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Anticonvulsant Activity of Carbamazepine and N^6-L-Phenylisopropyladenosine in Rabbits. Relationship to Adenosine Receptors in Central Nervous System

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POPOLI, P , M BENEDETTI AND A SCOTTI DE CAROLIS *Anticonvulsant activity of carbamazepine and N^6-L-phenylisopropyladenosine in rabbits Relationship to adenosine receptors in central nervous system* PHARMACOL BIOCHEM BEHAV **29**(3) 533–539, 1988 —The present work deals with an EEG and behavioral study on the effects of carbamazepine (CBZ) and N^6-L-phenylisopropyladenosine (L-PIA) against the convulsions due to caffeine and pentylenetetrazole (PTZ) in rabbits Pretreatment with L-PIA (1, 3 and 4 mg/kg) caused a dose-related inhibition of the motor convulsions and the EEG "grand mal" ictal seizure induced by caffeine (75 mg/kg IV) On the contrary, L-PIA given at the high dose of 5 mg/kg IV partially inhibited the EEG and motor seizures elicited by PTZ (20 mg/kg IV) CBZ completely antagonized the EEG and motor convulsions induced by caffeine, while exerted only a protective action towards the EEG and motor convulsions due to PTZ The administration of an ineffective dose of CBZ (5 mg/kg IV) was able to enhance the protective action of L-PIA towards caffeine-induced convulsions This synergistic action between CBZ and L-PIA is also present towards the spike-and-wave complexes elicited by PTZ (10 mg/kg) These results confirm that the purinergic system plays an important role in the regulation of the CNS excitability They suggest therefore, that the anticonvulsant properties of CBZ may be at least partially explained by an influence of this drug on the purinergic system

L-PIA CBZ Caffeine PTZ A_1-A_2 Adenosine receptors

IT has been shown that adenosine and adenosine derivatives have sedative and hypnotic effects [16]. Anticonvulsant effects have been reported in mice susceptible to audiogenic seizures [11] and in rats treated with various types of convulsants [6].

Many authors [7, 19, 22] reported that caffeine and other methylxanthines possess, at high doses, convulsant effects in animals and humans The central stimulatory effects of xanthines have been proposed to correlate with their interactions with central A_1 adenosine receptors [4,17] On the other hand, it has been suggested that caffeine-induced seizures may be mediated *via* benzodiazepine (BDZ) receptors In fact, it is known that methylxanthines antagonize some effects of BDZ in animals [13] and humans [18], and that Ro 15-1788, the BDZ antagonist, blocks caffeine-induced seizures in mice [20].

In a previous paper [14], we reported that a small dose (0.05 mg/kg IV) of N^6-L-phenylisopropyladenosine (L-PIA), a specific ligand of A_1 adenosine receptors, was able to completely antagonize the effects of caffeine (25 mg/kg IV) on the electrically-induced hippocampal *after discharge* in rabbits, while Ro 15-1788 was unable to affect it These data confirm that the proconvulsant action of caffeine could be mediated by an effect on adenosine receptors and suggest that a potential species variation should exist in the mediation of caffeine-induced effects. In particular, rabbits may be different from rodents as regards the interplay between benzodiazepinergic and adenosinergic mechanisms.

Carbamazepine (CBZ) is currently used to treat various forms of epileptic seizures, however, the mechanism of its anticonvulsant action has not been clearly established. CBZ displaces the binding *in vitro* to synaptosomal membranes prepared from rat brain of several adenosine ligands such as [^{3}H]diethylphenylxanthine (DPX) and [^{3}H]cyclohexyladenosine (CHA) [12] and of the adenosine agonist [^{3}H]N^6-L-phenylisopropyladenosine (L-PIA) [15] It has been reported an antagonism of the anticonvulsant action of CBZ by some methylxanthines (caffeine, theophylline) [2,16], further suggesting an influence of CBZ on the purinergic system. Weir *et al* [21] have hypothesized that CBZ, only at the highest concentrations, may act as A_2 adenosine antagonist The nature of CBZ interactions, occurring at therapeutic doses [21], at the A_1 re-

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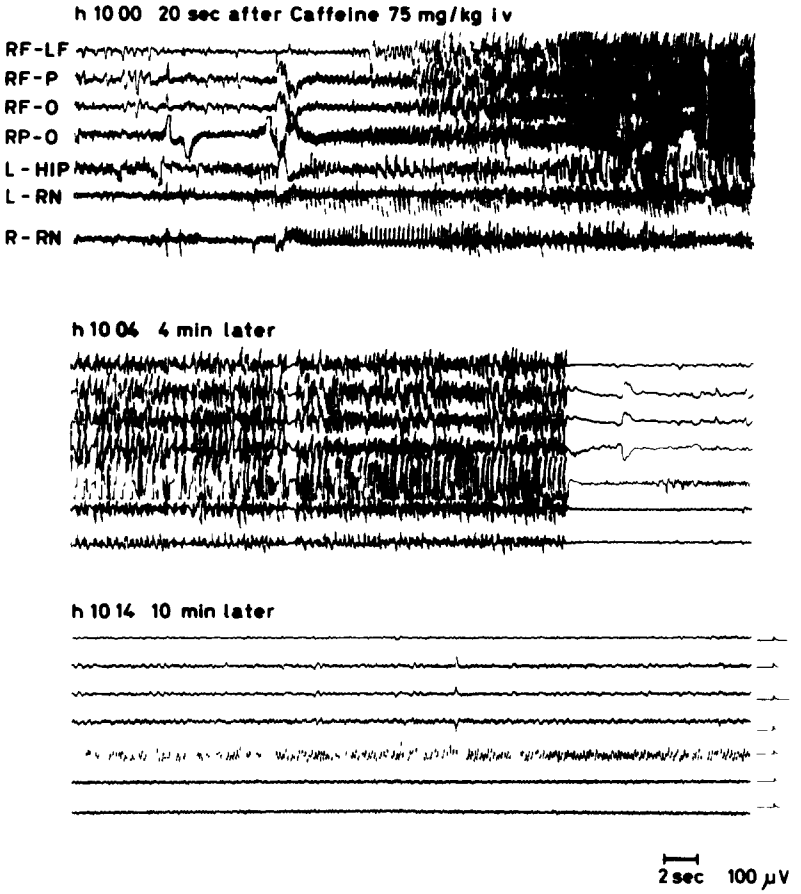

FIG 1 EEG seizures induced by caffeine in the rabbit Upper record caffeine (75 mg/kg IV) elicited, within a few seconds, EEG "grand mal" ictal seizures characterized by high voltage (300–500 μV)-high frequency (10–20 Hz) spikes which started in red nucleus and then spread to the hippocampus and to all the cortical regions Middle record 4 min later, the convulsive pattern was followed by a postictal depression Lower record 10 min later, the EEG appeared desynchronized Leads L left, R right, F anterior sensorimotor cortex, P posterior sensorimotor cortex, O optic cortex, HIP dorsal hippocampus, RN red nucleus

ceptors is still unclear Skerritt *et al* [15] suggested that CBZ may possess both A_1 receptor agonist activity and A_2 receptor antagonistic activity The hypothesis that CBZ may exert some of its anticonvulsant effects by acting as a partial agonist at adenosine receptors has also been proposed [16]

The purpose of the present experiments was to further investigate the anticonvulsant properties of both L-PIA and CBZ An EEG and behavioral study on the effects of L-PIA and CBZ against the convulsions induced by caffeine was undertaken in rabbits Moreover, experiments were carried out in order to study the influence of L-PIA and CBZ on the effects of pentylenetetrazole (PTZ)

METHOD

Electroencephalographic recordings were obtained from 130 adult male rabbits The animals were prepared for the acute EEG experiments under local anaesthesia with 2% xylocaine. Six screw electrodes were fixed over the sensorimotor and optic cortices Concentric deep electrodes were placed into the dorsal hippocampus and the red nucleus according to a technique described previously [10] Rabbits were then placed in a restraining box and were connected through long wires to an EEG Galileo apparatus (Model E 10b Polygraph) Postmortem histological examinations confirmed the location of the deep electrodes

All compounds were administered intravenously. PTZ, caffeine benzoate and L-PIA were dissolved in water, CBZ was dissolved in a mixture of 40 parts of polyethylenglycol and 60 parts of water Drug doses refer to the weight of the base

Student's t-test was used to assess the significance between the different groups of experiments

RESULTS

Motor and EEG Effects of Caffeine and PTZ

Caffeine Previous experiments performed in this laboratory [13] have demonstrated that caffeine at the doses ranging from 10 to 50 mg/kg caused EEG desynchronization The duration of this effect was dose-related and varied from 10 to 60 minutes Behavioral signs of the arousal were noticed after administration of high doses (25–50 mg/kg) the animals

TABLE 1

INFLUENCE OF L-PIA AND CBZ ON THE MOTOR CONVULSIONS INDUCED BY CAFFEINE AND PTZ IN RABBITS

Treatment (mg/kg IV)	No Animals	No Convulsions	Percent of Protective Effect
CA 75	10	10	—
L-PIA 1 + CA 75	8	6	25%
L-PIA 3 + CA 75	10	4	60%†
L-PIA 4 + CA 75	6	—	100%‡
CBZ 20 + CA 75	6	—	100%‡
CBZ 5 + CA 75	6	6	—
L-PIA 1 + CBZ 5 + CA 75	6	2	66 6%†
L-PIA 3 + CBZ 5 + CA 75	6	—	100%‡
PTZ 20	6	6	—
L-PIA 5 + PTZ 20	7	4	42 8%§
DZ 1 + PTZ 20	6	—	100%¶
CBZ 20 + PTZ 20	10	6	40%§
CBZ 20 + CA 10 + PTZ 20	6	6	—#

*=n s vs CA 75, †=$p<0$ 01 vs CA 75, ‡=$p<0$ 001 vs CA 75
§=$p<0$ 01 vs PTZ 20, ¶=$p<0$ 001 vs PTZ 20, #=$p<0$ 01 vs CBZ 20 + PTZ 20

presented raising of the head and ears and widening of the eyes

A total of 10 rabbits were injected with 75 mg/kg of caffeine This dose elicited a brief period of desynchronization followed by a "grand mal" ictal seizure usually starting in the hippocampal and red nucleus leads and then spreading to all cortical regions. The "grand mal" attack consisted of high voltage (300–500 μV)-high frequency (10–20 Hz) spikes which lasted for 0 5–3 minutes This pattern was followed by a postictal depression The EEG seizures were accompanied by chewing, tremors, head extension up to opisthotonus and tonic-clonic convulsions followed by death in 4 out of 10 animals (Fig. 1)

PTZ A total of 12 rabbits were injected with PTZ (10–20 mg/kg) PTZ (10 mg/kg) caused a brief period of desynchronization followed by the characteristic spike-and-wave complexes in the sensorimotor and associative cortices (Fig 4) This EEG pattern was occasionally accompanied by ear twitchings The dose of 20 mg/kg induced within 30–40 seconds a "grand mal" ictal seizure in cortical and subcortical regions in all animals The EEG "grand mal" attack consisted of continuous high voltage (300–600 μV) and high frequency (20 Hz) spikes lasting about 60 seconds Concomitantly, the animals showed a tonic extension of the head and of the hindlimbs This tonic phase was followed by a clonic one characterized by a progressive slowing of the spike frequency concomitant with repeated violent movements of the head and limbs Then a characteristic isoelectric pattern occurred, followed later by trains of spike-and-waves The electrical silence and the spike-and-waves were associated with the postictal behavioral depression and lack of response to stimuli

Effects of L-PIA on the Motor and EEG Convulsions Induced by Caffeine and PTZ

In a series of experiments carried out in 12 rabbits the influence of various doses of L-PIA on behavior and EEG was studied. Within 1 min following administration of L-PIA (1 mg/kg), only an EEG synchronization consisting of spindles and slow waves (3 Hz, 300 μV) occurred. Higher doses (2–3 mg/kg) elicited a slow waves pattern characterized by high voltage (400–500 μV) and reduced frequency (2 Hz) in sensorimotor optic cortex and hippocampal areas With the highest doses (4 and 5 mg/kg) the slowing of the record was much more marked up to the appearance of a cortical tracing without spindles, and full of synchronous slow waves (500–600 μV), a complete disruption of the theta hippocampal rhythm occurred At the same time, the animals showed sleep posture and muscle relaxation.

The influence of pretreatment (10 min before) with L-PIA on the convulsions due to caffeine (75 mg/kg) was studied in 3 groups of rabbits treated respectively with 1, 3 and 4 mg/kg L-PIA caused a dose related inhibition of the motor convulsions and the EEG "grand mal" ictal seizure elicited by caffeine (75 mg/kg) (see Table 1) L-PIA administered to 8 animals at the dose of 1 mg/kg was able to prevent motor convulsions and the EEG "grand mal" ictal seizure elicited by caffeine in 2 out of 8 animals These two animals showed a subconvulsive pattern characterized by scattered high voltage spikes associated with chewing and slight tremors. The dose of 3 mg/kg administered to 10 animals prevented caffeine-induced convulsions in 6 out of 10 animals Half of these animals showed the same subconvulsive pattern described above, while the remaining half presented an EEG desynchronization Full protection was observed in the 6 rabbits treated with L-PIA 4 mg/kg (Fig. 2) In none of the animals treated with L-PIA did caffeine induce death

The influence of pretreatment (10 min before) with a high dose (5 mg/kg IV) of L-PIA on the convulsions induced by PTZ (20 mg/kg IV) was studied in 7 rabbits L-PIA was able to prevent the EEG and motor convulsions only in 3 out of 7 animals (see Table 1). Instead of EEG "grand mal" ictal seizures, these animals presented spike-and-wave complexes with intermingled slow waves (3–5 Hz). In all animals L-PIA inhibited the tonic motor convulsions elicited by PTZ (lack opisthotonus) Lower doses of L-PIA were ineffective.

In order to better elucidate the nature of the antagonistic effects of L-PIA towards the convulsions due to both caffeine and PTZ, additional comparative experiments with

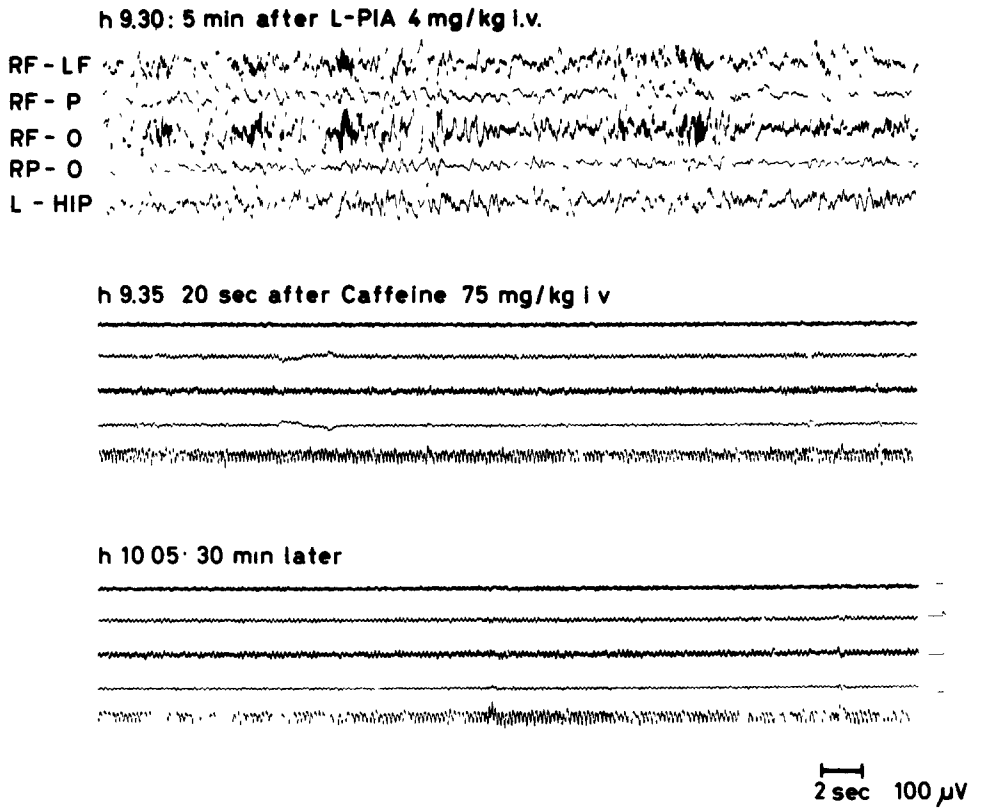

FIG 2 Antagonistic effects of L-PIA towards the convulsions due to caffeine in the rabbit Upper record L-PIA (4 mg/kg IV) elicited a slow waves pattern characterized by high voltage (500–600 μV)-reduced frequency (2 Hz) in the cortical leads and disruption of the theta hippocampal rhythm Middle record the injection of caffeine (75 mg/kg IV) did not induce EEG seizures when the animal was pretreated (10 min before) with L-PIA The EEG "grand mal" ictal seizures was replaced by a desynchronized pattern Lower record 30 min after the injection of caffeine the record appeared still desynchronized Leads See Fig 1

diazepam (1 mg/kg) were carried out in 6 rabbits None of the rabbits treated with 1 mg/kg of diazepam and challenged (10 min later) with PTZ 20 mg/kg exhibited tonic motor convulsions and the EEG "grand mal" ictal seizure The EEG modifications induced by diazepam were present in the record

Pretreatment with diazepam (1 mg/kg) was able to prevent the EEG and motor convulsions elicited by caffeine (75 mg/kg) only in 4 out of 6 animals Half of these ones showed, instead of EEG seizures, a long lasting EEG desynchronization The others presented short lasting bursts of spikes in optic and hippocampal areas

Effects of CBZ on the Motor and EEG Convulsions Induced by Caffeine and PTZ

The influence of various doses (5–20 mg/kg) of CBZ on behavior and EEG was studied in a separate series of experiments carried out in 8 rabbits One–two minutes after administration of CBZ at the doses of 5–10 mg/kg a slowing of the basal EEG activity occurred the spindles were present and associated with rare slow waves (200–400 μV, 3–4 Hz) in the sensorimotor and optic areas. Administration of 15–20 mg/kg of CBZ caused an EEG consisting in less frequent spindles and numerous slow waves, the disruption of theta waves occurred The EEG response to external stimulation was absent

The influence of the pretreatment (10 min before) with CBZ (20 mg/kg) on the convulsions due to caffeine (75 mg/kg) was studied in 6 rabbits CBZ was able to prevent the caffeine-induced EEG and motor seizures in 100% of the animals The EEG seizures were replaced by EEG desynchronization (Fig 3) Lower doses than 20 mg/kg of CBZ were ineffective

CBZ was weakly effective on the convulsions due to PTZ (20 mg/kg) PTZ was administered 10 min after CBZ treatment Only a dose of 20 mg/kg of CBZ was able to prevent the EEG and motor convulsions in 4 out of 10 animals Instead of EEG seizures, trains of spike-and-wave complexes accompanied by excitation and tremors and lasting 2 min were seen. Then the EEG effects of CBZ appeared again in the record and the animals were sedated Of the remaining 6 animals, 4 presented EEG and motor seizures followed by electrical silence, the other 2 exhibited spike-and-wave complexes lasting 100 seconds and followed by EEG and motor convulsions without opisthotonus

In a separate series of experiments carried out in 8 rabbits the influence of caffeine (10 mg/kg) on the protective action of CBZ towards PTZ-induced convulsions was studied The animals were treated with caffeine 5 min after CBZ and 5 min before PTZ. Caffeine (10 mg/kg) counteracted the protective effect of CBZ against PTZ-induced seizures A few seconds

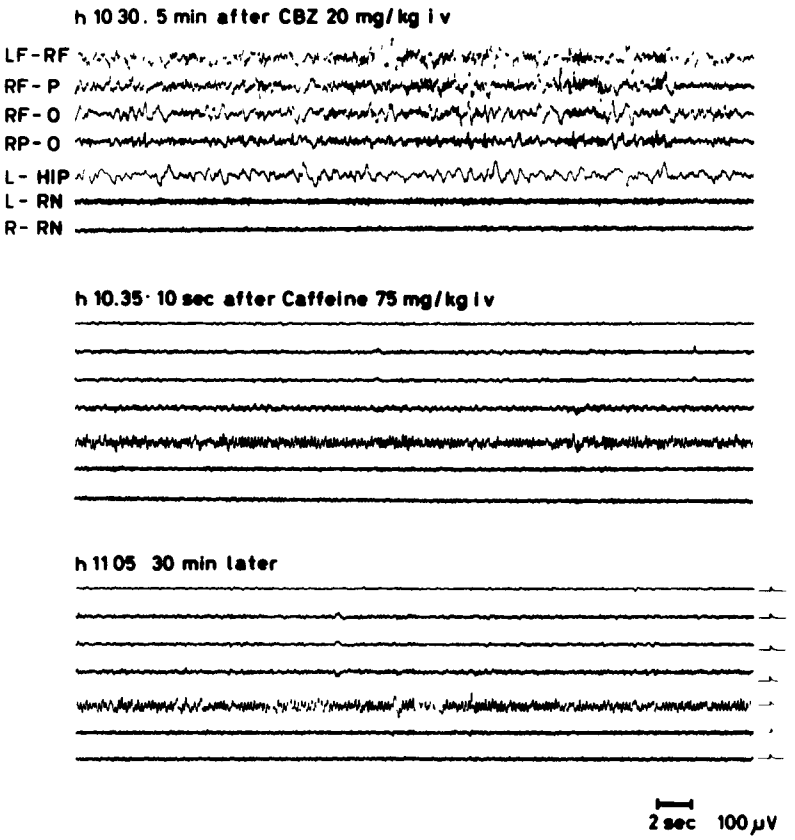

FIG 3 Antagonistic action of CBZ on the caffeine-induced seizures in the rabbit Upper record 5 min after the injection of CBZ (20 mg/kg IV) the EEG record was characterized by less frequent spindles and numerous slow waves (300–500 μV), the disruption of theta waves occurred Middle record the pretreatment (10 min before) with CBZ prevented the caffeine-induced EEG seizures The EEG "grand mal" ictal seizure was replaced by EEG desynchronization Lower record 30 min after the injection of caffeine the record appeared still desynchronized Leads See Fig 1

after the administration of PTZ (20 mg/kg), 100% of CBZ + caffeine treated animals presented the motor and EEG "grand mal" ictal seizure followed by electrical silence

Effects of Combined Treatment of CBZ + L-PIA on Caffeine-Induced Convulsions

The influence of pretreatment with CBZ (5 mg/kg) on the antagonistic effect of L-PIA (1 and 3 mg/kg) against the EEG and motor convulsions due to caffeine (75 mg/kg) was studied in 12 rabbits (see Table 1) Of the 6 animals pretreated with CBZ + L-PIA (1 mg/kg) 4 out of 6 animals did not exhibit EEG and motor convulsions after the administration of caffeine (75 mg/kg), while the remaining animals presented motor and EEG "grand mal" seizures (Table 1). None of the second group of animals pretreated with CBZ + L-PIA (3 mg/kg) exhibited caffeine-induced motor and EEG seizures

Effects of CBZ, L-PIA and CBZ + L-PIA on PTZ-Induced Spike-and-Wave Complexes

The influence of pretreatment with CBZ (20 mg/kg) and L-PIA (4–5 mg/kg) was studied in 8 animals. Animals pretreated either with CBZ or with L-PIA did not show spike-and-wave complexes which normally occur after PTZ 10 mg/kg (Fig 4) The combined administration of CBZ + L-PIA was studied in 6 animals Pretreatment with ineffective doses of both CBZ (10 mg/kg) and L-PIA (2 mg/kg) was able to prevent the appearance of spike-and-wave complexes elicited by PTZ (10 mg/kg) (Fig 4)

DISCUSSION

In the present experiments some aspects of the anticonvulsant activity of L-PIA and CBZ have been investigated in rabbits

Our results demonstrate that L-PIA is about two times more effective in antagonizing EEG and motor convulsions elicited by caffeine than in antagonizing those induced by PTZ These data further suggest that a block of central adenosine receptors can be linked to the epileptogenic effects of methylxanthines On the other hand, we reported that L-PIA counteracts, at a very low dose (0.05 mg/kg), the potentiating effect of caffeine on electrically-induced *after discharge* in rabbits [14] This fact shows that the anticonvulsant activity of L-PIA is more marked towards proconvulsant doses of methylxanthines than convulsant ones These data suggest that the convulsant action of

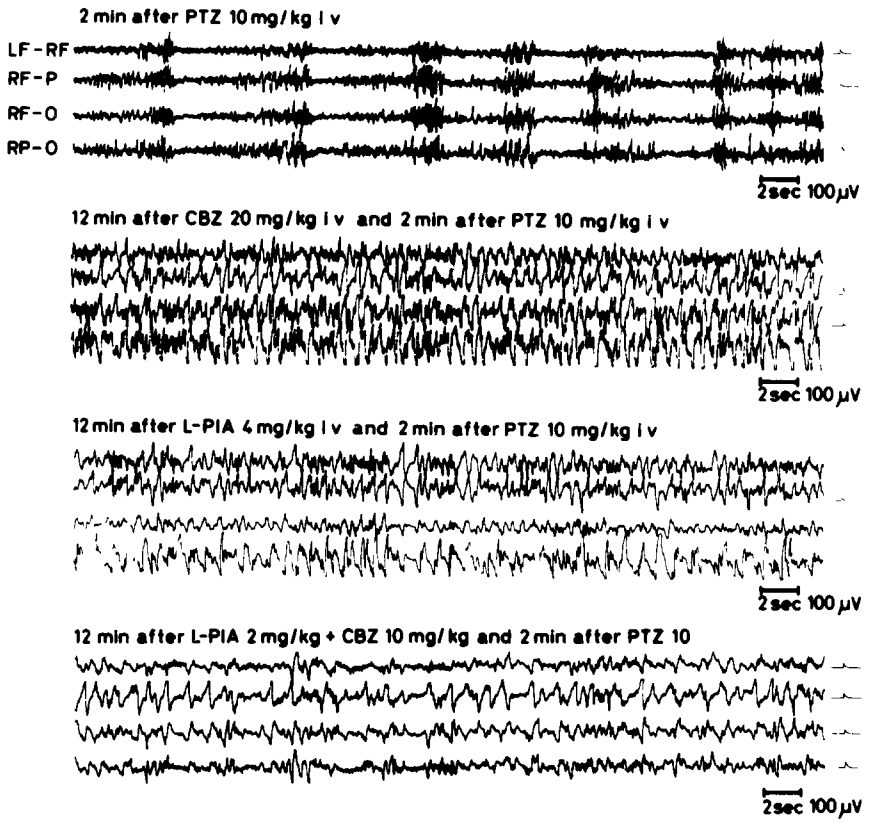

FIG 4 Effects of CBZ, L-PIA and CBZ + L-PIA towards PTZ-induced spike-and-wave complexes in the rabbit First record PTZ (10 mg/kg IV) induced characteristic, rhythmic spike-and-wave complexes in sensorimotor and associative cortices Second record the pretreatment (10 min before) with a high dose of CBZ (20 mg/kg IV) prevented the PTZ-induced spike-and-wave complexes Third record the pretreatment with a high dose of L-PIA (5 mg/kg IV) prevented the PTZ-induced spike-and wave complexes Fourth record the combined pretreatment with CBZ + L-PIA at lower doses (10 and 2 mg/kg respectively) Leads See Fig 1

methylxanthines can be mediated not only by A_1 purinergic receptors, as it appears demonstrated for the proconvulsant effects caused by slow doses, but also by other subclasses of adenosine receptors or by other neurotransmitter system correlated to them The fact that high doses of L-PIA (5 mg/kg) are required to antagonize at least partially PTZ-induced seizures confirms our previous data [14] showing that L-PIA is able to reduce the duration of the electrically-induced *after discharge* not modified by caffeine only at the highest dose (5 mg/kg) These results agree also with those of Bortolotto *et al* [3] who found that 2-chloroadenosine at the dose of 5 mg/kg blocks the evolution of either amygdaloid or hippocampal kindled seizures in rats. These findings suggest that L-PIA is weakly effective against convulsions electrically-induced or elicited by drugs having different action mechanism from methylxanthines

The mechanism of the anticonvulsant action of CBZ is still unknown. Recent studies focus the attention on the possible interactions of this drug with adenosine receptors Many authors [9,21] agree with the A_2 receptor antagonistic activity of CBZ, but the exact nature (agonist, partial agonist, antagonist) of its interaction at the A_1 receptors, responsible for its effects at the therapeutic doses [21], is not definitively explained Our results show that CBZ is able to prevent caffeine-induced convulsions at the dose of 20 mg/kg At the same dose, CBZ is more than two times less effective towards convulsions elicited by PTZ

The administration of an ineffective dose of CBZ (5 mg/kg) is able to enhance the protective action of L-PIA towards caffeine-induced convulsions L-PIA (1 mg/kg) does not significantly antagonize the caffeine-induced convulsions The antagonism becomes highly significant with the combined administration of L-PIA 1 mg/kg + CBZ 5 mg/kg. This synergistic action between CBZ and L-PIA is also present towards a non convulsant dose of PTZ (10 mg/kg) In fact, the spike-and-wave complexes elicited by 10 mg/kg of PTZ are prevented by the combined treatment of ineffective doses of L-PIA and CBZ (2 and 10 mg/kg respectively) A dose of caffeine (10 mg/kg), 7 5 times lower than the convulsant one, can revert the protective effects induced by CBZ against PTZ-induced convulsions These data agree with those of Skerritt *et al* [16], who found that theophylline pretreatment significantly decreased the anticonvulsant effects of CBZ against PTZ-induced seizures in mice

Nevertheless none of these experiments byself provide a direct evidence that CBZ interacts with A_1 adenosine receptors, our results are consistent with this hypothesis Other pharmacological studies are required to elucidate the central

and peripheral actions of CBZ in relation to the purinergic system

It is worth noting that an interaction with adenosine receptors could not be the only explanation of the anticonvulsant action of CBZ. In fact, recent studies reported that CBZ causes an increase of GABA concentration in the temporal cortex of amygdaloid-kindled rats [8] It has also a high inhibitory potency for the "peripheral type" benzodiazepine receptors [12] and a synergistic action on the dopaminergic system [1]

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REFERENCES

1 Barros, H M T and J R Leite Effects of acute and chronic carbamazepine administration on apomorphine-elicited stereotypy *Eur J Pharmacol* **123:** 345–349, 1986
2 Bernard, P , D Wilson, G Pastor, W Brown and T M Glenn Possible involvement of adenosine receptors in the electroshock anticonvulsant effects of carbamazepine, diphenylhydantoin, phenobarbital and diazepam *Pharmacologist* **25:** 164, 1983
3 Bortolotto, Z A , L E M Mello, L Turski and E A Cavalheiro Effects of 2-Chloroadenosine on amygdaloid and hippocampal kindled seizures *Arch Int Pharmacodyn* **277:** 313–320, 1985
4 Daly, J W , P ButtsLamb and W Padgett Subclass of adenosine receptors in the central nervous system interaction with caffeine and related methylxanthines *Cell Mol Neurobiol* **3:** 69–80, 1983
5 Dragunov, M , G V Goddard and R Laverty Is adenosine an endogenous anti-convulsant? *Epilepsia* **26:** 480–487, 1985
6 Dunwiddie, T V and T Worth Sedative and anticonvulsant effects of adenosine analogs in mouse and rat *J Pharmacol Exp Ther* **220:** 70–76, 1982
7 Gilbert, R M Caffeine as a drug of abuse In *Research Advances in Alcohol and Drug Problems,* Vol 3, edited by R J Gibbins, Y Israel and H Kalant New York Plenum Press, 1976
8 Higuchi, T , O Yamazaki, A Takazawa, N Kato, N Watanabe, Y Minatogawa, J Yamazaki, H Ohshima, S Nagaki, Y Igarashi and T Noguchi Effects of carbamazepine and valproic acid on brain immunoreactive somatostatin and γ-aminobutyric acid in amygdaloid kindled rats *Eur J Pharmacol* **125:** 169–175, 1986
9 Lewin, E and V Bleck Cyclic AMP accumulation in cerebral cortical slices effect of carbamazepine, phenobarbital and phenytoin *Epilepsia* **18:** 237–242, 1977
10 Longo, V G *Electroencephalographic Atlas for Pharmacological Research* Amsterdam Elsevier Publishing Company, 1962
11 Maitre, M , L Ciesielski, A Lehmann, E Rempf and P Mandel Protective effects of adenosine and nicotinamide against audiogenic seizure *Biochem Pharmacol* **23:** 2807–2816, 1974
12 Marangos, P J , R M Post, J Patel, K Zander, A Parma and S Weiss Specific and potent interactions of carbamazepine with brain adenosine receptors *Eur J Pharmacol* **83:** 175–182, 1983
13 Polc, P , E P Bonetti, L Pieri, R Cumin, R M Angioi, H Mohler and W E Haefely Caffeine antagonizes several central effects of diazepam *Life Sci* **28:** 2265–2275, 1981
14 Popoli, P , S Sagratella and A Scotti de Carolis An EEG and behavioural study on the excitatory properties of caffeine in rabbits *Arch Int Pharmacodyn* **290:** 5–15, 1987
15 Skerritt, J H , L P Davies and G A R Johnston Interaction on the anticonvulsant carbamazepine with adenosine receptors 1 Neurochemical studies *Epilepsia* **24:** 634–642, 1983
16 Skerritt, J H , G A R Johnston and S Chen Chow Interaction of the anti-convulsant carbamazepine with adenosine receptors 2 Pharmacological studies *Epilepsia* **24:** 643–650, 1983
17 Snyder, S H , S J Katims, Z Annau, R F Bruns and J W Daly Adenosine receptors and behavioral actions of methylxanthines *Proc Natl Acad Sci USA* **78:** 3260–3264, 1981
18 Stirt, J A Aminophylline is a diazepam antagonist *Anesth Analog* **60:** 767–768, 1981
19 Thithapandha, A , H M Maling and J R Gillette Effects of caffeine and theophylline on activity of rats in relation to brain xanthine concentrations *Proc Soc Exp Biol Med* **6:** 139–582, 1972
20 Vellucci, S V and R A Webster Antagonism of caffeine-induced seizures in mice by Ro 15-788 *Eur J Pharmacol* **97:** 289–293, 1984
21 Weir, R L , W Padgett, J W Daly and S M Anderson Interaction of anticonvulsant drugs with adenosine receptors in the central nervous system *Epilepsia* **25:** 492–498, 1984
22 Yarnell, P R and N S Chu Focal seizures and aminophylline *Neurology* **25:** 819–822, 1975