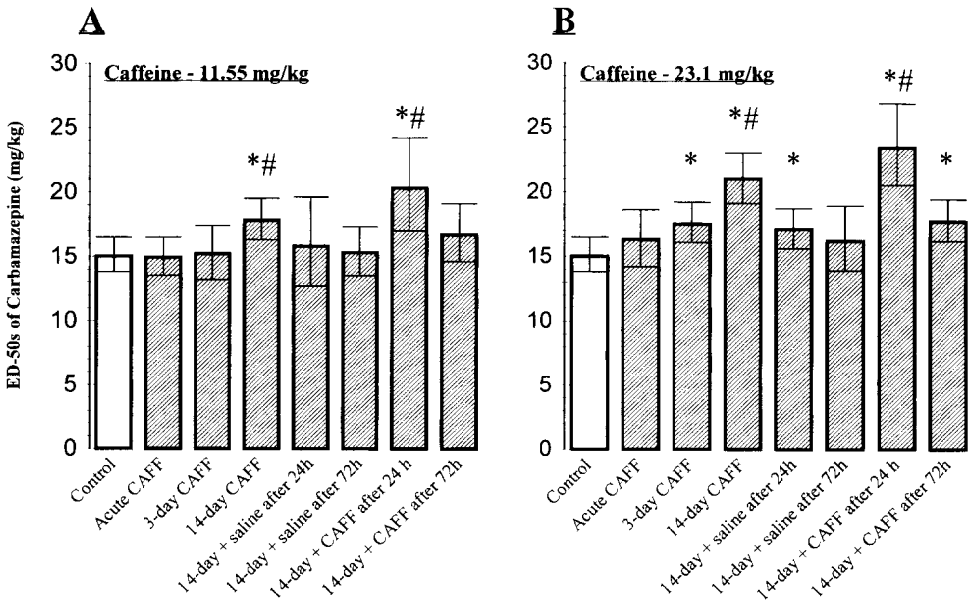

FIG. 2. Influence of caffeine (CAFF) treatment upon the anticonvulsive activity of carbamazepine in mice. Bars represent ED_{50} values of carbamazepine with respective 95% confidence limits (vertical lines). CAFF was administered in doses of 11.55 (A) 23.1 (B) mg/kg. For treatment protocol see Fig. 1. Carbamazepine was administered 60 min before the maximal electroshock. Statistical evaluation was carried out according to the method of Litchfield and Wilcoxon (19). Values of $*p$ and $\#p$ at least < 0.05 were considered to be significantly different from the control and acute CAFF group, respectively.

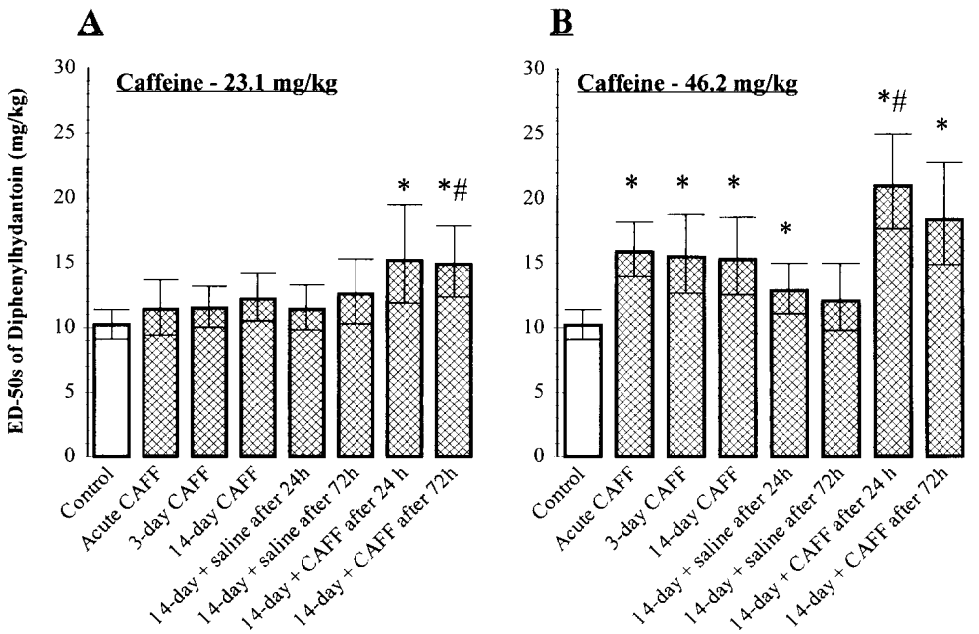

FIG. 3. Influence of caffeine (CAFF) on the protection offered by diphenylhydantoin. Bars represent ED_{50} values of diphenylhydantoin with respective 95% confidence limits (vertical lines). Caffeine was administered in doses of 23.1 (A) 46.2 (B) mg/kg. For treatment protocol see Fig. 1. Diphenylhydantoin was administered 120 min before the maximal electroshock. Statistical evaluation was carried out according to the method of Litchfield and Wilcoxon (19). Values of $*p$ and $\#p$ at least < 0.05 were considered significantly different from the control and acute CAFF group, respectively.

TABLE 1

INFLUENCE OF CHRONIC CAFFEINE AND A CHALLENGE DOSE OF CAFFEINE ON THE PLASMA LEVELS OF CARBAMAZEPINE AND DIPHENYLHYDANTOIN IN MICE

Treatment	Drug Plasma Levels (μg/ml)	
	CBZ (21 mg/kg)	DPH (15.3 mg/kg)
Control	5.4 ± 0.9	10.8 ± 1.5
14-day CAFF	4.5 ± 1.3	10.1 ± 2.3
14-day CAFF after 24 h	4.9 ± 1.0	11.1 ± 2.3

CBZ = carbamazepine, DPH = diphenylhydantoin, CAFF = caffeine. CBZ and DPH were injected at their ED_{50} values (the doses in parenthesis) against MES in combination with chronic CAFF, 60 and 120 min before decapitation, respectively. In combination with CBZ and DPH, CAFF was administered in doses of 23.1 and 46.2 mg/kg, respectively. Plasma levels of antiepileptics were measured in the control group, chronic CAFF group and in the group that received a challenge dose of CAFF 24 h after the 14-day treatment with CAFF had been completed. All drugs were injected IP. Table data are means ± SD of at least eight determinations. Statistical analysis was performed by Student's *t*-test. For further details refer to treatment protocol (Fig. 1).

DISCUSSION

The experimental data obtained in this study indicate that chronic CAFF (11.55–23.1 mg/kg) leads to a further impairment of the protective activity of CBZ against MES-induced seizures when compared to the effects of single CAFF injections. Similar results were obtained in relation to the anticonvulsant effectiveness of phenobarbital and valproate against MES in mice (16). Thus, there is rather sensitization to this effect rather than the tolerance after a long-term CAFF pretreatment. On the other hand, chronic CAFF (23.1–46.2 mg/kg) decreased the anticonvulsive activity of DPH to the same extent as did acute CAFF. But again, no tolerance was noted. Moreover, the ED_{50} values for both CBZ and DPH, evaluated 24 h after 14 days of treatment with CAFF (at its highest chronic dose), were significantly elevated in comparison with respective control groups. A strong impairment of the anticonvulsive action of CBZ and DPH was observed when a challenge dose of CAFF was injected following either 24 or 72 h injection-free periods. In addition, plasma levels of both antiepileptics were not changed by CAFF administered either acutely (6) or chronically. It was previously demonstrated that chronic CAFF, given according to the present treatment protocol, did not accumulate in murine plasma and had no influence on the plasma levels of phenobarbital and valproate (16). Therefore, it may be concluded that the observed interactions were not caused by pharmacokinetic mechanisms. However, CAFF was prepared and administered as an aqueous solution of sodium benzoate salt. It is unlikely that the benzoate component could account for the observed results. Francis and Fochtmann (14) demonstrated that sodium benzoate, administered IP (up to 200 mg/kg) 15 min prior to electroconvulsive stimulation, did not affect seizure length in rats. Consequently, it is very likely that the observed effects in the present study were caused by central actions of CAFF itself. Interestingly, Borowicz et al. (2) provided a clear-cut evidence that interactions between classical antiepileptics and methylxanthine derivatives may actually take place in the central nervous system. It was demonstrated that 8-(p-sulfophenyl)theophylline (a theophylline derivative with a limited penetration across the blood–brain barrier) did not affect the anticonvulsant action of conventional antiepileptics against MES-induced seizures in mice (2).

Several hypotheses were formulated to characterize the mechanism of CAFF action [for review see (21)]. Its ability to mobilize intracellular calcium ions, or inhibit phosphodiesterases are mechanisms that account for the CAFF action only in relatively high concentrations, which are very rarely found in vivo (21). Thus, great attention was focused on the ability of CAFF and other MX, to antagonize adenosine receptors. It is because CAFF and other MX are able to block exclusively adenosine receptors (A_1 and A_2 equipotentially) at plasma concentrations usually attained either after drinking one to three cups of coffee or due to the therapeutic dosage (21). Consequently, it is very likely that acute or chronic CAFF may act via a blockade of adenosine receptors. It is noteworthy that adenosine is a well-known inhibitory neurotransmitter in mammalian central nervous system (28). Its inhibitory role in the control of epileptogenesis has been also well characterized (20). Therefore, adenosine receptors seem to be a common denominator for both CAFF-mediated events and seizure control.

A number of classical antiepileptic drugs are known to modulate purinergic transmission. In case of CBZ, both antagonistic- and agonistic-like influence on the adenosine receptors were reported [(24) and (15), respectively]. DPH was shown to inhibit adenosine uptake into presynaptic terminals that resulted in the increase of the extracellular level of this neurotransmitter (24). It is not clear whether the different actions of CBZ and DPH on the purinergic system may account for the diverse effects of chronic CAFF on their protective action against MES. It is interesting that only in relation to DPH the purinergic component seems to be, at least partly, involved in its anticonvulsive action, because a nonxanthine adenosine antagonist, CGS 15943A, impaired the protective action of only DPH, leaving the action of phenobarbital, CBZ, and valproate unaltered against MES (9). This may indicate that the MX-induced impairment of the protective efficacy of conventional antiepileptics, with the exception of DPH, has probably nothing to do with the blockade of adenosine-mediated events.

Chronic exposure to CAFF may cause indirect changes in other neurotransmitter systems because CAFF, via adenosine receptors, which are linked to G-proteins, may, in turn, influence various neurotransmitter systems (25,27). Consequently, chronic CAFF-induced changes in other neurotransmitter systems may be involved in the impairment of the anticonvulsant action of conventional antiepileptic drugs. Our data also show that these alterations may persist over some periods of time because the impairment of CBZ's and DPH's anticonvulsive actions was observed 24 h after the chronic treatment with CAFF had been terminated. In addition, we are of opinion that changes induced by chronic CAFF, regardless of their nature, undergo the sensitization, because a challenge dose of CAFF caused a dramatic decrease in the anticonvulsant effectiveness of CBZ, DPH, phenobarbital, and valproate (16).

In conclusion, the results of the present study as well as our previous data demonstrate that no tolerance to the hazardous influence of CAFF on antiepileptic drugs develops following chronic CAFF treatment. However, the tolerance to numerous central actions of CAFF has been well documented [for review see (21)]. In contrast, the influence of CAFF on the protective activity of antiepileptics tends to increase over time. However, DPH differs from CBZ, phenobarbital, and valproate in this context, but its protective activity was also decreased after administration of a challenge dose of CAFF. If the experimen-

tal data could be extrapolated to clinical conditions, our results suggest that epileptic patients should avoid CAFF-containing beverages and medicines. This postulated restriction probably also concerns aminophylline, if it is to be used in epileptic patients for pulmonary reasons (30–32). From a theoretical point of view, it is interesting to note that after chronic CAFF a tolerance to certain effects may accompany a sensitization to the other ones. Finally, neither acute nor chronic CAFF modulated the seizure threshold, which may indicate that the lowered efficacy of the antiepileptic drugs tested was not due to proconvulsive effects of this methylxanthine derivative.

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