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Carbamazepine distinguishes between adenosine receptors that mediate different second messenger responses

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The mechanism of the therapeutic and prophylactic effects of carbamazepine (CBZ) in affective psychoses is unknown but may in part be related to the potent competitive interaction of CBZ with adenosine-binding sites in the brain. The anticonvulsant and sedative properties of CBZ are reminiscent of the effects evoked by adenosine-agonists and contrast sharply with the opposite actions of adenosine-antagonists like caffeine. However, indirect evidence suggests an antagonist- rather than an agonist-like activity of CBZ at adenosine-receptors. We have used various model systems, in which adenosine receptor subtypes mediate different second messenger-responses, to investigate this apparent paradox. CBZ was found to antagonize the A_1-receptor-mediated inhibition of cyclic AMP accumulation in cultured astroblasts and in GH_3-cells. Furthermore, CBZ also inhibits the adenosine-induced increase in the level of cyclic AMP in cultured astroblasts, which is mediated by low-affinity A_{2b}-receptors. In contrast, CBZ does not block the inhibition elicited by adenosine-agonists of the agonist-induced increased formation of inositolphosphates in human neutrophils, which is mediated by high-affinity A_{2a}-receptors. The specific antagonism by CBZ of A_1- but not of high-affinity A_{2a}-receptors was further supported by binding experiments using rat brain membranes. These results suggest that the paradox of CBZ's antagonistic effects at adenosine-receptors might be at least partially reconciled by a selective antagonistic action of CBZ at A_1 receptors but not at high-affinity A_{2a}-receptors.

Adenosine receptors; Cyclic AMP; Inositol phosphates; Astroglia; GH_3-cells; Neutrophils (human)

1. Introduction

The tricyclic iminostilbene-derivative carbamazepine (CBZ) is well known for its anticonvulsive properties and its efficacy in the treatment of paroxysmal pain syndromes. Over the last few years evidence has accumulated that CBZ is also effective in the treatment of acute mania and as a prophylactic agent in manic-depressive illness (for recent reviews see Elphick, 1988; Post, 1987, 1990; Schmidt and Greil, 1987). The anticonvulsive properties of CBZ may predominantly be due to allosteric blockade of voltage-sensitive Na^+-channels (for review see Catteral, 1987), while $GABA_B$ mechanisms may account for its antinociceptive properties (for review see Post, 1990). Among the various other potential mechanisms that may be responsible for CBZ's efficacy in affective psychoses (for review see Elphick, 1988; Post, 1987, 1990) its interaction with adenosine binding sites in the brain has received special attention (Fujiwara et al., 1987; Gasser et al., 1988; Marangos et al., 1985, 1987a,b,c; Phillis, 1984; Skerritt et al., 1983a, b; Weir et al., 1984). The clinical properties of CBZ are reminiscent of the anticonvulsive, sedative and anxiolytic effects of adenosine-agonists and contrast sharply to the opposite actions of adenosine-antagonists like caffeine (for review see Bridges et al., 1988). Although this would suggest that CBZ might have adenosine-agonist properties, there is substantial indirect evidence to the contrary. Chronic administration of CBZ to rats, like that of caffeine, results in persistent up-regulation of adenosine binding sites in the brain (Daval et al., 1989; Marangos et al., 1985, 1987b). In addition, CBZ's effects on adenosine binding sites are affected by temperature and guanyl nucleotides in a manner typical for adenosine antagonists (Marangos et al., 1987b).

Possible mixed agonist-antagonist properties of CBZ and/or differential effects on adenosine receptor subtypes have been suggested to account for this paradox (Post, 1987). Adenosine receptors have been originally distinguished as A_1-receptors that inhibit and A_2-receptors that activate adenylate cyclase (Londos et al., 1980;

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Van Calker et al., 1978, 1979). Based on more recent evidence indicating that adenosine receptor-regulated events might in several cases also be independent of cyclic AMP, adenosine receptors are now classified according to the structure-activity-relationship (SAR) of various adenosine analogues (Hamprecht and Van Calker, 1985). In addition, A_2-receptors could be further subdivided into high-affinity A_{2a}-receptors and low-affinity A_{2b}-receptors, which apparently also show differences in the SAR of newly developed adenosine-analogues (Bruns et al., 1987).

To assess directly the question of possible agonist or antagonist actions of CBZ at adenosine receptor subtypes, we have investigated the effects of CBZ in cellular model systems, in which adenosine receptor subtypes mediate different second messenger-responses. The results indicate that CBZ antagonizes the effects of adenosine at A_1-receptors but not at A_{2a}-receptors.

2. Materials and methods

2.1. Materials

Eagle's basal medium (with Earle's salts) without inositol was prepared by Serva, all other cell culture media and sera were obtained from Boehringer, Mannheim. Myo-[^{3}H]inositol (with PT6-271) was from Amersham, Ficoll-Hypaque from Pharmacia. 2-Chloro-N^6-[^{3}H]cyclopentyladenosine ([^{3}H]CCPA) was obtained from NEN, 8-cyclopentyl-1,3-[^{3}H]dipropylxanthine ([^{3}H]DPCPX) from Amersham. All other chemicals were from Sigma.

2.2. Cell culture

GH_3-cells were a gift from Dr. B. Hamprecht, Physiologisch-Chemisches Institut, Tübingen, F.R.G. They were cultivated in Ham's F 10 medium (Boehringer, Mannheim) containing 2.5% fetal calf serum and 15% horse serum (Boehringer) in plastic tissue culture flasks (Falcon or Costar) in a humidified atmosphere (5% CO_2) at 37°C. The medium was changed two to three times a week, depending on the cell density and the cells were subcultivated every 1-2 weeks. Cells were detached by vigorous pipetting, plated on tissue culture dishes 60 mm in diameter (Nunc) and grown to a cell density of 1-3 million cells per dish.

Astroblast cultures were prepared by mechanical dissociation of newborn mouse or rat brain and cultivated as described previously (Van Calker et al., 1979).

2.3. Isolation of neutrophils

Human neutrophils were isolated from heparinized whole blood obtained from healthy volunteers by means of sedimentation through dextran (0.6% w/v) followed by centrifugation through Ficoll-Hypaque and hypotonic lysis of contaminating erythrocytes (Dougherty et al., 1984; Boyum, 1984).

2.4. Measurement of inositol phosphate production

Washed neutrophils were suspended (50 million cells per ml) in Eagle's basal medium (with Earle's salts) without inositol containing deoxyribonuclease (50 U/ml), fetal calf serum (3%) and 50 μCi [^{3}H]inositol per ml and incubated at 37°C for 4-5 h in a shaking water bath. Thereafter cells were centrifuged, and washed two times with ice-cold Hank's balanced salt solution (HBSS) containing 20 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethansulfonic acid (HEPES), pH 7.4. 6 million cells were then incubated with HBSS at 37°C in the presence of cytochalasin B (5 μM), KCN (1 mM), LiCl (10 mM) and other additions as required in a final volume of 1 ml. Controls received the corresponding amount of vehicle (dimethylsulphoxide, final concentration 0.05%). The incubations were terminated at the desired times by addition of 1 ml ice-cold trichloroacetic acid (20% w/v). The samples were centrifuged and the pellet was washed once with distilled water. The combined supernatants were extracted with diethylether and fractionated by anion exchange chromatography on small Dowex columns as described previously (Van Calker et al., 1987).

Cultured GH_3-cells and astroblasts were labeled with [^{3}H]inositol, stimulated with drugs and analyzed for the formation of [^{3}H]inositol phosphates essentially as described previously for PC-12 cells (Van Calker et al., 1987).

2.5. Determination of cyclic AMP

Dishes containing GH_3-cells or astroblasts were washed twice with incubation buffer (118 mM NaCl, 4.7 mM KCl, 3 mM CaCl, 1.2 mM MgCl, 1.2 mM KH_2PO_4, 0.5 mM EDTA, 10 mM glucose and 20 mM HEPES, pH 7.4) and thereafter incubated at 37°C for 10 min with 2 ml of the same buffer containing the various additions. Controls received the same amount of vehicle (dimethylsulfoxide, final concentration 0.05%). The incubations were terminated by removal of the buffer and the addition of 1 ml ice-cold trichloroacetic acid (10% w/v). After removal of the trichloroacetic acid by extraction with diethyl ether (3 times 4 ml), the samples were fractionated by anion chromatography on small Dowex columns (Bio Rad AG 1 × 2) as described (Van Calker et al., 1979). The cyclic AMP content in the samples was determined by a commercially available protein binding assay (Amersham).

2.6. Radioligand binding

Membranes from whole rat brain and rat striatum were prepared as described previously (Lohse et al., 1987). Binding of [^{3}H]5′-*N*-ethylcarboxamido-adenosine ([^{3}H]NECA) (10 nM) in the presence of N^6-cyclopentyladenosine (CPA) (50 nM) to striatal membranes was performed according to Bruns et al. (1986) with the modifications described earlier (Lohse et al., 1987). Binding assays using [^{3}H]CCPA and [^{3}H]DPCPX were done as described previously (Lohse et al., 1987; Klotz et al., 1989).

3. Results

3.1. Effects of carbamazepine on adenosine A_1-receptors

Adenosine inhibits via A_1-receptors the increase in the accumulation of cyclic AMP, which is evoked in GH_3-cells by stimulation with vasoactive intestinal peptide (VIP) (Delahunty et al., 1988) (fig. 1). CBZ (50 μM) alone slightly reduces the VIP-induced stimulation of the accumulation of cyclic AMP (see legend to fig. 1). However, the most prominent effect of CBZ is a parallel shift to the right of the dose-response curve for the inhibitory action of adenosine (fig. 1). Similarly, also the A_1-receptor-mediated inhibition of the β-adrenoceptor-induced increased formation of cyclic AMP in cultured astroglia cells (Van Calker et al., 1978, 1979) is antagonized by CBZ (data not shown).

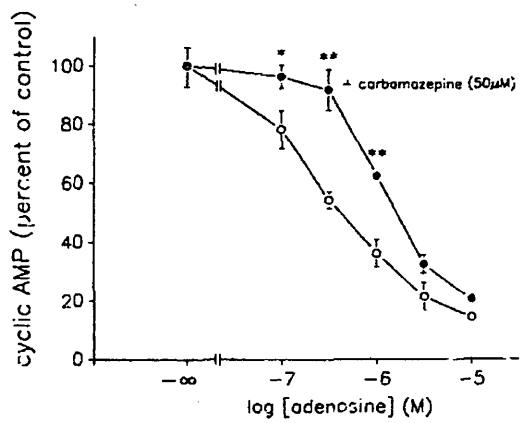

Fig. 1. Influence of carbamazepine (50 μM) on the inhibition by adenosine of the VIP-evoked increase in the level of cyclic AMP in GH_3-cells. Cells (1.6 million per dish) were incubated for 10 min in the presence of carbamazepine or vehicle (dimethylsulfoxide, final concentration 0.05%) and the various other additions. The cyclic AMP formed was assayed as described in Materials and methods. Controls (pmol cyclic AMP per million cells): basal, 1.0; VIP (0.1 μM), 101 ± 8 (= 100%); VIP + carbamazepine, 84 ± 7 (= 100%). Data given are means of triplicate determinations ± SD. SD's smaller than the size of the symbol are not shown. * $P < 0.05$, ** $P < 0.01$ (Student's t-test as compared to values without carbamazepine). Similar results were obtained in two additional independent experiments.

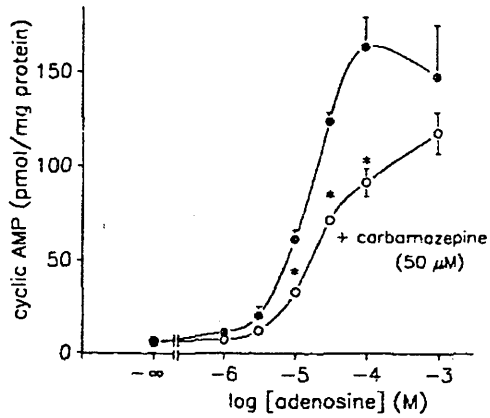

Fig. 2. Influence of carbamazepine (50 μM) on the increase in the level of cyclic AMP evoked by adenosine in cultured astroglia cells. Cells were obtained by mechanical dissociation of newborn rat brain and cultivated for 16 days as described previously (Van Calker et al., 1979). They were then incubated for 10 min with carbamazepine or vehicle, before the intracellular content of cyclic AMP was determined as described in Materials and methods. * $P < 0.01$. Other details are as in fig. 1. Similar results were obtained in two additional independent experiments.

3.2. Effects of carbamazepine on (low-affinity) adenosine A_{2b}-receptors

Adenosine and its analogues stimulate via adenosine A_2-receptors the accumulation of cyclic AMP in primary

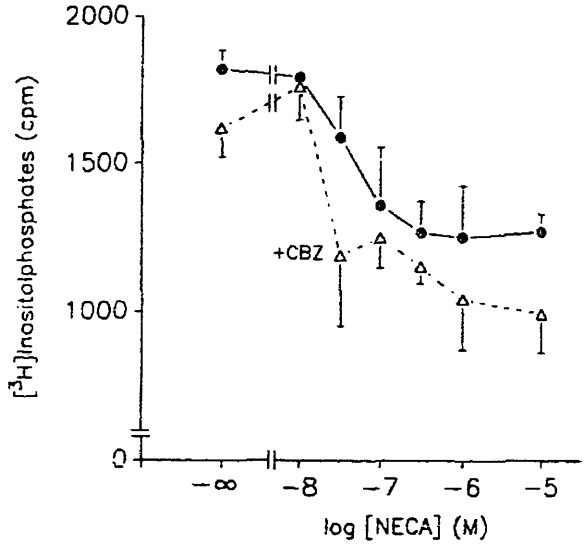

Fig. 3. Influence of carbamazepine (50 μM) on the inhibition by NECA of the fMLP-stimulated increase in the accumulation of inositol phosphates in human neutrophils. Neutrophils were isolated and stimulated with fMLP in the presence of carbamazepine or vehicle and various concentrations of NECA as described in Materials and methods. Similar results were obtained in two additional independent experiments.

cultures of perinatal rodent brain, mainly consisting of astroglia cells (Van Calker et al., 1979). The low-affinity A_2-receptors that mediate this effect resemble those which have been called A_{2b} (Bruns et al., 1987) and are found in virtually all grey matter areas of the brain (Daly et al., 1983). CBZ attenuates the increase in the level of cyclic AMP evoked by adenosine in the astroglia-rich cultures (fig. 2).

3.3. Effects of carbamazepine on the adenosine A_{2a}-receptor-mediated inhibition of inositol phosphate formation in human neutrophils

In human neutrophils adenosine and its analogues elicit only a minimal increase in the level of cyclic AMP but provoke a pronounced inhibition of the agonist-induced accumulation of inositol phosphates, which is independent of cyclic AMP (Van Calker and Steber, submitted). This effect is mediated via high-affinity adenosine A_2-receptors (Van Calker and Steber, submitted), which resemble those found e.g. in the striatum and called 'A_{2a}' (Bruns et al., 1987). In contrast to its effects on A_1- and A_{2b}-receptors, CBZ does not attenuate this effect but induces, if anything, rather a slight potentiation of the inhibition evoked by the adenosine-agonist 5′-*N*-ethylcarboxamidoadenosine (NECA) (fig. 3).

3.4. Effects of carbamazepine on the binding of radiolabeled A_1- and A_2-ligands at rat brain membranes

To further analyze the effects of CBZ at adenosine receptor subtypes we measured its interaction with A_1-receptors in binding assays with membranes from rat brain performed with the highly A_1-selective radioligands 2-chloro-N^6-[^{3}H]cyclopentyladenosine ([^{3}H]CCPA, an agonist) (Klotz et al., 1989) and 8-cyclopentyl-1,3-[^{3}H]dipropylxanthine ([^{3}H]DPCPX, an antagonist) (Lohse et al., 1987). The action of CBZ at high affinity A_{2a}-receptors was evaluated with membranes from rat striatum, using [^{3}H]NECA as a radioligand in the presence of N^6-cyclopentyladenosine (CPA) to block the binding to A_1-sites (Bruns et al., 1986). CBZ inhibited the binding of both [^{3}H]CCPA and [^{3}H]DPCPX to rat brain membranes (fig. 4). The displacement by CBZ of [^{3}H]DPCPX-binding was not influenced by the presence of 100 μM GTP. In contrast, CBZ did not affect at concentrations below 100 μM the binding of [^{3}H]NECA to striatal membranes (fig. 4).

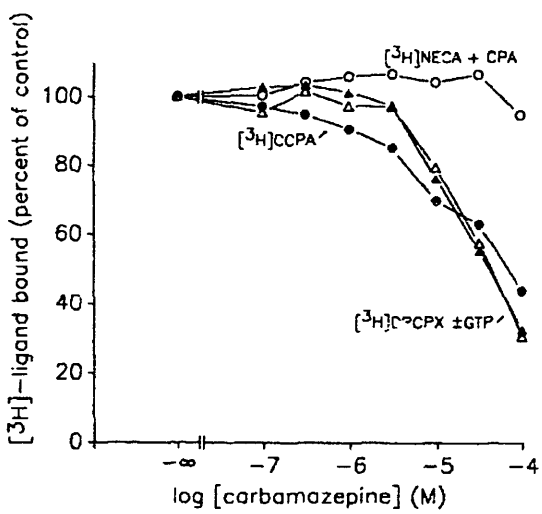

Fig. 4. Influence of carbamazepine on the binding of the radioligands [^{3}H]CCPA and [^{3}H]DPCPX to A_1-sites in rat brain membranes and of [^{3}H]NECA in the presence of CPA to A_2-sites in rat striatal membranes. Similar results were obtained in two additional independent experiments.

4. Discussion

The inhibitory effects of CBZ on adenosine-evoked second-messenger responses that are reported in the present study provide the first direct evidence that CBZ inhibits second messenger-responses mediated by adenosine A_1-receptors but not those mediated by high-affinity A_{2a}-receptors. CBZ induces a parallel shift to the right of the dose-response curve for the A_1-induced inhibition of the VIP-stimulated cyclic AMP accumulation in GH_3 -cells (fig. 1), as expected for a competitive interaction. In contrast, the A_{2a}-mediated inhibition of the fMLP-stimulated formation of inositol phosphates in human neutrophils is not antagonized by CBZ (fig. 3).

In addition to its antagonistic effect at A_1-receptors CBZ also inhibits the A_{2b}-receptor-mediated increase in cyclic AMP in cultured astroglia cells (fig. 2). Similarly, CBZ at high concentrations also attenuates the adenosine-evoked increase in the level of cyclic AMP in brain slices (Lewin and Bleck, 1977; Skerritt et al., 1983a; Weir et al., 1984), which is probably also mediated by low-affinity A_{2b}-receptors (Daly et al., 1983). These effects may be at least partially due to an antagonism of CBZ also at A_{2b}-receptors. However, the dose-response curve depicted in fig. 2 is not typical for a competitive interaction of CBZ with A_{2b}-receptors. Furthermore, by mechanisms other than competitive inhibition, CBZ also weakly attenuates the increase in the level of cyclic AMP evoked by the activation of putative A_{2a}-receptors in PC12 cells and platelets (Daly et al., 1988). Thus, mechanisms other than competitive inhibition could also account for the inhibition by CBZ of cyclic AMP accumulation in various tissues and cell types. A more detailed analysis of the mechanism of CBZ's inhibition of the adenosine-induced increase in cyclic AMP in astroblasts is hampered by the low affinity of the A_{2b}-receptors.

A selective interaction of CBZ with A_1-, but not A_{2a}-receptors was further supported by binding studies using [^{3}H]CCPA and [^{3}H]DPCPX as highly selective A_1-radioligands and [^{3}H]NECA in the presence of CPA as A_{2a}-radioligand (fig. 4). While the present work was in progress, similar conclusions have been drawn from binding studies performed with N^6-cyclohexyl-[^{3}H]adenosine and [^{3}H]NECA (Clark and Post, 1989).

CBZ's selective antagonism at A_1-receptors may explain why its profile of clinical and behavioral effects is different from that of non-selective adenosine-antagonists like theophylline and caffeine. Indeed, 8-cyclopentyltheophylline (CPT), which acts as a selective A_1-antagonist in vivo, does not have the stimulating effect on locomotor activity which occurs with theophylline. On the other hand, CPT has proconvulsant properties in animal models (for review see Bridges et al., 1988). Thus, CBZ's A_1-antagonistic properties are probably not involved in its anticonvulsant action, as already concluded from other evidence (Post, 1987).

Although apparently not involved in its anticonvulsive effects, the blockade of A_1-receptors by CBZ might be related to its efficacy as a prophylactic, antimanic and possibly also antidepressive agent in affective psychoses. Several A_1-antagonists show antidepressant-like activities in animal models (see Bridges et al., 1988 for review). In addition, effective antidepressive treatments like electroconvulsive shock (Newman et al., 1984; Gleiter et al., 1989) and REM sleep deprivation (Yanik and Radulovacki, 1987) up-regulate A_1-receptors, similar to chronic treatment with CBZ (Marangos et al., 1985, 1987b; Daval et al., 1989).

Some of CBZ's complex effects on various neurotransmitter systems seen in behavioral and biochemical studies (for review see Elphick, 1988; Post, 1987, 1990) could be indirectly mediated by the A_1-antagonistic action of CBZ, since the release of many excitatory and inhibitory neurotransmitters is inhibited by adenosine via A_1-receptors (for review see Bridges et al., 1988).

The use of CBZ as an alternative to lithium in the treatment of manic-depressive illness raises the question of whether or not there are also similarities in the biochemical effects of both drugs. The inhibitory effects of chronic lithium treatment on the agonist-stimulated increase in the accumulation of cyclic AMP (Belmaker, 1981; Ebstein et al., 1988) and inositol phosphates (Casebolt and Jope, 1989; Ebstein et al., 1988; Elphick et al., 1988; Godfrey et al., 1989; Kendall and Nahorski, 1987) may be involved in lithium's antimanic and prophylactic properties. CBZ inhibits the accumulation of cyclic AMP in brain slices stimulated by noradrenaline, ouabain and adenosine (Lewin and Bleck, 1977; Palmer et al., 1979; Skerritt et al., 1983a; Weir et al., 1984), although only at high concentrations. CBZ's effects on the agonist-evoked formation of inositol phosphates are controversial (Elphick et al., 1988; McDermott and Logan, 1989).

In addition to these possible direct effects on second messenger generation, CBZ might also interfere with the potent synergistic interactions of adenosine with various neurotransmitters in the regulation of both cyclic AMP and inositol phosphate formation (El-Etr et al., 1989; Hill and Kendall, 1987; Hollingsworth et al., 1986). The blockade by CBZ of A_1- and possibly also A_{2b}-receptors should inhibit these synergistic effects of adenosine and could thereby profoundly alter the regulation by various neurotransmitters of both second messenger systems. Thus, lithium ions and carbamazepine might, via different mechanisms, both elicit a dampening effect on second messenger generation that could be important for their similar profile of clinical efficacy in affective psychoses.

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