Carbamazepine-Induced Up-regulation of Voltage-dependent Na⁺ Channels in Bovine Adrenal Medullary Cells in Culture

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ABSTRACT

Treatment of cultured bovine adrenal medullary cells with carbamazepine (CBZ) for 5 days caused an increase in catecholamine secretion induced by veratridine, an activator of voltage-dependent Na⁺ channels. However, no increase was stimulated by carbachol, an agonist of nicotinic receptors, or by 56 mM K⁺, a depolarizing agent that activates voltage-dependent Ca²⁺ channels. CBZ (50 μg/ml) treatment enhanced veratridine-induced catecholamine secretion in a time-dependent manner (increases of 25%, 65% and 70% for 3, 5 and 7 days of treatment, respectively). CBZ treatment (5 days) increased veratridine-induced catecholamine secretion in a concentration-dependent manner (increases of 27%, 36%, 45% and 55% at 10, 15, 20 and 30 μg/ml of CBZ, respectively). CBZ treatment also increased ²²Na⁺ influx and ⁴⁶Ca²⁺ influx stimulated by veratridine. The stimulatory effect of CBZ treatment on catecholamine secretion was blocked by either actinomycin D or cycloheximide, an inhibitor of protein synthesis. Additive responses of catecholamine secretion and ²²Na⁺ influx induced by veratridine were associated with combined exposure of the cells to CBZ and dibutyryl cyclic AMP. CBZ treatment (30 μg/ml, 5 days) significantly increased the specific binding of [³H]saxitoxin to cell membranes. A Scatchard analysis of [³H]saxitoxin binding revealed that CBZ increased the Rmax value without any change in the dissociation constant. These findings suggest that CBZ up-regulates the density and activity of voltage-dependent Na⁺ channels.

CBZ, an anticonvulsant with a structure similar to that of the tricyclic antidepressant imipramine, is well known to be effective in the treatment of seizure disorder and has been shown to have subsidiary uses in trigeminal neuralgia and paroxysmal pain (Parnas et al., 1980). A recent report by Post et al. (1990) provided substantial evidence that CBZ induces acute antinamic effects. There are also several reports that CBZ is effective in acute depression (Neumann et al., 1984; Post et al., 1986; Small, 1990), in treatment of some schizophrenic patients (Hakola and Laulumaa, 1982) and in benzodiazepine and alcohol withdrawal (Denicoff et al., 1994). In regard to its mechanism, CBZ has been proposed to exert its effects by acting on various ion channels and receptors. For example, CBZ is known to inhibit sodium channels (Willow et al., 1984; McLean and Macdonald, 1986); to bind adenosine A1 (Clark and Post, 1990; Van Calleer et al., 1991), peripheral-type benzodiazepine (Weiss et al., 1985; 1986) and GABA receptors (Terrence et al., 1983; Motohashi et al., 1989); to enhance 4-aminopyridine-sensitive potassium currents (Zona et al., 1990; Olpe et al., 1991) and to inhibit NMDA-evoked Ca²⁺ influx (Lampe and Bigalke, 1990; Hough et al., 1996). The pharmacological mechanism by which CBZ exerts its clinical effects, however, is not well established.

Adrenal medullary cells that are derived from embryonic neural crest share many physiological and pharmacological properties with sympathetic postganglionic neurons. Bovine adrenal medullary cells contain at least three kinds of ion channels that are involved in catecholamine secretion (Wada et al., 1985). These are voltage-dependent Na⁺ channels (Amy and Kirshner, 1982), nicotinic ACh receptor-associated ion channels (Amy and Kirshner, 1982) and voltage-dependent Ca²⁺ channels (Kilpatrick et al., 1982). Ion channel-mediated catecholamine secretion has been extensively studied in the adrenal medullary cells, and the mechanism of catecholamine secretion from these cells is thought to be similar to that of neurotransmitter released from noradrenergic nerve terminals in the brain (Pocock and Richards, 1988). Accordingly, these cells are a good model for detailed analysis of the action of psychotropic drugs such as tricyclic and tetracyclic antidepressants (Arita et al., 1987) and lithium chloride (Terao et al., 1992) on the central noradrenergic neurons.

ABBREVIATIONS: CBZ, carbamazepine; dbc AMP, dibutyl cyclic AMP; H89, N-[2-[p-bromocinnamylamino]ethyl]-5-isouquinolinesulfonamide; KRP, Krebs-Ringer phosphate; STX, saxitoxin; TTX, tetrodotoxin; Kd, dissociation constant; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; Eagle’s MEM, Eagle’s minimum essential medium; DMSO, dimethyl sulfoxide.
Recently, we reported that short-term treatment (5 min) with CBZ inhibits catecholamine secretion by interfering with nicotinic ACh receptor-associated ion channels, voltage-dependent Na⁺ channels and N-type voltage-dependent Ca²⁺ channels in adrenal medullary cells (Yoshimura et al., 1995). However, there may be significant differences between the action of CBZ on ion channels in acute and chronic treatments, and chronic CBZ treatment is necessary to achieve clinical efficacy for neuropsychiatric disorders. In the present study, we investigated the effect of long-term treatment (5 days) with CBZ on catecholamine secretion in bovine adrenal medullary cells.

Materials and Methods

Materials. KRP buffer containing (mM) NaCl 154, KCl 5.6, MgSO₄ 1.1, CaCl₂ 2.2, NaH₂PO₄ 0.85, Na₂HPO₄ 2.15 and glucose 10 was oxygenated by bubbling with 100% O₂ for at least 30 min and adjusted to pH 7.4. Drugs and chemicals used in this study were: Eagle’s MEM (Nissui Seiyaku, Tokyo), CBZ, carbachol, veratridine, cycloheximide, actinomycin D and dibcAMP (Sigma Chemical Co., St Louis, MO), H89 (Seikagaku, Osaka, Japan), TTX (Sankyo, Tokyo), [22Na]Cl (6–17 Ci/mmol) and [3H]STX (20–40 Ci/mmol) (New England Nuclear, Boston, MA) and [⁴⁴Ca]Cl₂ (0.5–2 Ci/mmol) (Amersham International, Amersham, UK).

Isolation of bovine adrenal medullary cells and their primary culture. Fresh bovine adrenal glands were obtained by collagenase digestion of slices of adrenal medulla, as reported previously by Yanagihara et al. (1979). Cells were plated at a density of 4 × 10⁶ cells/dish (Falcon 35 mm) and maintained in a monolayer culture in Eagle’s MEM containing 10% calf serum, 60 μg/ml amidobenzylpenicillin, 100 μg/ml streptomycin, 0.3 μg/ml amphotericin B and 3.0 μg/ml cytosine arabinoside at 37°C under 5% CO₂/95% air (Yanagihara et al., 1994) in a culture chamber. After 2 days of culturing, the cells were used for experiments. For the treatment of cells with CBZ, the culture medium was replaced with fresh CBZ medium once in 3 days. The CBZ solution was prepared by dissolving CBZ in DMSO, followed by dilution into Eagle’s MEM. To avoid a possible influence of DMSO on cells, all culture media, including control, were adjusted to a final concentration of 0.1% DMSO, a level that has no effect on the ion channel-mediated secretion of catecholamines (data not shown).

Secretion of catecholamines. The secretion of catecholamines was measured as described previously (Yanagihara et al., 1979). After 5 days of CBZ treatment, the cells were washed three times with ice-cold KRP buffer and then reacted with a KRP buffer containing various secretagogues in the absence of CBZ at 37°C for 5 min. The reaction was terminated by aspiration and transference of the incubation medium into a tube containing a perchloric acid (final concentration, 0.4 M). Catecholamines (norepinephrine plus epinephrine) in the cells. Total catecholamines were quantified by detaching cells from the dish, transferring them into the tube containing perchloric acid (final concentration, 0.4 M) and centrifuging them. Catecholamines in the supernatant were assayed as described above.

Influx of [²²Na⁺] and [⁴⁴Ca⁺⁺]. The influx of [²²Na⁺] and [⁴⁴Ca⁺⁺] was measured as described by Wada et al. (1985). Cells treated with CBZ for 5 days were washed three times with ice-cold KRP buffer and incubated with 1.5 μCi of [²²NaCl] or [⁴⁴CaCl₂] at 37°C for 5 min in 1 ml of KRP buffer in the presence of veratridine (100 μM). Then the cells were rapidly washed four times with 1 ml of ice-cold KRP buffer and solubilized with 1 ml of 10% Triton X-100. [²²Na] in the cells was counted by a gamma counter (Aloka ARC-2005), and [⁴⁴Ca]⁺⁺ in the cells was counted by a liquid scintillation counter (Beckman LS-7000). The influx of [²²Na⁺] and [⁴⁴Ca⁺⁺] was calculated from the initial specific radioactivity of these ions in the incubation medium (KRP buffer).

[³H]STX binding. After treatment with CBZ (30 μg/ml) for 5 days, the cells were washed with ice-cold KRP buffer and incubated with 1 to 20 nM [³H]STX in 1 ml of KRP buffer at 4°C for 15 min in the absence (total binding) or presence (nonspecific binding) of 1 μM TTX. Cells were immediately washed twice with ice-cold KRP buffer, solubilized in 10% Triton X-100 and counted for radioactivity. Specific binding was calculated as the total binding minus the nonspecific binding.

Statistical analysis. All experiments were performed in duplicate or triplicate, and each experiment was repeated at least three times. Data obtained were given as the mean ± S.D. Statistical evaluation of unpaired observations was performed using Student’s t test. When more than two means were compared, ANOVA was used. If a significant F value was found, Dunnett’s or Scheffe’s test for multiple comparisons was carried out to identify differences among groups. The former was used when the sample numbers were equal, the latter when the numbers were unequal.

Results

Effects of 5 days of CBZ treatment on catecholamine secretion induced by carbachol, veratridine and high K⁺. Carbachol (300 μM), an activator of nicotinic ACh receptor-associated ion channels, induced the secretion of catecholamines; the secreted fraction was 8% of the total catecholamines. Veratridine (100 μM), an activator of voltage-dependent Na⁺ channels, and 56 mM K⁺, a depolarizing agent, increased the catecholamine secretion to 9% and 8.5% of total catecholamines, respectively. Treatment with CBZ (30 μg/ml) for 5 days significantly increased the catecholamine secretion induced by veratridine (a 67% increase as compared with veratridine alone) (fig. 1). However, CBZ (30 μg/ml) did not increase the secretion of catecholamines induced by carbachol or high K⁺.

Effects of various concentrations of CBZ on catecholamine secretion induced by veratridine. Treatment with CBZ at concentrations of 10 to 30 μg/ml for 5 days significantly increased, in a concentration-dependent manner, the secretion of catecholamines induced by veratridine (fig. 2). The secretion was increased by 27%, 36%, 45% and 55% above the control (CBZ, 0 μg/ml) for 10, 15, 20 and 30 μg/ml of CBZ, respectively.

Change in veratridine-induced secretion of catecholamines after treatment with CBZ. CBZ (30 μg/ml) increased the secretion of catecholamines induced by veratridine in a time-dependent manner (3–7 days) (fig. 3). A significant increase in the catecholamine secretion was observed after treatment for 3 days (a 25% increase above the control at day 0), and the maximal level of catecholamine secretion was reached after 5 (65% increase over the control) to 7 days (70% increase over the control).

Effects of CBZ on [⁴⁴Ca⁺⁺] influx and [²²Na⁺] influx induced by veratridine. Veratridine (100 μM) caused a
Results

Treatment with CBZ (10 and 20 μg/ml) for 5 days increased the veratridine-induced catecholamine secretion by 60% of the control value. Actinomycin D (1 μg/ml), a drug used to inhibit the activity of DNA-dependent RNA polymerase, did not influence the catecholamine secretion but halted the increase of the catecholamine secretion caused by CBZ (fig. 5A). In addition, cycloheximide (1 μg/ml), an inhibitor of ribosomal synthesis of proteins, also reduced CBZ-increased catecholamine secretion to almost the same levels as in control cells or cells treated with cycloheximide alone (fig. 5B).

Effects of dbc AMP, H89 and CBZ on catecholamine secretion and 22Na⁺ influx induced by veratridine. A previous report (Yuhi et al., 1996) describes how a derivative of cAMP (an activator of cAMP-dependent protein kinase) increases the number of functional voltage-dependent Na⁺ channels in cultured bovine adrenal medullary cells. In the present study, the authors found that dbc AMP (1 mM) also increased veratridine-induced catecholamine secretion and 22Na⁺ influx. Simultaneous treatment with dbc AMP (1 mM) and CBZ (30 μg/ml) caused an additive increase in catecholamine secretion and 22Na⁺ influx stimulated by veratridine (fig. 6). Furthermore, H89 (an inhibitor of cAMP-dependent protein kinase) (10 μM) failed to influence either basal or CBZ-increased catecholamine secretion or 22Na⁺ influx induced by veratridine (fig. 6).

Effects of treatment with CBZ on [³H]STX binding. When cells were incubated with various concentrations (1–20 nM) of [³H]STX, the specific binding of [³H]STX was saturable (fig. 7A). Treatment with CBZ (20 μg/ml) for 5 days increased the specific binding of [³H]STX. A Scatchard plot analysis revealed that CBZ increased $B_{max}$ values from 18 ± 2 to 28 ± 2 fmol/4 × 10⁶ cells without altering $K_D$ values (control, 5.1 ± 1.1 nM; CBZ, 5.0 ± 1.0 nM) (fig. 7B).

Discussion

Long-term treatment with CBZ specifically influences voltage-dependent Na⁺ channel-mediated secretion of catecholamines. In the present study, treatment of adrenal medullary cells with CBZ enhanced catecholamine secretion induced by veratridine in a concentration-depen-
dent manner (10–30 μg/ml) (fig. 2). The concentrations of CBZ used (10–30 μg/ml) were slightly higher than those (6–12 μg/ml) usually recommended for treating neuropsychiatric disorders (McNamara, 1995). CBZ (10–20 μg/ml, 5 days) also increased veratridine-induced 22Na+ influx and 45Ca+ influx in a manner similar to that for catecholamine secretion (fig. 4). As shown in our previous study (Wada et al., 1985), the influx of Na+ via voltage-dependent Na+ channels causes a depolarization of cell membranes, which in turn stimulates the influx of Ca2+ via voltage-dependent Ca2+ channels and triggers the secretion of catecholamines. Therefore, it is likely that CBZ treatment enhances 22Na+ influx mediated through voltage-dependent Na+ channels, with resultant increases of 45Ca2+ influx and catecholamine secretion. Our previous study showed that short-term treatment (5 min) with CBZ inhibits both nicotinic ACh receptor-asso-

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Fig. 4. Effects of CBZ on 45Ca2+ influx (panel A) and 22Na+ influx (panel B) induced by veratridine. The cells were washed three times with ice-cold KRP buffer and stimulated with veratridine (0.1 mM) at 37°C for 5 min after pretreatment with or without CBZ (10 and 20 μg/ml) for 5 days. 45Ca2+ influx and 22Na+ influx were measured (see “Materials and Methods”) and expressed as nmol/4×106 cells. Data are means ± S.D. from 3 to 4 experiments carried out in duplicate. * P < .01 compared with control (CBZ, 0 μg/ml).

Fig. 5. Effects of actinomycin D (panel A) and cycloheximide (panel B) on catecholamine secretion induced by veratridine in CBZ-treated cells. The cells were washed three times with ice-cold KRP buffer and stimulated with veratridine (0.1 mM) at 37°C for 5 min after pretreatment with or without CBZ (20 μg/ml), actinomycin D (1 μg/ml), cycloheximide (1 μg/ml), CBZ plus actinomycin D, and CBZ plus cycloheximide, respectively, for 5 days. Data are means ± S.D. from three experiments carried out in triplicate. * P < .01 compared with control.

Fig. 6. Effects of dbc AMP, H89 and CBZ on catecholamine secretion (panel A) and 22Na+ influx (panel B) induced by veratridine. After pretreatment with or without dbc AMP (1 mM), H89 (10 μM), CBZ (30 μg/ml), dbc AMP plus CBZ, and H89 plus CBZ, respectively, for 5 days, the cells were washed three times with ice-cold KRP buffer and stimulated with veratridine (0.1 mM) at 37°C for 5 min in the absence of CBZ, H89 and dbc AMP. Catecholamine secretion and 22Na+ influx were measured. Data are means ± S.D. from three experiments carried out in triplicate. * P < .01 compared with control. + P < .01 compared with dbc AMP or CBZ.
induced up-regulation of Na+ pharmacological features. The precise mechanism of CBZ-cretion stimulated by carbachol, an activator of nicotinic ml, 5 days), however, had little effect on catecholamine se-

These findings suggest that CBZ treatment mediates the of [3H]STX was due to the increased number of binding sites, to cell membranes (fig. 7A). The increase in specific binding was calculated as the difference between total and nonspecific binding. Data shown are for one typical experiment representative of five separate experiments. A) Specific binding was calculated as the difference between total and nonspecific binding. Data shown are for a typical experiment representative of four separate experiments. * P < .01 compared with control.

Fig. 7. Effects of treatment with CBZ on specific binding of [3H]STX. The cells were washed three times with ice-cold KRP buffer and incubated with 1 to 20 nM of [3H]STX in 1 ml KRP buffer at 4°C for 15 min in the absence (total binding) or presence (nonspecific binding) of 1 μM TTX after pretreatment with (○) or without (□) CBZ (20 μg/ml) for 5 days. A) Specific binding was calculated as the difference between total and nonspecific binding. Data shown are for a typical experiment representative of five separate experiments. B) Scatchard plot analysis of [3H]STX specific binding. Data shown are for one typical experiment representative of four separate experiments. * P < .01 compared with control.

-associated ion channels and voltage-dependent Ca++ channels, as well as voltage-dependent Na+ channels, in cultured ad-

renal medullary cells (Yoshimura et al., 1995). CBZ (30 μg/ ml, 5 days), however, had little effect on catecholamine secretion stimulated by carbachol, an activator of nicotinic ACh-associated ion channels, or on 56 mM K+, a depolarizing agent that activates voltage-dependent Ca++ channels (fig. 1). These results indicate that long-term treatment with CBZ enhances catecholamine secretion specifically by acting on voltage-dependent Na+ channels.

Up-regulation of voltage-dependent Na+ channels by CBZ treatment. Treatment of adrenal medullary cells with CBZ for 5 days increased the specific binding of [3H]STX to cell membranes (fig. 7A). The increase in specific binding of [3H]STX was due to the increased number of binding sites, but not to the change in the affinity toward [3H]STX (fig. 7B). These findings suggest that CBZ treatment mediates the up-regulation of Na+ channel proteins without altering their pharmacological features. The precise mechanism of CBZ-induced up-regulation of Na+ channels remains to be determined. Both actinomycin D, which inhibits the activity of DNA-dependent RNA polymerase, and cycloheximide, which inhibits ribosomal synthesis of proteins, halted the stimulatory effect of CBZ on veratridine-induced secretion (fig. 5), which suggests that CBZ treatment induces the up-regulation of Na+ channels via a de novo synthesis of its channel proteins in the cells. A previous report by Yuhi et al. (1996) showed that treatment of cultured adrenal medullary cells with dbc AMP up-regulated the functional voltage-dependent Na+ channels. In the present study, the effects of dbc AMP and CBZ on veratridine-induced catecholamine secretion, as well as on 22Na+ influx, were almost additive; furthermore, H89 (an inhibitor of cAMP-dependent protein kinase) failed to abolish the stimulatory effect of CBZ treatment (fig. 6). These results suggest that CBZ up-regulates voltage-dependent Na+ channels by a mechanism that is independent of cAMP.

Taouis et al. (1991) demonstrated that in vivo treatment with mexiletine, an antiarrhythmic drug, for 7 days induces up-regulation of rat cardiac Na+ channels. The blockade of spontaneous electrical activity by bupivacaine, a local anesthetic, and TTX (Scherman and Catterall, 1984) or ethanol (Brodie and Sampson, 1990) has been shown to increase TTX-sensitive Na+ channels in cultured skeletal muscle cells. The authors of these studies speculate that the electrical activity regulates the number of TTX-sensitive Na+ channels through a Ca++-mediated feedback system. Furthermore, treatment for 2 weeks with phenytoin, an anticonvulsant, enhanced the expression of voltage-dependent Na+ channel mRNA, and subsequently increased the number of functional Na+ channels in the brains of genetically seizure-susceptible (E1) and control (ddY) mice (Sashihara et al., 1994). The present results obtained using CBZ are compatible with those obtained with phenytoin. Both CBZ and phenytoin are anticonvulsive agents that block Na+ channels in short-term treatment (Wil-

low and Catterall, 1982; McLean and Macdonald, 1984, 1986; Yoshimura et al., 1995). However, Yamamoto et al. (1996) recently reported that treatment (4 days) of cultured adrenal medullary cells with insulin up-regulates the functional Na+ channels without causing any change in the level of mRNA encoding the Na+ channel α-subunit. It would therefore appear that further studies are needed to examine the effect of CBZ exposure on levels of Na+ channel mRNA in cultured adrenal medullary cells.

Antidepressive and anticonvulsive effects of CBZ. In the present study, we found that the increase in veratridine-induced secretion of catecholamines was significant after CBZ treatment for 3 days and that it reached the maximal level after 5 to 7 days (fig. 3). This may be related to the antidepressive effects of CBZ, which occur at about 1 or 2 weeks after CBZ administration (Post et al., 1994). The original catecholamine hypothesis for the affective disorders postu-
tulated that depression is characterized by a deficiency of functional norepinephrine and that the brain norepinephrine levels are recovered by treatment with antidepressants (Bun-

ney and Davis, 1965). Although current available evidence does not suggest uniform increases or decreases in nor-
epinephrine or its metabolites in plasma and cerebrospiral fluid of depressed patients, results of studies to date are consistent with some forms of bipolar depression being associated with decreased norepinephrine release and metabolism and some forms of unipolar depression being associated with increased norepinephrine release and metabolism (Schildkrut et al., 1978; Siever and Uhde, 1984). Therefore, the present find-
ings suggest the possibility that long administration of CBZ induces a change in voltage-dependent Na+ channels and hence modulates norepinephrine release in brain noradrenergic neurons of depressive patients.

Furthermore, the anticonvulsant effects of CBZ might also be influenced by modulation of the noradrenergic neuron activity in the brain, because DBA/2 mice, which are prone to running fits that lead to generalized myoclonic with tonic flexion and extension in response to loud auditory stimuli, have a central deficiency in norepinephrine (Schlesinger et al., 1965). Moreover, rats that are genetically prone to epilepsy, and particularly the progeny of those most susceptible to seizure, have been shown to have low levels of brain norepinephrine (Laird et al., 1983). Furthermore, decreasing central norepinephrine levels in the rats increase their susceptibility to seizure (Jouve and Laird, 1981), whereas increasing central norepinephrine levels or treating with alpha-1, beta-1 or beta-2 adrenoceptor agonists reduces the intensity of seizures (Ko et al., 1982, 1983).

There is another report that norepinephrine is involved in seizure susceptibility and CBZ activity (Crønelli et al., 1981). This study showed that clonidine, reported to decrease the firing rate of noradrenergic neurons, reduces the electroconvulsive thresholds and the anticonvulsant effect of CBZ and that, by contrast, yohimbine, a substance known to block alpha-2 adrenergic receptors activated by clonidine, has anticonvulsant activity of the same order as CBZ in rat brain. Further investigation of this possibility might help clarify whether in vivo administration of CBZ influences functional voltage-dependent Na+ channels, and thus norepinephrine levels, in the rat brain.

In conclusion, long-term treatment with CBZ up-regulated the functional voltage-dependent Na+ channels in cultured adrenal medullary cells. The present findings add to our understanding of the mechanism by which CBZ acts in the treatment of neuropsychiatric disorders.

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