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LIPOPHILIC AMINO ALCOHOLS WITH CALCIUM CHANNEL BLOCKING ACTIVITY

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Abstract—A series of novel lipophilic amino alcohols, analogs of the anticholinergic drug vesamicol, were evaluated for Ca^{2+} channel blocking activity. The effects of these drugs on depolarization-induced intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) transients were examined in single NG108-15 cells and dorsal root ganglion (DRG) neurons in culture. $[Ca^{2+}]$ was recorded with the Ca^{2+} indicator Indo-1 and a dual emission microfluorimeter. Structure–activity studies indicated that features required for Ca^{2+} channel blocking activity were distinct from those required for anticholinergic activity. In particular, the Ca^{2+} channel blocking activity was insensitive to the configuration at the chiral center, whereas the anticholinergic activity was clearly enantioselective. One of the most active compounds, 3-(3-bromophenyl)-2-hydroxy-1-[1-(4-phenylpiperidinyl)]propane (**2b**), was characterized in more detail. This compound inhibited the dihydropyridine-sensitive Ca^{2+} channel response in NG108-15 cells, evoked by depolarization with 50 mM K^+, with an IC_{50} of 5 μM. Field potential stimulation of DRG neurons elicited $[Ca^{2+}]_i$ transients mediated by at least three Ca^{2+} channel subtypes; compound **2b** inhibited the entire Ca^{2+} channel response with an IC_{50} of 1 μM. A key element required for Ca^{2+} channel blocking activity was the presence of an electron withdrawing substituent on the pendant phenyl ring. Modification of the amino alcohol structure may lead to more potent compounds with broad spectrum Ca^{2+} channel blocking activity. These structures provide a new chemical starting point for the development of Ca^{2+} antagonists.

Calcium antagonists are a structurally diverse group of drugs which block Ca^{2+} flux through voltage-gated Ca^{2+} channels [1, 2]. Clinically used Ca^{2+} channel blockers can be divided into four groups: the phenylalkylamines (e.g. verapamil), the benzothiazepines (e.g. diltiazem), the dihydropyridines (e.g. nifedipine) and the piperazines (e.g. flunarizine). Other, less selective agents which inhibit Ca^{2+} channels include prenylamine and perhexiline which also inhibit Na^+ channels. Additionally, a broad range of compounds, which exert their primary pharmacological actions at other sites, will interfere with Ca^{2+} influx, as exemplified by the phenothiazine antipsychotics [3] and benzodiazepine drugs [4]. Ca^{2+} antagonists have proven useful clinically as vasodilators and antiarrythmic drugs [5, 6]. They also show promise as protective agents limiting the Ca^{2+} overload which accompanies reperfusion injury in the heart [7] and certain neurodegenerative disorders [8].

There are multiple types of Ca^{2+} channels [9] of which at least four, designated T, N, L and P, have been described in neurons [10–13]. Ca^{2+} channel subtypes can be distinguished on the basis of their unitary conductance, voltage dependence of activation, and kinetics of inactivation. There has been great interest in the development of drugs which act specifically at these different channel types. All four classes of clinically used Ca^{2+} antagonists interact with L-type Ca^{2+} channels at distinct binding sites [14]. Less potent agents have been reported to act at T-type channels [15] and high concentrations of verapamil, diltiazem and dextromethorphan have been shown to inhibit non-N/non-L-type responses [16]. Peptide toxins show specificity for Ca^{2+} channel subtypes; for example, ω-conotoxin GVIA (ω-CgTx)‖ generally inhibits N-type channels [17–19], ω-agatoxin IV inhibits P-type channels [20], and *Grammostola spatulata* venom inhibits dihydropyridine-insensitive channel types [21]. Novel chemical structures with Ca^{2+} channel blocking activity are of interest because they may lead to new drugs that are tissue specific or selective for Ca^{2+} channel subtypes.

Vesamicol [*trans*-2-(4-phenylpiperidino)cyclohexanol] is a simple lipophilic amino alcohol with neuromuscular blocking activity in rodents [22]. It acts largely by inhibiting both the uptake of acetylcholine into synaptic vesicles and the release of acetylcholine from cholinergic terminals [23]. The inhibition of acetylcholine uptake is caused by high-affinity binding of vesamicol to its receptor, a cytoplasmically oriented site associated with the vesicular acetylcholine transporter [24, 25].

In addition to anticholinergic activity, we found that some acyclic derivatives of vesamicol inhibited [^{3}H]nitrendipine binding to rat brain membranes.¶

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‖ Abbreviations: ω-CgTx, ω-conotoxin GVIA; $[Ca^{2+}]_i$, intracellular free Ca^{2+} concentration; DRG, dorsal root ganglion; HEPES, 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid; and EGTA, ethylene glycol bis (β-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid.

¶ Efange SMN, Michelson RH and Dutta AK, unpublished observations.

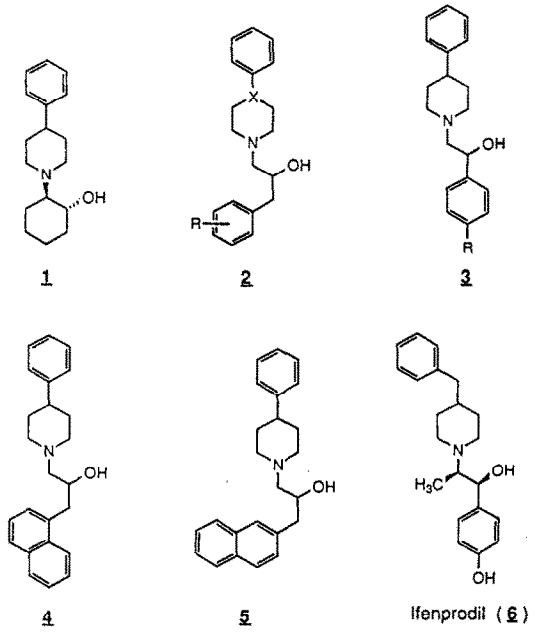


Fig. 1. Structures of vesamicol (**1**), ifenprodil (**6**) and the lipophilic amino alcohols (**2–5**) used in this study.

In this report, we describe the Ca^{2+} channel blocking activity of a series of compounds structurally related to vesamicol [26]. These simple lipophilic acyclic amino alcohols inhibited the depolarization-induced increase in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) in neuroblastoma × glioma hybrid NG108-15 cells and in rat DRG neurons. These structures provide a new chemical starting point for the development of Ca^{2+} channel blocking agents.

METHODS

Chemistry. The synthesis and characterization of these compounds have been described previously [26]. All experiments were conducted with the corresponding hydrochlorides of the compounds shown in Fig. 1.

Cell culture. NG108-15 cells (passages 20–30) were grown in culture as previously described [27]. Briefly, cells were plated onto glass coverslips (25 mm round) at a density of 3×10^4 cells/coverslip and maintained in Dulbecco's Modified Eagle's Medium supplemented with 5% fetal bovine serum, 0.1 μM hypoxanthine, 10 μM aminopterine, 17 μM thymidine in a humidified atmosphere of 95% air and 5% CO_2 at 37°. After 1–2 days, growth medium was replaced with serum-free medium containing 5 μM forskolin to induce cellular differentiation. Differentiated cells were used after 5–6 days.

Neurons from the dorsal root ganglion (DRG) were grown in primary culture as previously described [28]. Briefly, ganglia from 1- to 3-day-old Sprague–Dawley rats were dissected from the thoracic and lumbar regions and incubated at 37° in collagenase-dispase (0.8 and 6.4 U/mL, respectively) for 20–30 min. Ganglia were dissociated into single cells by trituration through a flame-constricted pipette. Cells were plated onto laminin-coated glass coverslips (25 mm round) and grown in Ham's F12 medium supplemented with 5% heat-inactivated rat serum,

Table 1. Inhibition by lipophilic amino alcohols of Ca^{2+} channels in NG108-15 cells and [^{3}H]-vesamicol binding to *Torpedo* synaptic vesicles

Compound*	R	X	Inhibition of Ca^{2+} influx† (%)	Inhibition of [^{3}H]vesamicol binding† (IC_{50}, nM)
1			27 ± 11	34 ± 6
(+)-**2a**	p-Br	C H	86 ± 6	328 ± 108
(−)-**2a**	p-Br	C H	82 ± 8	36 ± 5
2b	m-Br	C H	90 ± 2	73 ± 17
2c	p-OH	C H	0 ± 6	220 ± 54
2d	m-OH	C H	26 ± 6	520 ± 30
2e	m-OMe	C H	28 ± 8	115 ± 14
2f	H	C H	39 ± 10	ND
2g	m-Br	N	84 ± 5	990 ± 102
2h	p-Br	N	83 ± 8	1540 ± 260
3a	H		27 ± 5	ND
3b	Br		85 ± 5	30 ± 5
4	2,3-benzo	C H	96 ± 2	1400 ± 300
5	3,4-benzo	C H	71 ± 11	145 ± 15

* Root structures are shown in Fig. 1.

† Ca^{2+} channel blocking activity was determined as described in the legend of Fig. 2 using 10 μM drug. Inhibition is the difference between peak 1 and peak 2 expressed as a percentage of peak 1. Results are means ± SEM of at least three experiments.

‡ Vesamicol binding data were taken from Ref. 26. Values are means ± SD for the inhibition of [^{3}H]vesamicol binding to *Torpedo californica* synaptic vesicle membranes.

ND = not determined.

50 ng/mL nerve growth factor, 4.4 mM glucose, 2 mM L-glutamine, 1% Eagle's Minimum Essential Medium 100 × vitamins and penicillin/streptomycin (100 U/mL and 100 μg/mL, respectively). Cultures were maintained at 37° in a humidified atmosphere of 5% CO_2. Cells were used 4–9 days after plating.

Instrumentation. $[Ca^{2+}]_i$ was monitored in single cells using Indo-1 and a dual emission microfluorimeter. For excitation of Indo-1, light from a 75 W Xe arc lamp was passed through a monochromator (Photon Technologies Inc.) set to 350 nm (slit width = 2 nm) and collimated with a parabolic mirror. For epifluorescence excitation, light was reflected from a dichroic mirror (380 nm, Omega Optical) through a 70× phase-contrast oil immersion objective (Leitz, numerical aperture 1.15). Emitted light was sequentially reflected off dichroic mirrors (440 and 516 nm) through band pass filters (405/20 and 495/20 nm, respectively) to photomultiplier tubes operating in the photon counting mode (Thorn EMI). Cells were illuminated with transmitted light (610 nm long pass) and visualized with a video camera placed after the second emission dichroic. Recordings were defined spatially with a rectangular diaphragm. The photomultiplier outputs (5 V pulses) were integrated by passing signals through 8-pole Bessel filters at a cut-off frequency of 2.5 Hz. These signals were then input to two channels of a direct-memory-access analog-to-digital converter (Indec Systems) continuously sampling at 200 Hz. Data points were averaged to give a final sampling rate of either 1 or 10 Hz.

Calibration. After completion of an experiment, the microscope stage was adjusted so that no cells or debris occupied the field of view defined by the diaphragm, and background light levels were determined (typically less than 5% of cell counts). Autofluorescence from cells not loaded with Indo-1 was undetectable. Records were later corrected for background and ratio values were recalculated. Ratio values were converted to $[Ca^{2+}]_i$ by the equation $[Ca^{2+}]_i = K\ \beta\ (R - R_{min})/(R_{max} - R)$, in which R is the 405/495 nm fluorescence emission ratio and $K = 250$ nM, the dissociation constant for Indo-1 [29]. The maximum ratio (R_{max}), the minimum ratio (R_{min}), and the constant β (the ratio of the emitted fluorescence measured at 495 nm in the absence and presence of saturating Ca^{2+}) were determined in neurons by treatment with ionomycin in the absence (1 mM EGTA) and presence of saturating Ca^{2+} (5 mM Ca^{2+}). The system was recalibrated following any adjustment to the apparatus. Values for R_{min}, R_{max}, and β ranged from 0.22 to 0.23, 2.43 to 2.82 and 3.46 to 3.54, respectively.

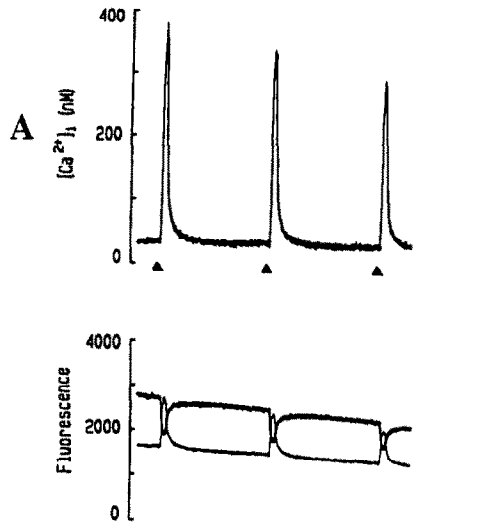
Experimental procedure. DRG and NG108-15 cells were loaded with Indo-1 by incubation in 2 μM Indo-1 acetoxymethyl ester in HEPES-buffered Hanks' salt solution containing 0.5% bovine serum albumin for 45–60 min at 37°. Hanks' buffer was composed of the following (in mM): HEPES, 20; NaCl, 137; $CaCl_2$, 1.3; $MgSO_4$, 0.4; $MgCl_2$, 0.5; KCl, 5.0; KH_2PO_4, 0.4; $NaHPO_4$, 0.6; $NaHCO_3$, 3.0; and glucose, 5.6. The coverglass was then mounted in a flow through chamber [30] and placed on the stage of the microfluorimeter. Loading was terminated by washing with Hanks' buffer for 20–30 min prior to starting an experiment. The chamber was superfused at a rate of 2 mL/min and solutions were selected with a multi-port valve coupled to several reservoirs. Experiments were performed at room temperature. K^+-induced depolarization was produced by elevating K^+ from 5 to 50 mM with K^+ exchanged for Na^+, reciprocally. For field potential stimulation, the chamber was equipped with platinum electrodes connected to an electrical stimulator (Grass Instruments). Cells were stimulated once every 4 min with a train of 10 pulses (1 msec pulse duration) delivered at 10 Hz. The $[Ca^{2+}]_i$ transient resulting from this type of stimulus was dependent on action potential generation by the neurons [31].

RESULTS

NG108-15 cells were grown in serum-free, 5 μM forskolin medium for 5–6 days, during which time the flat polygonal cells differentiated into rounded cells which extended fine processes and expressed voltage-sensitive Ca^{2+} channels. Activation of voltage-gated Ca^{2+} channels was assessed in single cells by measuring $[Ca^{2+}]_i$ with Indo-1-based microfluorimetry, as described in Methods. Cells were depolarized by superfusion with 50 mM K^+ for 30 sec, resulting in large $[Ca^{2+}]_i$ increases of reproducible amplitude (Fig. 2A; peak 2/peak 1 = 90 ± 3%; N = 4). The response evoked by 50 mM K^+ in these cells was blocked completely by the dihydropyridine Ca^{2+} channel blocker nitrendipine with an IC_{50} of 1.9 nM [32].

We used this well-characterized Ca^{2+} influx paradigm to screen a series of novel amino alcohol analogs for Ca^{2+} channel blocking activity (Table 1; Fig. 1). Each compound was tested at a concentration of 10 μM. Compound **2d** had modest Ca^{2+} channel blocking activity as shown in the representative record in Fig. 2B. Compound **2b** was one of the most active compounds as shown in Fig. 2C. All of the compounds tested showed at least partial reversal upon washout, similar to that shown in Fig. 2, panels B and C. A complete concentration–response curve for compound **2b** is displayed in Fig. 3 (IC_{50} = 5 μM). This compound inhibited Ca^{2+} influx in a concentration-dependent manner and blocked the entire response. The response was not significantly different from 0 in the presence of 30 μM compound **2b**.

Comparison of the Ca^{2+} channel blocking activity of these compounds with their potency in displacing [^{3}H]vesamicol binding to *Torpedo* synaptic vesicles shows clearly that Ca^{2+} antagonist and anticholinergic activity of these drugs have different structural requirements [26]. For example, compound **4**, which was most active in the Ca^{2+} influx assay, was a poor competitor for [^{3}H]vesamicol binding, in contrast to vesamicol (compound **1**) which was a poor Ca^{2+} channel blocking agent, but a potent anticholinergic (Table 1). Furthermore, Ca^{2+} channel blocking activity was insensitive to the configuration of the chiral center as shown in Table 1 (compare (+)-**2a** to (−)-**2a**). Both enantiomers produced a similar degree of inhibition when tested at 3 μM; (−)-**2a** and (+)-**2a** produced 45 ± 12 and 59 ± 9% inhibition (N = 5), respectively. In contrast, anticholinergic



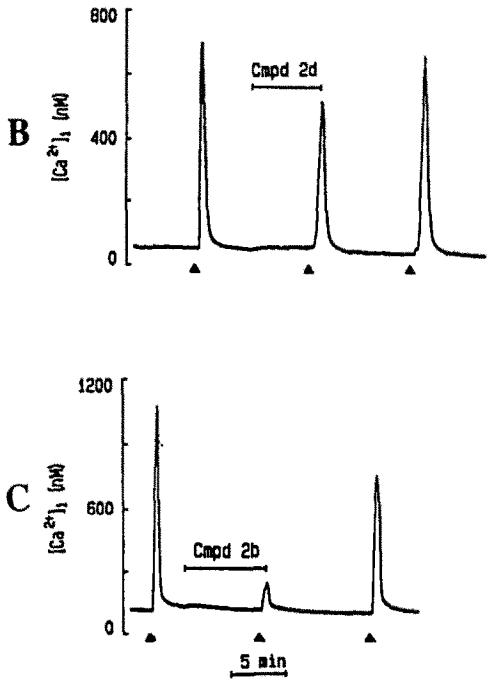


Fig. 2. Inhibition of depolarization-induced $[Ca^{2+}]_i$ transients in NG108-15 cells by lipophilic amino alcohols. (A) Multiple depolarization-induced $[Ca^{2+}]_i$ transients were elicited at 10-min intervals in single NG108-15 cells by 30-sec superfusion with 50 mM K^+-containing HEPES Hanks' buffer as indicated by filled triangles. The second response was 90 ± 3% of the first and the third response was 77 ± 4% of the first (N = 4). Lower traces display unprocessed intensity values representing the Ca^{2+} bound (405 nm—thin line) and unbound (495 nm—thick line) forms of Indo-1. (B) A representative trace showing the effect of compound **2d** (10 μM), which inhibited the response by 26 ± 6%. (C) Effect of compound **2b** (10 μM), which inhibited the $[Ca^{2+}]_i$ transient by 90 ± 2%. Horizontal bars indicate times during which drugs were applied. The records are representative of at least three replicates. Note differences in scale of Y-axes.

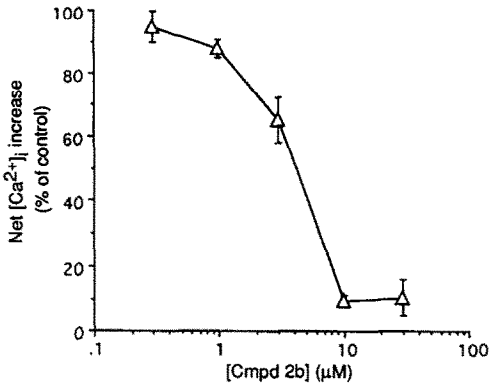


Fig. 3. Concentration-dependent inhibition of depolarization-induced $[Ca^{2+}]_i$ transients by compound **2b**. Data are presented as means ± SEM (N ≥ 3), with each response in the presence of compound **2b** expressed as a percentage of the response before drug application (IC_{50} = 5 μM). The average net $[Ca^{2+}]_i$ increase for the control responses was 674 ± 109 nM (N = 28).

activity was clearly enantioselective, exhibiting a preference for the levorotatory enantiomer (compare (+)-**2a** to (−)-**2a**).

Evaluation of the data in Table 1 reveals certain structural features important for Ca^{2+} channel blocking activity. Clearly the parent compound, vesamicol (compound **1**), was not as active as the acyclic amino alcohol analogs. Varying the chain length of the aliphatic portion of the molecule from 3 to 2 carbons produced little change in Ca^{2+} channel blocking activity. For example, compounds (+)-**2a** and **3b** were equally active. Replacement of the phenylpiperidyl group with the phenylpiperazyl moiety also failed to produce a significant change in activity as indicated by comparing (+)- or (−)-**2a** with **2h**.

The introduction of substituents on the pendant phenyl group of **2** produced the most significant changes in Ca^{2+} channel blocking activity. All effective compounds contained lipophilic electron withdrawing substituents on this phenyl ring. However, the activity was not influenced by the position of a given substituent on the ring [compare (+)-**2a** or (−)-**2a** to **2b** and **2g** to **2h**]. On the other hand, the presence of electron donating substituents resulted in a dramatic loss of activity (**2d** or **2e** to **2b**, (+)-**2a** or (−)-**2a** to **2c**). This reduction in activity cannot be attributed to steric effects since the hydroxyl and bromo substituents are comparable in size; additionally, replacement of the phenyl moiety with a naphthyl group resulted in some of the most active analogues (**4** and **5**), suggesting significant bulk tolerance in this region of the binding site.

We further evaluated compound **2b** for activity on different Ca^{2+} channel subtypes. Field potential stimulation of rat DRG neurons grown in primary culture evoked action potentials which trigger Ca^{2+} entry through voltage-gated Ca^{2+} channels. In contrast to 50 mM K^+-evoked $[Ca^{2+}]_i$ transients in NG108-15 cells, field potential stimulation of rat

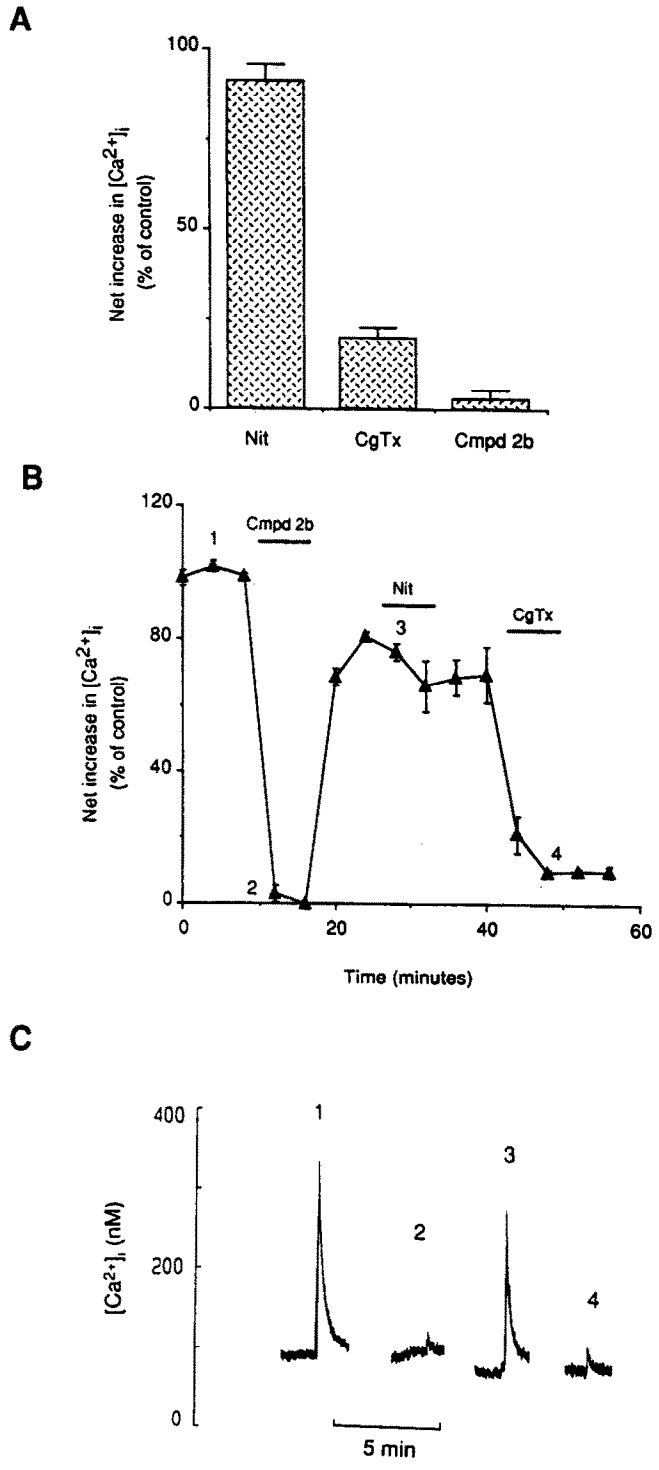


Fig. 4. Inhibition of field potential-evoked $[Ca^{2+}]_i$ increases in rat DRG neurons by compound **2b**. (A) Net $[Ca^{2+}]_i$ increases (means ± SEM) are plotted as a percent of the control response (325 ± 30 nM) in the presence of various Ca^{2+} channel inhibitors: Cmpd **2b**, 10 μM compound **2b**; Nit, 1 μM nitrendipine; and CgTx, 100 nM ω-CgTx. Each drug was tested on four or more individual cells. (B) Net $[Ca^{2+}]_i$ increases (means ± SEM, N = 3) were normalized to the mean of the first three depolarization-induced $[Ca^{2+}]_i$ transients in the absence of drug (330 ± 28 nM) and plotted versus time in experiments where all three compounds were applied sequentially. Drug presence is indicated by labeled bars: Cmpd **2b**, 10 μM compound **2b**; Nit, 1 μM nitrendipine; CgTx, 100 nM ω-CgTx. (C) Representative $[Ca^{2+}]_i$ transients recorded at time points indicated in B. The four transients were recorded from the same cell.

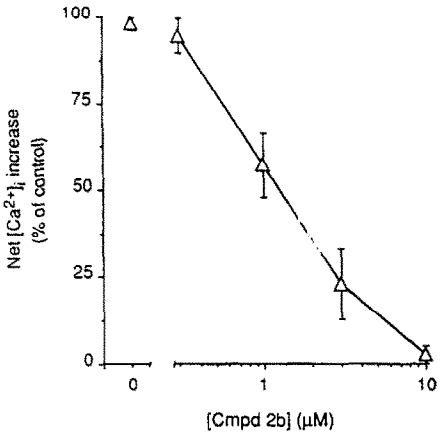


Fig. 5. Concentration-dependent inhibition of electrically evoked $[Ca^{2+}]_i$ transients in DRG neurons by compound **2b**. Responses in the presence of compound **2b** are expressed as a percentage of the response prior to application of the drug. The average net $[Ca^{2+}]_i$ increase for the control responses was 305 ± 28 nM (N = 22). Data are presented as means ± SEM (N ≥ 4).

DRG neurons resulted in a $[Ca^{2+}]_i$ transient which was primarily mediated by N-type Ca^{2+} channels (Fig. 4). Nitrendipine inhibited the rise in $[Ca^{2+}]_i$ by 9% which was not statistically significant (N = 7), while ω-CgTx blocked 81% of the response ($P < 0.001$; N = 4). Action potential-mediated Ca^{2+} influx in DRG neurons has been shown to be mediated in part by low threshold T-type Ca^{2+} channels consistent with a sum of nitrendipine and ω-CgTx sensitive components of less than 100% [33]. A 10 μM concentration of compound **2b** blocked the entire field potential-induced increase in $[Ca^{2+}]_i$ in rat DRG neurons, suggesting that at least three Ca^{2+} channel subtypes were blocked by this compound. The effects of compound **2b** reversed readily (Fig. 4, B and C). As shown in Fig. 5, compound **2b** inhibited the field potential-induced response in a concentration-dependent manner with an IC_{50} of 1 μM, similar to that observed for inhibition of the predominantly dihydropyridine-sensitive high K^+-evoked response in NG108-15 cells (Fig. 3). The graded inhibition produced by compound **2b** is inconsistent with an action on Na^+ channels which would be predicted to produce all-or-none type block, since Na^+ channels mediate action potentials which are not graded.

DISCUSSION

A series of lipophilic amino alcohols, acyclic analogues of the anticholinergic drug vesamicol, were evaluated for Ca^{2+} channel blocking activity. Structure–activity studies indicated that structural features required for Ca^{2+} channel blocking activity were distinct from those required for anticholinergic activity. A key element required for Ca^{2+} channel blocking activity was the presence of an electron withdrawing substituent on the pendant phenyl ring. One of the most active compounds, 3-(3-bromophenyl) - 2 - hydroxy - 1 - [1 - (4 - phenylpiperidinyl)] propane (compound **2b**), was characterized in more detail. This compound inhibited the L-type Ca^{2+} channel response in NG108-15 cells, evoked by depolarization with 50 mM K^+, with an IC_{50} of 5 μM. Field potential stimulation of DRG neurons elicited $[Ca^{2+}]_i$ transients mediated by at least three Ca^{2+} channel subtypes; ω-CgTx-sensitive, N-type Ca^{2+} channels were predominant. Compound **2b** inhibited all Ca^{2+} channel subtypes recruited by action potentials in these cells with an IC_{50} of 1 μM.

The amino alcohols described here are structurally different from the four major classes of Ca^{2+} antagonists which inhibit voltage-sensitive Ca^{2+} channels (phenylalkylamines, benzothiazepines, dihydropyridines and piperazines). Ca^{2+} antagonists are a heterogeneous class of compounds presumably acting at several distinct but allosterically coupled binding sites on the Ca^{2+} channel [14]. Furthermore, drugs which interact with Ca^{2+} binding proteins such as calmodulin also have Ca^{2+} channel blocking activity [3]. The amino alcohols described here are related to a small group of anti-ischemic agents represented by ifenprodil (Fig. 1). The latter, an antihypertensive and anti-ischemic agent, has been shown to possess modest direct Ca^{2+} channel blocking activity [34], but is better known for its actions as an *N*-methyl-D-aspartate (NMDA) receptor antagonist [35, 36]. Ifenprodil interacts with a polyamine binding site on the NMDA receptor [37]. In addition, ifenprodil, as well as vesamicol, exhibits α-adrenoceptor blocking activity [38, 39]. We have not yet evaluated the lipophilic amino alcohols described here for effects at the α-adrenoceptor or the NMDA receptor. Future structure–activity studies will determine whether a common binding site for these compounds is present on both voltage-sensitive and receptor-operated Ca^{2+} channels.

Compound **2b** was not selective for a particular Ca^{2+} channel subtype, since it inhibited completely the depolarization-induced $[Ca^{2+}]_i$ transients in both 50 mM K^+-stimulated NG108-15 cells, a predominantly L-type response, and in field potential-stimulated DRG neurons, a predominantly N-type response. The compound was slightly more potent in the N- versus the L-type Ca^{2+} channel assay (1 vs 5 μM, respectively). Previously described organic Ca^{2+} channel blockers which act at multiple voltage-sensitive Ca^{2+} channel subtypes are more potent at the L-type, dihydropyridine-sensitive Ca^{2+} channel [16]. Presently, we do not know whether these compounds are selective for Ca^{2+} channels. The graded inhibition produced in the field potential assay suggests that these compounds do not interfere with Na^+ channels since the production of action potentials is not graded. The rather modest micromolar potency of these compounds suggests that they may not be especially selective. However, a limited series of modifications to the pendant phenyl ring produced large changes in Ca^{2+} channel blocking activity, raising the possibility that future work may yield more potent compounds. Ca^{2+} channel blockers which inhibit all channel subtypes might be predicted to be too non-selective for clinical

use. However, a broad spectrum Ca^{2+} antagonist might be useful as a protective agent from Ca^{2+} overload. A drug selective for Ca^{2+} channels, but not specific for channel subtype would be a useful tool for exploring the role of voltage-sensitive Ca^{2+} channels in physiological processes. Inorganic cations are often useful Ca^{2+} channel blockers, but they are not always compatible with physiological experiments. Organic compounds such as verapamil, diltiazem and dextromethorphan will inhibit multiple Ca^{2+} channel subtypes [16] at concentrations many fold higher higher than necessary for inhibition at L-type Ca^{2+} channels. The compounds described here provide a new chemical starting point for the development of Ca^{2+} antagonists. Development of the amino alcohol structure may lead to more potent compounds with broad spectrum Ca^{2+} channel blocking activity.

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