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Mechanisms of Action of Carbamazepine and Its Derivatives, Oxcarbazepine, BIA 2-093, and BIA 2-024*

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Carbamazepine (CBZ) has been extensively used in the treatment of epilepsy, as well as in the treatment of neuropathic pain and affective disorders. However, the mechanisms of action of this drug are not completely elucidated and are still a matter of debate. Since CBZ is not very effective in some epileptic patients and may cause several adverse effects, several antiepileptic drugs have been developed by structural variation of CBZ, such as oxcarbazepine (OXC), which is used in the treatment of epilepsy since 1990. (S)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (BIA 2-093) and 10,11-dihydro-10-hydroxyimino-5*H*-dibenz[*b*,*f*]azepine-5-carboxamide (BIA 2-024), which were recently developed by BIAL, are new putative antiepileptic drugs, with some improved properties. In this review, we will focus on the mechanisms of action of CBZ and its derivatives, OXC, BIA 2-093 and BIA 2-024. The available data indicate that the anticonvulsant efficacy of these AEDs is mainly due to the inhibition of sodium channel activity.

KEY WORDS: Antiepileptic drugs; mechanisms of action; carbamazepine; oxcarbazepine; BIA 2-093; BIA 2-024.

INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting about 50 million people worldwide. Phenobarbital, one of the first compounds utilized in the treatment of epilepsy, was introduced in 1912. Since then, several antiepileptic drugs (AEDs) have been developed, but only some of them have become established. It is estimated that the majority of epileptic patients are treated with only four drugs: phenobarbital, phenytoin, carbamazepine (CBZ) and valproic acid. CBZ (5*H*-dibenz[*b*,*f*]azepine-5-carboxamide) was introduced in the early sixties, and has become the most frequently prescribed drug for the treatment of several forms of epilepsy. CBZ is also used in the treatment of neuropathic pain (1) and in psychiatric disorders (2).

CBZ is an iminodibenzyl derivative, structurally similar to the tricyclic antidepressants (Fig. 1). This drug is extensively metabolized in the liver, and only 1% of the administered dose is excreted in the unchanged form. The main oxidative pathway involves the formation of an active metabolite, carbamazepine-10,11-epoxide (3), which possesses anticonvulsant properties similar to those of CBZ.

Overall, the treatment with CBZ is effective and safe. However, approximately 30–40% of epileptic patients do not respond very well to the treatment (4) and CBZ may cause some adverse effects. For example,

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acute CBZ toxicity at therapeutic doses affects central nervous system and gastrointestinal system, causing sedation, ataxia, dizziness, nausea, vomiting, constipation and diarrhea. Long-term treatment with CBZ may modify plasma lipids, changes the concentration of sex hormones, produces hyponatremia, increases appetite and causes weight-gain, reduces the number of white blood cells and induces several allergic reactions (2). CBZ may also interact with other AEDs or with other drugs, such as antibiotics, contraceptives and calcium channel blockers (5,6), and induces its own hepatic metabolism and that of a variety of other drugs. CBZ may also induce multiple cytochrome P450 subfamilies (7).

In recent years, several AEDs have been developed to improve the treatment of seizures resistant to treatment with currently available anticonvulsants, and to improve the tolerability and safety of AEDs. The anticonvulsant efficacy of these new drugs, such as vigabatrin, lamotrigin, gabapentin, felbamate and oxcarbazepine (OXC), does not seem to be greater than that of first generation drugs, but they are better tolerated and have lower adverse effects and interactions (8).

Oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine) (Fig. 1) was developed by structural variation of CBZ, and was introduced in 1990 (9). There exist striking species differences in the metabolism of OXC. In rats and dogs, the parent compound persists in fairly high concentrations, whereas in humans and other primates OXC is almost immediately converted to the main active metabolite, 10,11-dihydro-10-hydroxy-*5H*-dibenz[*b,f*]azepine-5-carboxamide (10-hydroxycarbazepine; 10-OH-CBZ). In these cases, it is considered a prodrug. OXC and CBZ have a comparable anticonvulsant efficacy, but OXC has the advantage of a low incidence of allergic reactions, enzyme induction and side effects (10,11). The main adverse effect of OXC is hyponatriemia, which may occur more frequently than with CBZ, but it is rarely symptomatic (8).

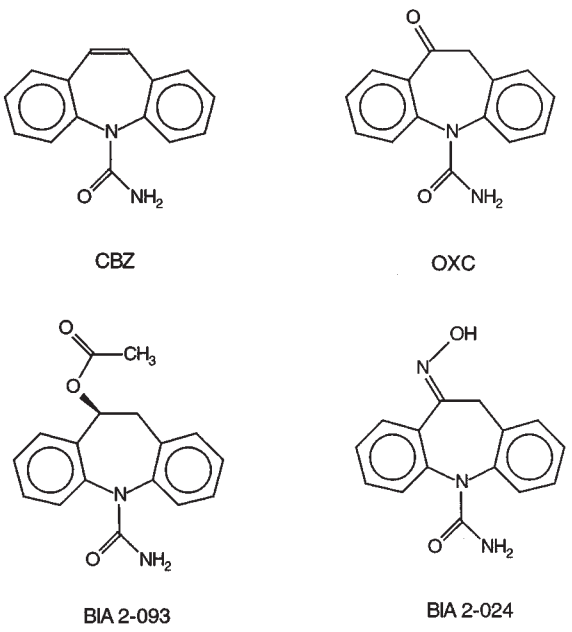

Fig. 1. Structural formulae of carbamazepine (CBZ), oxcarbazepine (OXC) and of two dibenz[*b,f*]azepine-5-carboxamide derivatives, BIA 2-093 and BIA 2-024.

In recent years, new drugs with anticonvulsant properties and structural features similar to established AEDs have been developed. (S)-(−)-10-acetoxy-10,11-dihydro-*5H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-093) and 10,11-dihydro-10-hydroxyimino-*5H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-024) are new putative AEDs (Fig. 1), developed by BIAL (Portela & Co., Portugal), chemically related to CBZ and OXC, but specifically designed to circumvent their further degradation to toxic metabolites. BIA 2-093 and BIA 2-024 were found to be effective anticonvulsants. Both compounds exerted protective effects against seizures induced by maximal electroshock and were also effective in protecting rats against convulsions induced by metrazol, having greater or similar anticonvulsant potency than that of reference compounds, CBZ or OXC (12,13).

It is widely accepted that the majority of AEDs act by more than one mechanism. This review focuses on the mechanisms of action of CBZ and of its derivatives, OXC, BIA 2-093 and BIA 2-024.

Carbamazepine. A large body of evidence indicates that CBZ may interact with different types of channels and receptors, as summarized in Table I. The main target of CBZ are voltage-dependent sodium channels. CBZ and carbamazepine-epoxide reduce the frequency of sustained repetitive firing of action potentials in cultured mammalian central neurons. CBZ inhibits high frequency but not low frequency firing (15,16). Such voltage- or frequency-dependent block is ascribed to a voltage-dependent inhibitory effect on voltage-gated sodium channels. It has been shown that the inhibition of sodium currents in cultured neuroblastoma cells and in small cells from adult rat dorsal root ganglia is more potent at more depolarized potentials (17,18). Therefore, it appears that the inactivated conformation of sodium channels has a higher affinity to CBZ than the resting conformation, and that the drug can prevent the transition of the inactivated channels to the closed state (19,20).

Several biochemical experiments corroborate the electrophysiological observations. Thus, it was demon-

Table I. Mechanisms of Action of Carbamazepine and Its Derivatives

	CBZ	OXC	BIA 2-024 and BIA 2-093	References
Voltage-gated Na^+ channels	Inhibition	Inhibition	Inhibition	12, 17–22, 94–97, 103, 105, 106
Voltage-gated Ca^{2+} channels	Inhibition	Inhibition	No effect	15, 24–31, 35, 98
Voltage-gated K^+ channels	Potentiation Inhibition No effect	Potentiation	ND[a]	32, 36–41, 95
Adenosine receptors	A_1 receptor antagonism A_2 receptor antagonism A_2 agonism	A_1 receptor antagonism	ND	42–44, 47, 48, 99
Serotonergic system	Increase of extracellular serotonin concentration	ND	ND	51–53
Dopaminergic system	Increase of dopaminergic transmission	Increase of dopaminergic transmission	ND	48, 59–62, 101
Glutamergic system	Inhibition of glutamate release	Inhibition of glutamate release	Inhibition of glutamate release	35, 55, 65–69
Peripheral-type benzodiazepine receptors (PBRs)	Interaction with PBRs	ND	ND	78–80
cAMP	Decrease of basal and stimulated cAMP level	ND	ND	44, 85, 92

[a] ND, not determined.

strated that CBZ blocks [^{3}H]batrachotoxin or [^{3}H]batrachotoxinin A 20-α-benzoate binding to synaptosomes. This effect is more evident at depolarizing conditions (12,21). CBZ also inhibits the $^{22}Na^+$ influx stimulated by batrachotoxin in cultured neuroblastoma cells and rat brain synaptosomes (22) and stimulated by veratridine in cortical synaptosomes (12). The site of interaction of several voltage-dependent blockers is on the cytosolic side of the alpha subunit of Na^+ channels, probably within the ion-conducting pathway, as shown by site-directed mutagenesis (23).

An increasing number of findings indicate that CBZ has also calcium antagonistic properties. A decade ago, Elliot proposed that the efficacy of CBZ in the treatment of seizures could be due to a frequency-dependent block of sodium currents and a block of calcium currents (15). Such calcium antagonistic properties would explain the similarities in the depressant action of CBZ and organic calcium antagonists on epileptic paroxysmal depolarizations (24,25). Indeed, CBZ reversibly suppresses the calcium-dependent components of action potentials and markedly reduces the calcium currents, presumably L-type, in cultured rat sensory spinal ganglion cells (26,27). In cultured bovine adrenal medullary cells, CBZ and CBZ-10,11-epoxide inhibit the secretion of catecholamines by interfering with N-type voltage-sensitive calcium channels (28,29). Schumacher et al. (30) also demonstrated that CBZ produces a reversible, concentration-dependent inhibition of high voltage-activated calcium currents, without affecting voltage-dependent activation, in human hippocampal granule cells. More recently, we reported that CBZ inhibits L-type calcium channels in cultured rat hippocampal neurons stimulated with glutamate receptor agonists (31). These findings clearly indicate that CBZ has calcium antagonistic properties. However, it is important to mention that the effects of CBZ were not significant at therapeutic serum levels of CBZ (17–51 μM) in some studies (15,30,31). Moreover, CBZ did not inhibit calcium currents in rat cortical (32) and human cortical neurons (33). In human neuroblastoma cells, CBZ had little effect at concen-

trations that are therapeutically relevant (34). We also found that CBZ does not affect the calcium channels coupled to the exocytotic release of glutamate, in hippocampal nerve terminals (35). Therefore, it is not clear whether the anticonvulsant efficacy of CBZ may be also due to the modulation of calcium currents.

The effects of CBZ on K^+ channels have also been investigated. Olpe et al. (36) found that the depressant effect of CBZ is attenuated by barium chloride and 4-aminopyridine, two potassium-channel blockers, suggesting that CBZ may interfere with potassium fluxes. Indeed, CBZ enhances outward, voltage-dependent K^+ currents in rat neocortical cells (32). However, CBZ also blocks delayed K^+ currents (37) and calcium-activated K^+ currents (38). It was also reported that CBZ does not affect K^+ currents (37,39–41). Taking this into account, it is not clear whether the modulation of K^+ channels contribute to the anticonvulsant efficacy of CBZ.

It has been proposed that the anticonvulsant, as well as the therapeutic and prophylactic effects of CBZ in affective psychoses may, in part, be related to the potent interaction of CBZ with adenosine-binding sites in the brain. Indeed, several reports have demonstrated that CBZ acts as an antagonist at adenosine A_1 receptors (42–44). Application or chronic treatment with CBZ induces up-regulation of adenosine A_1 receptors in astrocytes (45) and rats (46), respectively. Although previous results also indicate that CBZ may act as an adenosine A_2 receptor antagonist (47), Van Calker et al. (44) demonstrated that CBZ is not an antagonist of high-affinity A_{2a} adenosine receptors. Conversely, it was reported that CBZ is an adenosine A_2 receptor agonist (48). These findings suggest that the effects of CBZ may also result from effects on both adenosine A_1 and A_2 receptors. However, binding studies and the observation that a specific adenosine A_1 receptor antagonist have no effect on the anticonvulsant action of CBZ suggest that the alteration of adenosine A_1 receptor activity is not an important mechanism for the anticonvulsant efficacy of CBZ (43,49,50).

A large body of evidence indicates that serotonin has anticonvulsant properties in several seizure models. CBZ causes large increases in extracellular serotonin concentration and produces dose-related anticonvulsant effects in both genetically epilepsy-prone rats (GEPRs) and non-epileptic Sprague-Dawley rats (51–53). The effects of CBZ were not prevented by tetrodotoxin and by removal of calcium, suggesting that the enhancement of serotonin release is not dependent on sodium channel function and does not take place by exocytosis (53). Moreover, Dailey et al. (54) also found that CBZ induces the release of serotonin by a mechanism that does not involve the serotonin transporter. It was also demonstrated that therapeutic concentrations of CBZ enhance serotonin turnover and transmission in hippocampus (55). Therefore, it appears that serotonin release may play a role in the anticonvulsant efficacy of CBZ, as well as in the efficacy of CBZ in the treatment of affective disorders.

The inhibition of serotonin uptake by CBZ was also recently reported (56). This effect probably reflects an affinity of CBZ for biogenic amine transporters. However, binding studies demonstrated that CBZ does not displace serotonergic radioligands, indicating that the anticonvulsant effect of CBZ cannot be attributed to a direct action at the serotonin recognition site (57).

Some data also suggest that CBZ may alter dopamine function (58). CBZ enhances dopamine release and turnover and causes differential alterations of monoamine levels in discrete brain regions (48,59–62). These effects on dopaminergic system may be, at least partially, involved in the mechanisms of action of CBZ. However, indirect clinical evidence, such as lack of parkinsonian side effects and tardive dyskinesia, suggests that CBZ does not act by blocking dopamine receptors (63).

It is widely accepted that glutamate is involved in the initiation and propagation of seizures. A large body of evidence established that NMDA and non-NMDA receptors play a crucial role in seizure activity and are potential targets for AEDs (64). Therefore, the inhibition of either glutamate release or ionotropic glutamate receptors might contribute to the efficacy of anticonvulsants against epileptic seizures. CBZ reduces the release of glutamate evoked by potassium, veratrine or veratridine from hippocampus, cerebral cortex or brain slices (55,65–68), presumably due to its sodium channel blocking properties. Moreover, CBZ inhibits the release of glutamate from cortical and hippocampal synaptosomes evoked by veratridine or 4-aminopyridine, but not that evoked by KCl, indicating that CBZ blocks presynaptic sodium channels, but not calcium channels (35,69). This group of results suggests that the inhibition of glutamate release may contribute, at least partially, to the anticonvulsant properties of CBZ. However, Waldemeier et al. (67,68) suggested that it is uncertain whether the effects of CBZ are relevant at anticonvulsant doses in vivo, since inhibition of electrically-induced glutamate release requires much higher concentrations of CBZ than the release elicited by veratrine.

Previous reports indicate that CBZ may also interact with the function of ionotropic glutamate receptors. Indeed, it was demonstrated that CBZ blocks NMDA-induced currents in cultured spinal cord neu-

rons (70), prevents the elevation of $[Ca^{2+}]_i$ induced by kainate (71), inhibits NMDA-induced depolarizations in cortical wedges (72), prevents convulsions produced by administration of NMDA (73), inhibits NMDA-evoked calcium influx in rat cerebellar granule cells, particularly under depolarizing conditions, by a mechanism that is independent of the NMDA and glycine recognition sites (74), and attenuates responses to AMPA in rat cortical wedges (75). However, Phillips et al. (75) demonstrated that the anticonvulsant effects of CBZ are unlikely to involve antagonism of ionotropic glutamate receptors. Furthermore, Grant et al. (76) showed that CBZ is inactive in displacing binding to [^{3}H]dizocilpine, a selective non-competitive NMDA antagonist, at concentrations substantially higher than the therapeutic brain levels. We recently found, in hippocampal neurons, that ionotropic glutamate receptors are not directly affected by CBZ, and that the neurotoxic effect caused by CBZ is not prevented by NMDA and AMPA receptor antagonists (77).

Experimental evidence has suggested that "peripheral-type" benzodiazepine receptors (PBRs) may play a role in epilepsy and antiepileptic drug action, and anticonvulsant drugs, such as CBZ, may exert some of their effects through PBRs. Indeed, Marangos et al. (78) showed for the first time that CBZ interacts with PBRs, labeled with [^{3}H]Ro 5-4864 (4′-chlorodiazepam), in rat brain membranes. An interaction of CBZ with PBRs was also observed in primary cultures of astrocytes (79). In addition, it was shown that Ro 5- 4864 blocks the anticonvulsant effect of CBZ on amygdala-kindled seizures in rats (80), and that chronic CBZ treatment up-regulates the binding of [^{3}H]PK 11195, an antagonist of PBRs, to platelets of epileptic patients (81). Since PBRs are also present in lymphocytes, some immunological alterations caused by CBZ treatment may be due to its interaction with these receptors (82). This group of findings clearly indicates that CBZ interacts with PBRs at therapeutically relevant concentrations. However, there is no clear evidence showing that this interaction contributes to the anticonvulsant effects of CBZ. It has been postulated that abnormal increases in brain cyclic AMP (cAMP) may play a role in the pathophysiology of seizure disorders (83) and bipolar affective disorders (84). Twenty five years ago, it was reported that CBZ decreases the basal cAMP levels in cerebrospinal fluid (CSF) of rabbits, and partly inhibits the rise in cAMP after electrically-induced convulsions, suggesting the involvement of cAMP in epileptic discharge and in the mechanism of action of CBZ (85). After that, it was also demonstrated that CBZ depresses basal levels of cAMP in cerebral cortex and cerebellum (86), inhibits cAMP accumulation induced by ouabain, norepinephrine, veratridine or adenosine, in rat and mice cortex slices (44,86–89), and prevents pentylenetetrazol-induced rise in cyclic AMP (90). It was also reported that CBZ decreases the levels of cAMP in CSF of manic patients (91). More recently, Chen et al. (92) demonstrated that CBZ inhibits both basal and forskolin-stimulated cAMP production in C6 cells. The molecular mechanisms by which CBZ causes this inhibitory effect are not completely clarified. However, the results suggest that CBZ inhibits the activity of adenylyl cyclase (AC), as well as the downstream pathways of AC activation. In addition to these effects on the cAMP system, it was recently shown that NO-mediated mechanisms might be also involved in the anticonvulsant actions of CBZ (93).

In conclusion, it is clear that CBZ does not act by a single mechanism (Table 1). The therapeutic use of CBZ in several disorders (epilepsy, mood disorders and neuropathic pain) and the findings that CBZ may act at different levels (channels, receptors and signalling pathways) clearly indicates that there is no single cellular action of CBZ. However, for a particular situation, it remains to be elucidated which mechanisms are involved and which is the contribution of each mechanism for the therapeutic effect of CBZ.

Oxcarbazepine. Much evidence indicates that OXC and its monohydroxy derivative, 10-OH-CBZ, may act on several ion channels and receptors. Indeed, since the chemical structure of OXC is similar to that of CBZ, the mechanisms of action may be similar. OXC and 10-OH-CBZ inhibit sustained, high frequency, repetitive firing of cultured spinal cord neurons due to an inhibitory effect on voltage-dependent sodium channels. This effect was found to be voltage- and frequency-dependent (94–97). Neurochemical studies also showed that OXC binds to sodium channels and modulates sodium entry in cortical synaptosomes (12).

Concerning a possible effect of OXC on Ca^{2+} channels, it was demonstrated that the active metabolite of OXC, 10-OH-CBZ, dose-dependently reduces high-voltage-activated Ca^{2+} channels evoked by membrane depolarization in isolated cortical and striatal neurons, but dihydropyridine-sensitive channels are not involved (98). Such as in the case of CBZ, OXC does not affect presynaptic Ca^{2+} channels coupled to the exocytotic release of glutamate in hippocampal synaptosomes (35).

The blockade of penicillin-induced bursts may be used as a measure of antiepileptic efficacy through an effect on potassium channels. 10-OH-CBZ was shown to reduce the frequency of penicillin-induced epileptiform discharges in hippocampal slices, this effect

being antagonized by 4-aminopyridine, a potassium channel blocker (95). Thus, it appears that 10-OH-CBZ acts on potassium channels involved in the generation of burst discharges.

Similarly to CBZ, OXC may also act as an antagonist of adenosine A_1 receptors. Deckert et al. (99) demonstrated that OXC displaces [^{3}H]DPCPX in human hippocampus. It was also shown that OXC inhibits [^{3}H]-L-phenylisopropyladenosine and [^{3}H]-N-ethylcarboxamidoadenosine binding to adenosine A_1 and A_2 receptors, respectively, at therapeutic plasma levels (100), suggesting that the anticonvulsive effects of OXC may be due to an action on adenosine A_1 and A_2 receptors.

Since CBZ possesses a dopaminergic effect, and OXC exhibits an antidepressive-like effect in the learned helplessness and forced swimming test, Joca et al. (101) evaluated whether the antidepressive effect of OXC could be mediated by dopaminergic system, and the results obtained suggest that OXC can enhance dopaminergic transmission.

We recently found that OXC inhibits the evoked release of endogenous glutamate from hippocampal nerve terminals, this effect being mediated by the inhibition of voltage-sensitive sodium channels (35), but it is uncertain whether this inhibitory effect on glutamate release also contributes to the anticonvulsant effects of OXC. In addition, we also found that the activation of ionotropic glutamate receptors is not affected by OXC (102).

To our knowledge, there are no reports related with possible effects of OXC on serotonergic neurons, "peripheral-type" benzodiazepine receptors, cAMP system and NO-mediated mechanisms. Although OXC may also affect these systems, it is currently accepted, as in the case of CBZ, that the main mechanism of action of this drug is the inhibition of voltage-dependent sodium channels.

BIA 2-093 and BIA 2-024. BIA 2-093 and BIA 2-024 were recently found to be effective anticonvulsants. Both compounds conferred a dose-dependent protection against convulsions induced by maximal electroshock and metrazol (12,13,103). Though chemically related to CBZ and OXC, BIA 2-093 and BIA 2-024 were specifically designed to achieve an improvement in antiepileptic efficacy by circumvention of degradation to toxic metabolites, such as epoxides, and the avoidance of enanteomeric impurity and unnecessary production of enantiomers or diastereoisomers of metabolites and conjugates. In fact, OXC gives origin to both the S(+)- and R(−) enantiomer of the 10-OH-CBZ, which are further converted to the inactive *trans*-diol metabolite (104). In contrast, BIA 2-093 leads to an enantiomerically pure metabolism, originating the long lasting S(+)-10-OH-CBZ, due to its reduced propensity to originate the inactive *trans*-diol metabolite (104). The major metabolite of BIA 2-024 is the inactive BIA 2-254 (10,11-dihydro-10-nitro-5*H*-dibenz[*b,f*]azepine-5-carboxamide), which implies a not very common oxidation of an oxime derivative to the corresponding nitro-compound (103). BIA 2-093 and BIA 2-024, like CBZ, displace [^{3}H]-batrachotoxinin A 20-α benzoate binding to rat cortical synaptosomes, indicating that both drugs interact with receptor site 2 of voltage-dependent sodium channels in a competitive manner (12,103,105). BIA 2-093 inhibits, in a concentration-dependent manner, the uptake of $^{22}Na^+$ in the same preparation, in both cases with higher potency than that of CBZ and OXC (12, 105). More recently, BIA 2-093, like CBZ, was found to inhibit Na^+ currents in the mouse neuroblastoma cell line N1E-115, in a voltage-dependent way by an interaction predominantly with the inactivated state of the channel (106). Over the range of neuronal resting membrane potentials likely to be encountered in the brain in situ (−70 to −90 mV), BIA 2-093 displayed a similar inhibitory potency to CBZ. The potency of inhibition was highly sensitive to holding potential, increasing with depolarization. Holding the membrane potential at a less negative voltage is known to increase the proportion of channels in the slow inactivated state. The voltage dependence suggests that BIA 2-093 has a much higher affinity for the inactivated state of the channel compared with the resting state (106). The affinity of BIA 2-093 for resting Na^+ channels (K_R = 3315 μM) was about 3-fold lower than that of CBZ (K_R = 984 μM). The affinity of BIA 2-093 for inactivated sodium channels (K_i = 99.9 μM) was about 2-fold lower than that of CBZ (K_i = 47.8 μM). In the therapeutic context, a higher K_R compared to a K_i for a compound would indicate a functional selectivity for rapidly firing ("epileptic") neurons over neurons displaying normal activity (106).

We also found that BIA 2-024 and BIA 2-093 inhibit the release of endogenous glutamate evoked by 4-aminopyridine or veratridine in a concentration-dependent manner, in hippocampal synaptosomes, due to inhibition of voltage-sensitive sodium channels (35), although with lower potency than CBZ and OXC. Contrarily, it was shown that BIA 2-093 is more potent than CBZ and OXC at inhibiting the release of glutamate induced by veratrine from striatal slices (107). Moreover, CBZ, OXC and BIA 2-093, at the minimal effective dose in the maximal electroshock

test, failed to inhibit veratridine-induced release of aspartate and glutamate (108). Therefore, it is not clear whether the inhibition of glutamate release may contribute to the anticonvulsant effects of these AEDs. We recently also found that BIA 2-024 and BIA 2-093 do not affect voltage-sensitive calcium channels and ionotropic glutamate receptors (35,102).

In contrast to CBZ and OXC, BIA 2-093 and BIA 2-024 were found to be less effective in producing neurological impairment, having the highest protective index among other dibenz[*b,f*]azepine-5-carboxamide derivatives (12,103). We also found that BIA 2-024 and BIA 2-093 are less toxic to hippocampal neurons than CBZ and OXC. Surprisingly, OXC was even more toxic than CBZ (77). These characteristics indicate that BIA 2-093 and BIA 2-024 may be useful in man for the treatment of epilepsy, as well as for some other nervous system disorders, such as trigeminal neuralgia and affective disorders.

Concluding Remarks. This review has focused on the mechanisms of action of CBZ and its derivatives, OXC, BIA 2-093 and BIA 2-024 (Table I). All 4 drugs inhibit sodium channel activity, and this may be the main mechanism of their anticonvulsant effects. Voltage-gated calcium channels were inhibited by CBZ and OXC, although perhaps not at therapeutically relevant concentrations, but not by BIA 2-093 and BIA 2-024. Accordingly, this effect may be not significant for the anticonvulsant activity of these drugs. CBZ and its derivatives inhibited glutamate release, but the correlation between a decreased glutamate release and the anticonvulsant activity of these drugs is uncertain. Both CBZ and OXZ antagonized the A_1 adenosine receptor, increased dopaminergic transmission and potentiated voltage-gated potassium channels, but the possible effects of BIA 2-093 and BIA 2-024 on these parameters are unknown. A CBZ-mediated increase in extracellular serotonin concentration, an interaction of CBZ with peripheral-type benzodiazepine receptors, and a decrease in basal and stimulated level of cAMP may also be of importance for the anticonvulsant action of CBZ, but it remains to be studied whether OXZ, BIA 2-093 and BIA 2-024 exert similar effects.

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