0026-895X/91/050609-06$03.00/0

MOLECULAR PHARMACOLOGY, 39:609-614

ACCELERATED COMMUNICATION

Aminoalkyl Structural Requirements for Interaction of Lidocaine with the Class I Antiarrhythmic Drug Receptor on Rat Cardiac Myocytes

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Received August 14, 1990; Accepted February 5, 1991

SUMMARY

The structural and physicochemical determinants of binding of lidocaine and several of its aminoalkyl homologs to specific sites associated with the sodium channel were assessed using a radioligand assay and freshly isolated rat cardiac myocytes. The two series of closely related lidocaine homologs that were studied were composed, first, of homologs differing in the length of the link between the arylamide and amine domains of the molecule and, second, of homologs differing in the number of carbons attached to the terminal amine. Drug affinity was measured with a radioligand binding assay, using [^{3}H]batrachotoxinin A 20α-benzoate and freshly isolated cardiac myocytes. The affinities of the homologs were then compared with the pK_a values, partition coefficients, distribution coefficients, and molecular structure of the homologs, to determine the relationship between the affinity for the receptor and the physicochemical and structural properties of the drug. Optimal binding was obtained with a link between the arylamide and amine domains that was two carbons in length. The affinity of the drug for the receptor was optimal with four or more amino-terminal carbons, and the precise arrangement of the carbons was not important. Each of the amino-terminal carbons independently contributed 0.3 kcal of free energy of binding, suggesting that the carbons dissolve in a hydrophobic pocket. The evolving picture of a drug structure that is optimal for receptor binding is one of a compound with a two-carbon arylamide-amine link and four or more amino-terminal carbons.

The antiarrhythmic effect of class I drugs is thought to be mediated by their interaction with a receptor that is associated with the cardiac sodium channel (1–3). This report is aimed at an understanding of some of the structural and physicochemical determinants of class I drug binding to the receptor. Most class I drugs structurally consist of an aromatic lipophilic residue connected, via a linking alkyl chain, to a hydrophilic amine group. Recently, we used stereoisomers of antiarrhythmic drugs to show that the orientations of both the aromatic and amine groups with respect to the rest of the molecule are important determinants of class I drug binding to the cardiac sodium channel (4, 5). Our method uses the sodium channel-specific toxin [^{3}H]BTX-B, with which we have identified a receptor for class I antiarrhythmic drugs that is associated with sodium channels that are present on rat cardiac myocytes (3, 6). Class I antiarrhythmic drugs inhibit [^{3}H]BTX-B binding reversibly, stereospecifically, and at pharmacologically relevant concentrations, with the same rank order of potency *in vivo* as *in vitro*, suggesting that binding is relevant to clinical effect (3).

The purpose of the present study was to investigate more closely the roles of the link and amine groups in class I antiarrhythmic drug binding to the sodium channel. Specifically, the goal was to determine whether the affinities of closely related structural homologs of the prototypic class I drug lidocaine (Fig. 1) for the class I drug receptor correlated with physicochemical properties of the compounds, such as pK_a, octanol-water partition coefficient, or distribution coefficient, or with specific structural features of the homologs.

Materials and Methods

Myocyte preparation. Cardiac myocytes were isolated from adult male Sprague-Dawley rats (200–250 g) by collagenase dispersion, using the method of Kryski *et al.* (7), as previously described (6). This method routinely yielded about 60 mg (dry weight) of myocytes, which corresponds to 1.2×10^7 cells (7, 8). The cells were 75–90% viable rod-shaped cells that excluded Trypan blue and were tolerant of 1 mM calcium.

Radioligand binding. Binding assays were performed as described

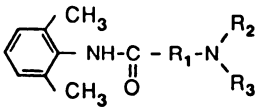
This work was supported by grants from the Medical Research Council of Canada, the Alberta Heritage Foundation for Medical Research, and the Alberta Heart and Stroke Foundation. R.S.S. is a Canadian Heart Foundation Scholar.

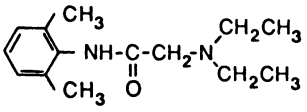
ABBREVIATIONS: [^{3}H]BTX-B, [^{3}H]batrachotoxinin A 20α-benzoate; ATX, sea anemone toxin II; GX, glycinexylidide; MEGX, monoethylglyinexylidide; EMGX, ethylmethylglyinexylidide; BSA, bovine serum albumin.

previously (3). Myocytes (6×10^5/assay) in 50 μl of incubation buffer (minimum essential medium with 50 μM $CaCl_2$ and 0.1% BSA) were incubated with 1.3 μM ATX, 13 nM [^{3}H]BTX-B (50 Ci/mmol), and 0.13 mM tetrodotoxin for 60 min at 37° (see Ref. 9 for a review of sodium channel toxins). Tetrodotoxin was added to prevent sodium influx and cell death; without tetrodotoxin, no specific binding is observed (6, 10). Various concentrations of drugs were included in the incubations. Assays were done in parallel with tubes containing 0.4 mM aconitine to define nonspecific binding. Reactions were terminated by the addition of 10 ml of Krebs-Henseleit-BSA buffer (127 mM NaCl, 2.33 mM KCl, 1.30 mM KH_2PO_4, 1.23 mM $MgSO_4$, 25 mM $NaHCO_3$, 10 mM glucose, 50 μM $CaCl_2$, 1% BSA) equilibrated with 95% O_2/5% CO_2 and incubated at 37° for 1 min; filtered through a Whatman GF-C 24-mm filter; and washed 4 times with 5 ml each of rinse buffer (25 mM Tris·HCl, pH 7.4, 130 mM NaCl, 5.5 mM KCl, 0.8 mM $MgSO_4$, 5.5 mM glucose, 50 μM $CaCl_2$). The filters were then dried and counted in 10 ml of Econofluor scintillation fluid. The retained radioactivity represents [^{3}H]BTX-B bound to myocytes.

The rationale for the incubation and filtration conditions has been described previously (6). These conditions provide a maximal reduction in background and scatter, with a minimal reduction in specific binding. The total wash time was 45 sec. Initial control experiments showed that under these conditions less than 10% of the specifically bound [^{3}H]BTX-B dissociated from the complex. Under these reaction conditions (13 nM [^{3}H]BTX-B, 0.13 mM tetrodotoxin, 1.3 μM ATX), about 60–75% of the total radioactivity retained on the filters was bound specifically to the [^{3}H]BTX-B binding site.

Experimental design and statistical analysis. A paired experimental design was used to overcome any artifactual differences that might be produced by day-to-day variability in cell preparations or toxins. IC_{50} values of each homolog were determined in parallel with that of lidocaine, using common cell preparations and toxin concentrations. The IC_{50} value for drug binding was defined as the concentration of the drug that inhibited specific [^{3}H]BTX-B binding by 50%. The IC_{50} values were estimated with the use of Hill plots, but the curvilinear figures were drawn by hand. Each homolog was tested at least three times on separate days with fresh drug solutions. The statistical significance of the difference between the mean IC_{50} values of homologs and lidocaine for inhibition of [^{3}H]BTX-B binding was assessed using a paired Student's test. Paired results are expressed as IC_{50} of lidocaine/IC_{50} of homolog.





LIDOCAINE

	Homolog	R_1	R_2	R_3	Carbons, $R_2 + R_3$
Series A	Lidocaine	CH_2	C_2H_5	C_2H_5	4
	L30	C_2H_4	C_2H_5	C_2H_5	4
	W6603	C_3H_6	C_2H_5	C_2H_5	4
	W82139	C_4H_8	C_2H_5	C_2H_5	4
Series B	GX	CH_2	H	H	0
	MEGX	CH_2	H	C_2H_5	2
	EMGX	CH_2	CH_3	C_2H_5	3
	RAD241	CH_2	CH_3	C_3H_7	4
	LIDOCAINE	CH_2	C_2H_5	C_2H_5	4
	RAD244	CH_2	CH_3	C_4H_9	5
	L48	CH_2	C_2H_5	C_3H_7	5
	RAD242	CH_2	CH_3	C_5H_{11}	6

Fig. 1. Molecular structures of lidocaine and related homologs.

Drug selection and physicochemical properties. Two series of closely related lidocaine homologs were chosen for study (Fig. 1). Series A consisted of homologs differing in the length of the chain (residue R_1) between the arylamide and amine domains of the molecule. These were lidocaine, L30, W6603, and W82139. Series B consisted of homologs differing in the number of carbon atoms (residues R_2 and R_3) attached to the amino-terminal portion of the molecule. These were GX, MEGX, EMGX, L48, lidocaine, RAD241, RAD242, and RAD244. The octanol-water partition coefficients, °P, and pK_a values of the compounds other than W82139 were taken from the work of Bokesch *et al.* (11). The values for W82139 were taken from Tenthorey *et al.* (12), respectively. All the pK_a values in the latter study were calculated by titration in distilled water at 23°. The distribution coefficient, Q, which is the ratio of the base form of the compound in the hydrophobic phase to the total compound in the hydrophilic phase at pH 7.4, was determined as $\log Q = \log {}^{o}P - \log(1 + 10^{pK_a - 7.4})$. Log$Q$ can be used to estimate the concentration of a compound in the hydrophobic phase, based upon its pK_a and partition coefficient °P (13).

Materials. [^{3}H]BTX-B was purchased from New England Nuclear (Boston, MA); collagenase from Cooper Biomedical (Malvern, PA); and tetrodotoxin, aconitine, BSA, lidocaine, and ATX from Sigma Chemical Co. (St. Louis, MO). The lidocaine homologs other than W82139 were kindly provided by ASTRA Pharmaceuticals (Westboro, MA). W82139 was graciously provided by Dr. P. D. McMaster, College of the Holy Cross (Worcester, MA).

Results

Homologs differing in the length of the arylamide-amine link (series A). The four homologs in series A each inhibited [^{3}H]BTX-B binding in a concentration-dependent fashion, with mean IC_{50} values ranging from 24 μM to 201 μM. Results of typical experiments are shown in Fig. 2 (*left*). The ratio of the IC_{50} value of lidocaine to that of W6603 was 0.20. The mean IC_{50} values were 52 ± 19 μM for lidocaine (42 experiments) and 201 ± 43 μM for W6603 (three experiments) (Table 1), and the mean paired ratio of IC_{50} of lidocaine/IC_{50} of W6603 was 0.24 ($p < 0.05$). The mean IC_{50} value for L30 (five experiments) was 24 ± 10 μM and the mean paired ratio

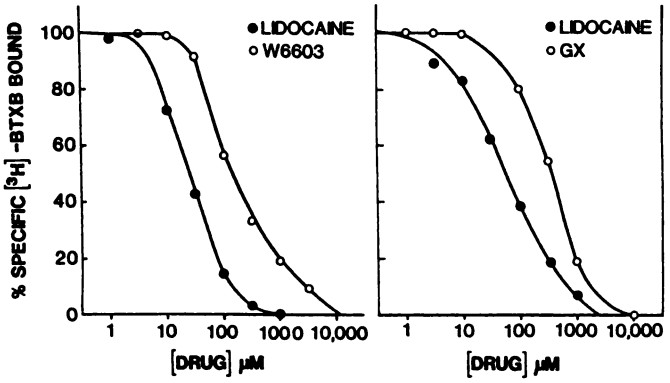


Fig. 2. Effects of lidocaine and W6603 (*left*) and lidocaine and GX (*right*) on the binding of [^{3}H]BTX-B to myocytes. Myocytes (6×10^5/point) were incubated with 13 nM [^{3}H]BTX-B, 0.13 mM tetrodotoxin, 1.3 μM ATX, and various concentrations of lidocaine and its homologs for 60 min. Specifically bound [^{3}H]BTX-B was measured as described in Materials and Methods. The IC_{50} values of lidocaine and W6603 (*left*) were 34 and 170 μM, respectively. The IC_{50} values of lidocaine and GX (*right*) were 65 and 366 μM, respectively.

TABLE 1

IC_{50} values of lidocaine homologs having different arylamide-amine chain lengths (R_1)

R_1, substituents as described in Fig. 1. *n*, number of determinations. Each ratio is the mean of three to five ratios determined in paired experiments. °P, pK_a, and log*Q* values for lidocaine and the homologs are derived from data taken from Bokesch *et al.* (11).

Homolog	R_1	*n*	IC_{50}	IC_{50} of lidocaine/ IC_{50} of homolog	Hill number	pK_a	°P	log*Q*
			μM					
Lidocaine	CH_2	42	52 ± 19	1.0	0.9 ± 0.2	7.7	190	1.803
L30	C_2H_4	5	24 ± 10[a]	1.73	0.8 ± 0.1	9.0	549	1.13
W6603	C_3H_6	3	201 ± 43[a]	0.24	0.8 ± 0.1	9.5	1585	1.097
W82139	C_4H_8	3	175 ± 58[a]	0.31	0.9 ± 0.2	10.0[b]	4574	1.099

[a] Significant difference between IC_{50} of homolog and IC_{50} of lidocaine, $p < 0.05$.
[b] Data from Tenthorey *et al.* (12).

of IC_{50} of lidocaine/IC_{50} of L30) was 1.73 ($p < 0.05$), whereas for W82139 the mean IC_{50} value was 175 ± 58 μM and the mean IC_{50} ratio was 0.31 ($p < 0.05$).

The mean Hill numbers, IC_{50} values, pK_a values, °*P* values (partition coefficients), and log*Q* values (distribution coefficients) for the three chain-length homologs in series A are presented in Table 1. The mean Hill numbers ranged from 0.8 to 0.9, with a global mean Hill number of 0.84 ± 0.22. The pK_a values ranged from 7.7 to 9.5, and octanol-water partition coefficients from 190 to 4574. Log*Q* values ranged from 1.097 to 1.803. None were significantly related to the IC_{50} values. Fig. 3 (*left*) graphically demonstrates that the lowest IC_{50} value occurs with a link chain length of two carbons.

Homologs differing in the number of the aminoalkyl substituents (series B). All homologs in series B inhibited [^{3}H]BTX-B binding in a concentration-dependent manner, with mean IC_{50} values ranging from 51 μM to 375 μM. A typical experiment is shown in Fig. 2 (*right*). In this example, the ratio of the IC_{50} value of lidocaine to that of GX was 0.18. The mean IC_{50} value for four experiments was 375 ± 95 μM for GX, and the mean ratio of IC_{50} of lidocaine/IC_{50} of GX was 0.14 ($p < 0.05$; Table 1). Thus, GX is considerably less potent than lidocaine in inhibiting [^{3}H]BTX-B binding.

The mean Hill numbers, IC_{50} values, pK_a values, partition coefficients, and distribution coefficients of all lidocaine homologs differing in aminoalkyl substituents are presented in Table 2. The mean Hill numbers ranged from 0.7 to 1.4, with a global mean of 0.9 ± 0.2. Lidocaine homologs having less than four amino carbons inhibited [^{3}H]BTX-B binding with IC_{50} values significantly higher than that of lidocaine, whereas homologs with four or more amino carbons inhibited [^{3}H]BTX-B binding with IC_{50} values similar to that of lidocaine. The pK_a values of the homologs ranged from 7.40 to 8.04 and were unrelated to the IC_{50} values of the homologs. The partition coefficients (°*P*) increased from 2.80 (GX; no amino carbons) to 1585 (RAD242; six amino carbons) and increased with the number of amino carbons. Similarly, log*Q* increased with the number of amino carbons, from −0.016 for GX to 2.899 for RAD242. The relationship between the IC_{50} values and the number of amino carbons is depicted in Fig. 3 (*right*). The IC_{50} value decreased with the number of amino carbons, with minimal IC_{50} values occurring with four or more carbons. Thus, optimal binding occurs with compounds having four or more amino-terminal carbons.

Discussion

The principal new finding in this work is that the affinity of structurally closely related homologs of lidocaine for the cardiac sodium channel is optimal for a compound with an arylamide-

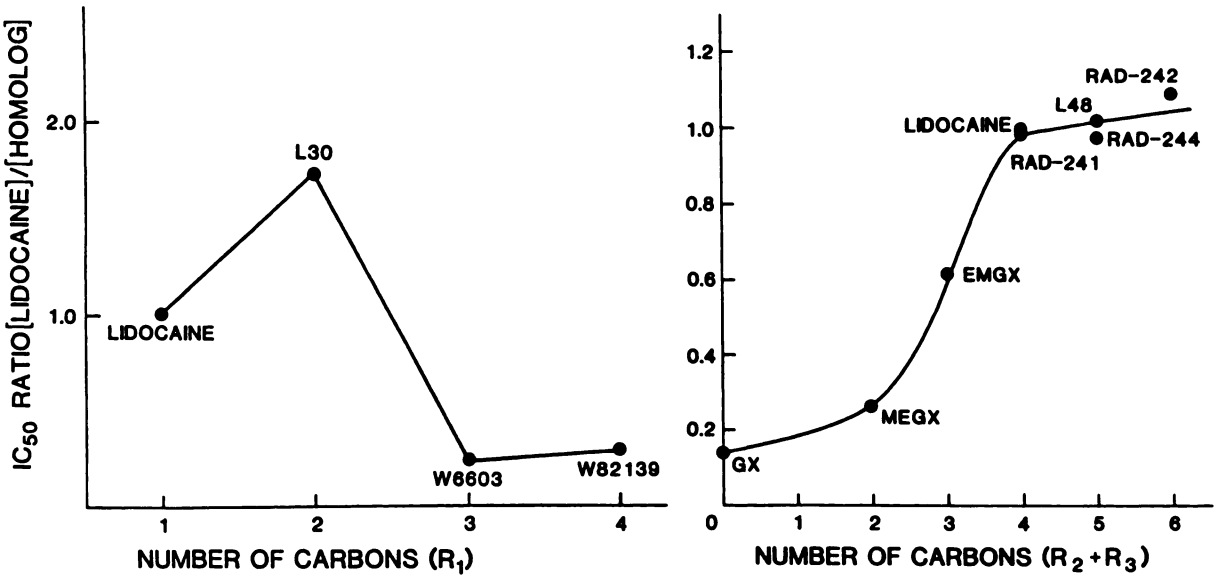


Fig. 3. Relationship between the IC_{50} ratio and the length of the arylamide-amine link (*left*) or the number of aminoalkyl carbons (*right*), for lidocaine and its structural homologs. Values for IC_{50} of lidocaine/IC_{50} of homolog were taken from Tables 1 and 2.

TABLE 2

IC_{50} values of lidocaine homologs having various amine substituents (R_2 and R_3)

R_2 and R_3, amine substituents as described in Fig. 1. *n*, number of determinations. Each ratio is the mean of three to five ratios determined in paired experiments. °*P*, pK_a, and log*Q* values for lidocaine and all homologs except GX and MEGX are derived from data taken from Bokesch *et al.* (11). The values for GX and MEGX are from Broughton *et al.* (14).

Homolog	R_2	R_3	*n*	IC_{50}	IC_{50} of lidocaine/ IC_{50} of homolog	Hill number	pK_a	°P	logQ
				μM					
GX	H	H	4	375 ± 95[a]	0.14	1.1 ± 0.6	7.68	2.8	−0.016
MEGX	C_2H_5	H	5	198 ± 77[a]	0.26	0.8 ± 0.2	8.04	21	0.592
EMGX	CH_3	C_2H_5	3	73 ± 11[b]	0.61	0.7 ± 0.2	7.60	66	1.408
RAD241	CH_3	C_3H_7	3	60 ± 18	0.98	1.2 ± 0.7	7.70	190	1.803
Lidocaine	C_2H_5	C_2H_5	42	52 ± 19	1.0	0.9 ± 0.2	7.70	190	1.803
L48	C_2H_5	C_3H_7	3	51 ± 28	1.02	0.7 ± 0.1	8.00	549	2.403
RAD244	CH_3	C_4H_9	3	61 ± 10	0.97	1.4 ± 0.9	7.60	549	2.328
RAD242	CH_3	C_5H_{11}	4	60 ± 43	1.19	0.9 ± 0.2	7.40	1585	2.899

[a] Significant difference between IC_{50} of homolog and IC_{50} of lidocaine, $p < 0.01$.
[b] Significant difference between IC_{50} of homolog and IC_{50} of lidocaine, $p < 0.05$.

amine link of two carbons and four or more amino-terminal carbon substituents.

Previous studies (11, 13–16) that have addressed the structure-activity relationships of how class I antiarrhythmic drugs interact with the sodium channel have led to relatively few firm conclusions about precise structural contributions, for two reasons. First, the studies generally (but not universally) have characterized sodium channel blockade by series of drugs that are structurally poorly related, thus precluding the elucidation of structure-activity relationships for specific structural aspects of the drugs. Second, the use of electrophysiological techniques has paradoxically made elucidation of structure-activity rules for binding to the receptor more difficult. In order to exhibit electrophysiological evidence of sodium channel blockade, the drugs must perform several functions. They must access the drug receptor (either via the hydrophobic membrane or through a hydrophilic pore in the channel), bind to the receptor, block sodium influx, dissociate from the receptor, and, finally, leave the membrane-sodium channel milieu to return to the extracellular or intracellular fluid space. All of these events contribute to drug action, and the multitude of effects has made difficult the elucidation of structure-activity rules for the interaction of drugs with the receptor itself. However, electrophysiological studies may provide useful information about drug movement through the membrane and about differences in binding sites and/or affinities as the channel passes through various states. For example, studies with class I drugs and myocardial sodium channels have indicated that both open channel block (16) and the onset of block (13) correlate with the lipid solubility of the drugs, whereas the dissociation of drugs from the channel is faster for smaller drugs (13, 16). The latter data have led to the proposition that these drugs exit the channel via a cylindrical pore with a radius of 4.1 Å (13).

The present study is an approach to understanding the precise structural features of drugs that govern drug interactions with the receptor itself. An equilibrium radioligand binding assay has been used to circumvent the rate-dependent effects of drug access to and egress from the receptor (17). Drug affinities for this receptor have been shown previously to correlate closely with clinically observed drug serum concentrations (3). The confounding effects in the study of drugs with diverse structures have been minimized by the use of test compounds in two series of closely related structural homologs of the class I drug lidocaine. The relationships of affinities of these homologs for the receptor with their known physicochemical properties and with specific structural features will be explored below.

Series A. The three homologs in series A were chosen to evaluate the role of the length of the arylamide-amine link in drug binding. The mean IC_{50} values of lidocaine (one carbon), L30 (two carbons), W6603 (three carbons), and W82139 (four carbons) were 52, 24, 201, and 175 μM, respectively. These values do not correlate with pK_a, partition coefficient, or distribution coefficient and suggest by exclusion that there may be a distribution coefficient, pK_a, or length of the link that is optimal for drug binding. However, the difference between the distribution coefficients for L30 and W6603 (which are 13.5 and 12.5, respectively) is much less than the difference between their mean IC_{50} values (which are 24 and 201 μM, respectively). As well, the principal effect of pK_a on drug structure is on the ratio of the charged and neutral forms. An "optimal" pK_a would suggest that the receptor recognizes the ratio of charged to neutral forms. To date, there is little evidence for this concept. Thus, although we have not directly demonstrated that these physicochemical explanations are incorrect, we favor the conclusion that the length of the chain *per se* and, therefore, the specific molecular shape of the compound are important in drug binding.

A similar conclusion was reached by Lloyd and Andrews (18) in their study of the conformations of 14 drugs that interact with the central nervous system. They found that most of these and other central nervous system-active drugs have a phenyl ring and a nitrogen carbon, separated by a two- to five-atom chain. In comparison, Bokesch *et al.* (11) found that lengthening of the link reduced the ability of homologs to cause tonic impulse blockade in nerve sodium channels. This appeared to correlate with the increased hydrophobicity of homologs with longer links. However, our results suggest that it is the length of the link, rather than changes in drug hydrophobicity, that modulates affinity of the drug for the receptor.

Series B. The IC_{50} values for homolog binding to the receptor decrease as the number of amino-terminal carbons increases, with an asymptotic value for IC_{50} being approached with compounds having four or more carbons. The mean IC_{50} values for GX (no amino-terminal carbons), lidocaine (four amino-terminal carbons), and RAD242 (six amino-terminal carbons) were 375, 52, and 60 μM, respectively.

This finding is supported by the work of Broughton *et al.*

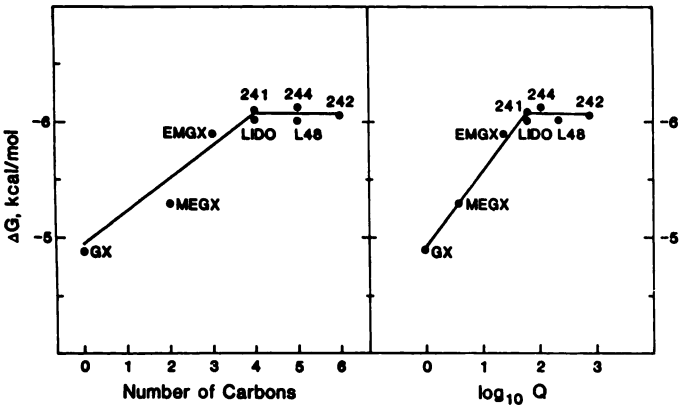


Fig. 4. Relationship between the estimated free energy of binding (ΔG) (kcal/mol^{-1}) of drug homologs and the total number of amino carbons (*left*) or log$Q$ (*right*).

(14), who compared the ability of GX, MEGX, and lidocaine to cause use-dependent block of sodium channels in guinea pig papillary muscle. Lidocaine, MEGX, and GX had a decreasing order of potency. The half-maximal concentration of lidocaine was slightly higher than 30 μM, whereas the half-maximal concentrations of MEGX and GX were substantially greater than 30 and 120 μM, respectively. Our results are consistent with those of Broughton *et al.* (14), in terms of not only rank order of potency but also absolute potency.

The IC_{50} values for these homologs were not related solely to changes in physicochemical constants. For compounds with zero to four amino-terminal carbons, the IC_{50} values progressively decreased as the partition coefficients and distribution coefficients increased. However, the differences between the IC_{50} values cannot be explained on the basis of partition coefficients alone, because lidocaine (IC_{50}, 52 μM) had a partition coefficient of 190, whereas RAD242 (IC_{50}, 50 μM) had a partition coefficient of 1585. Similarly, the differences in IC_{50} values cannot be explained on the basis of log$Q$ alone, because lidocaine (IC_{50}, 52 μM) had a log$Q$ of 1.803, whereas RAD242 (IC_{50}, 60 μM) had a log$Q$ of 2.899.

Thus, the differences in IC_{50} values for the homologs with differing numbers of amino carbons cannot be ascribed solely to differences in partition coefficient, pK_a, or log$Q$. These data, therefore, suggest that drug structure is important and that four or more amino-terminal carbons are optimal for drug binding. Two specific structural models might account for this. The first model proposes that the length of the longest aminoalkyl chain is critical. However, lidocaine (longest chain, two carbons) and RAD242 (longest chain, five carbons) have similar IC_{50} values. The second model proposes that the distribution of the amino carbons is important. However, lidocaine (which has two aminoethyl groups) and RAD241 (which has aminomethyl and aminopropyl groups) have similar IC_{50} values. Thus, optimal binding occurs with four or more amino-terminal carbons, but the precise distribution of these carbons does not appear to be important.

Interaction of molecular structure and physicochemical properties. The relative imprecision of the structural requirement for four amino-terminal carbon atoms suggests that their contribution cannot be explained by a simple lock and key receptor model. An alternative possibility is that these carbons might dissolve in a hydrophobic pocket that can accommodate up to four carbons. This model predicts, first, that each of the carbons should contribute independently and equally to the free energy of binding and, second, that the free energy of binding should be proportional to log$Q$. The free energy of binding can be estimated if one assumes that the dissociation constant, K_D, for drug binding is similar to the IC_{50} value. The free energy of binding, ΔG, may be estimated from the equation $\Delta G = -RT\ln(1/K_D)$ (Ref. 19). These predictions were tested by correlation of the estimated ΔG with the number of amino carbons (Fig. 4, *left*) and with log$Q$ (Fig. 4, *right*). ΔG decreases linearly with the number of amino-terminal carbons from zero to four carbons, to an asymptotic value of −6.1 Kcal, with a linear regression coefficient of 0.976. Each carbon appears to contribute 0.3 kcal to the free energy of binding. Fig. 4 also displays the very close correlation ($r = 0.996$) between ΔG and log$Q$. These correlations are consistent with the notion that the amino-terminal carbons dissolve in a hydrophobic pocket that can accommodate up to four carbons.

Limitations. There are potential limitations in this study. It is unable to address the effect of drugs and particular drug structures on transitions between different channel states. As well, the use of IC_{50} as an approximation of K_D ignores the likelihood that class I drugs bind with different affinities to different states of the channel. Indeed, in this report drugs bind with a mean Hill number of about 0.9 (3), suggesting that they each bind to a single state. This may reflect binding to closed channels (20). We cannot eliminate the possibility that the variability in Hill numbers might reflect either different degrees of cooperativity or different numbers of binding sites for each drug. However, given the close structural similarity among the homologs, it seems more likely that the variability in the observed Hill numbers reflects experimental error, rather than different, but drug-specific, mechanisms of binding. Thus, for practical purposes, the measured IC_{50} values in this assay reflect the K_D of binding to a single state.

Importantly, the affinities of drugs for the receptor in this model correlate extremely well with their clinically observed serum concentrations, over 3 orders of magnitude (3). Thus, the different affinities of homologs for the receptor in this model should reflect clinically relevant structure-activity relationships.

Conclusions. A radioligand model of the class I drug receptor that is associated with the cardiac sodium channel has been used to derive simple structure-activity relationships for two series of lidocaine homologs. The evolving picture of an optimum class I drug structure is one that contains a two-carbon arylamide-amine link and four or more amino carbons. This suggests that the receptor precisely recognizes a two-carbon link and that it may have a hydrophobic pocket that can accept up to four amino carbons.

Acknowledgments

We are grateful to Ms. J. Johnson (ASTRA) for providing the lidocaine homologs, to Ms. D. Swinton for expert assistance in preparing this manuscript, and to Dr. P. D. McMaster for providing W82139.

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