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Voltage-gated Na^+ channel ligands and ATP: relative molecular similarity and implications for channel function

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Abstract

The voltage-gated sodium channel (VGNC) is targeted by naturally occurring ligands and drugs of diverse structure. ATP modulates VGNC current in-vitro but is given little prominence in models describing channel function. This computational study uses superimposition and molecular fitting to investigate relative molecular similarity within the structures of ATP and VGNC ligands. A motif of 3 linked atoms (C-N-C) in the adenine ring of ATP satisfies the fitting of a wide range of anticonvulsant structures. An alternative group (N-C-N) provides one fitting motif for the ester and amide groups of local anaesthetic drugs; protonated amine and aromatic groups in the same conformers fit to a second motif in the adenine ring. Analogous structures from other drug classes with VGNC blocking activity give the same molecular fits to ATP. Structures fitted to the adenine ring of ATP occlude the intra-molecular space between the nucleoside and triphosphate chain in approximation to their established blocking, activating or neutral effects on Na^+ current. The findings are discussed in terms of drug preferences for VGNC states and channel requirements for ATP.

Introduction

Voltage-gated sodium channel (VGNC) blocking action, a primary mechanism of anticonvulsant, anti-arrhythmic and local anaesthetic drugs, is evident in several other drug classes. Antihistamine, antidepressant, anticholinergic and anti-inflammatory drugs all show use-dependent inhibition of Na^+ current, although they may not achieve useful therapeutic blocking concentrations. With reference to the above drug classes, Kuo et al (2000) have described a common structural motif of diphenyl rings separated by C-C or C-N bonds that facilitates classification of VGNC blocking action in terms of drug potency and channel state. Group 1 drugs, represented by phenytoin, show binding to inactivated channels. Group 2 drugs with charged amine groups (e.g. imipramine) have a high affinity for inactivated channels and some affinity for resting channels. The third group is represented by structurally similar drugs with a negligible effect on Na^+ current. The diphenyl motif has an important role in blocking the Na^+ channel. The protonated alkylamine chain is an important functional group for drugs outside the anticonvulsant class.

Several anticonvulsant pharmacophore models have emphasised the importance of aryl ring systems although valpromide, a drug with a phenytoin-like profile in tests evaluating maximal electroshock treatment and VGNC function (Tasso et al 2004), has no ring structure. Unverferth et al (1998) derived a general pharmacophore model from molecular dynamics simulations, consisting of at least 1 aryl ring, an electron donor atom and hydrogen bond acceptor/donor unit (HAD) in close proximity to an NH group. This model has been simplified by Tasso et al (2004) to an acceptor/donor unit (polar region) and lipophilic moiety, each comprising a 3 atom motif.

The therapeutic benefits of channel-blocking drugs for cardiac and neuronal pathologies are explained by the conversion of a low-affinity resting channel conformation into a high-affinity open or inactivated state, a process accompanied by complex frequency- and voltage-dependent changes (Ragsdale et al 1996; Cronin et al 2003). The receptor responsible for use-dependent block of the Na^+ channel becomes available for drug binding during channel activation, and subsequent conformational gating changes cause the slow binding

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rates of the inactivated channel (Yang & Kuo 2002). Channel conductance is also influenced by protons, which shift voltage range gating by neutralising the surface charges of carboxyl groups within the channel vestibule (Khan et al 2002).

One other significant characteristic of Na^+ channels in the context of this study is modulation of their kinetic properties by nucleotides, especially adenosine triphosphate (ATP). The high intracellular concentration of ATP and its release during hypoxic damage provides a potential for multiple pharmacologic effects (Schweibert & Zsembery 2003), including ion channel gating. Extracellular ATP causes a leftward shift in the Na^+ channel activation curve of a neuronal hippocampal cell line with a size effect on the Na^+ current that is dependent on the cell membrane potential (El-Sherif et al 2001). Tetrodotoxin-sensitive and -resistant Na^+ currents in rat dorsal ganglion neurons are, respectively, inhibited or increased by the external application of ATP (Park al 2004). Voltage-clamp recording data of Rola & Szulczyk (2004) demonstrate that the amplitude and density of the VGNC current from postganglionic sympathetic neurons increase without ATP in the intracellular solution. The Na^+current shows faster activation and inactivation, less steady-state inactivation and slower recovery from inactivation than neurons with the nucleotide.

This study investigates relative molecular similarity within the structures of ATP and drugs with recognised VGNC blocking action, with the aim of further clarifying their modulatory role on Na^+-channel function. The rationale for the study is provided by the aforementioned regulatory effects of ATP on VGNC function and evidence of drug receptor pharmacophores within purine nucleotide structures (Williams et al 2004). Several atomic groups in the adenine ring system relate to the described anticonvulsant and local anaesthetic motifs and these require further investigation.

Materials and Methods

The molecular structures selected for study are comprised of anticonvulsant and local anaesthetic classes of drug: VGSC-blocking drugs with some evidence of anticonvulsant or local anaesthetic action; drugs of similar structure with no blocking action (analogous drug group); the neurotoxins saxitoxin and batrachotoxin. The anticonvulsant structures contain the main chemical groups of this class — phenytoin (hydantoin), lamotrigine (triazine), felbamate (carbamate), zonisamide (sulphonamide), carbamazepine (carboximide), valproic acid (fatty acid), ethosuximide (succinimide). The local anaesthetic structures contain ester (tetracaine, pethidine) and amide (lidocaine) linkages. The drugs in the analogous group include diclofenac, phenylbutazone, tripelennamine, diphenhydramine, benztropine and imipramine, which were assessed for VGNC-blocking activity by Kuo et al (2000).

Charge calculations, conformational analysis and the building, superimposition and fitting of molecular structures were undertaken using the Nemesis program (Oxford Molecular version 2.1). A low-energy conformer of ATP was generated from the structure in the Nemesis library file, and the other structures were built from contents of the program fragment file. Alkylamine derivatives, ATP and saxitoxin are considered in their charged form. The final structures are minimum energy conformers obtained by conformational analysis and minimisation within the Nemesis program. Molecular structures are fitted to the adenine ring of ATP on the basis of 3-point pharmacophores comprised of atoms of similar type, inter-atomic distance and partial charge. Quality of fit of the molecular structures is expressed in terms of inter-atomic distance and root mean square (RMS) value.

Results

The common pharmacophore for the anticonvulsant and ATP structures is based on a 3-atom motif present in phenytoin (Figure 1). The local anaesthetic pharmacophores are based on the amide and ester groups of lidocaine and tetracaine, respectively, and the protonated amine group and phenyl ring system within these structures.

The fitting of superimposed anticonvulsant drug conformers to three adjacent atoms (C6-N9-C5) in the imidazole moiety of the adenine ring is given in Figure 2. The reduction in partial charge on atoms C5 and C6, attributable to contiguous N or O atoms, carboxyl or carbamate groups, is a common feature in the drug and adenine ring structures. Structural similarity between diclofenac and the tricyclic ring structure of carbamazepine is evident. In general, structures containing

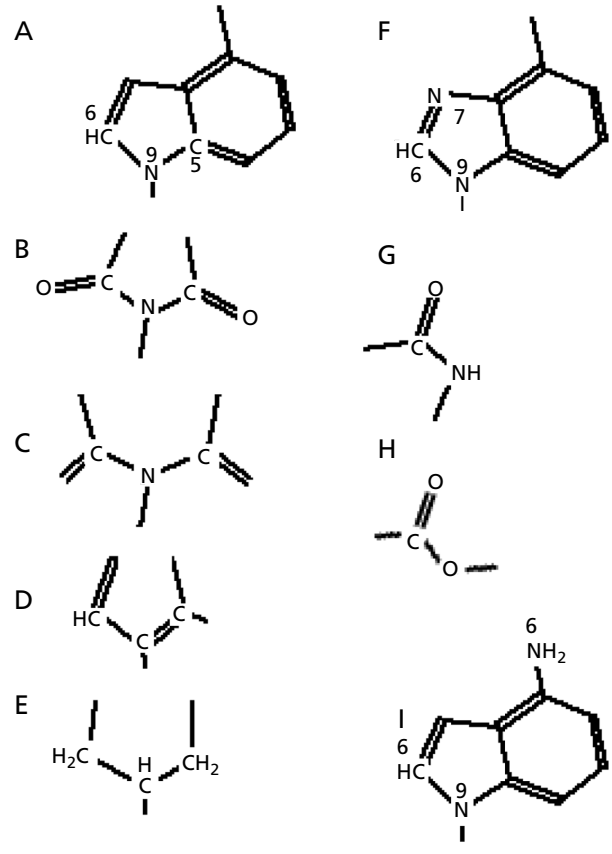

Figure 1 Schematic representation of the three fitting motifs for anticonvulsant (column 1) and local anaesthetic (column 2) drugs within the adenine ring (A, F, I): phenytoin, ethosuximide (B); carbamazepine (C); zonisamide, lamotrigine (D); felbamate, valproic acid (E); lidocaine (G); tetracaine (H).

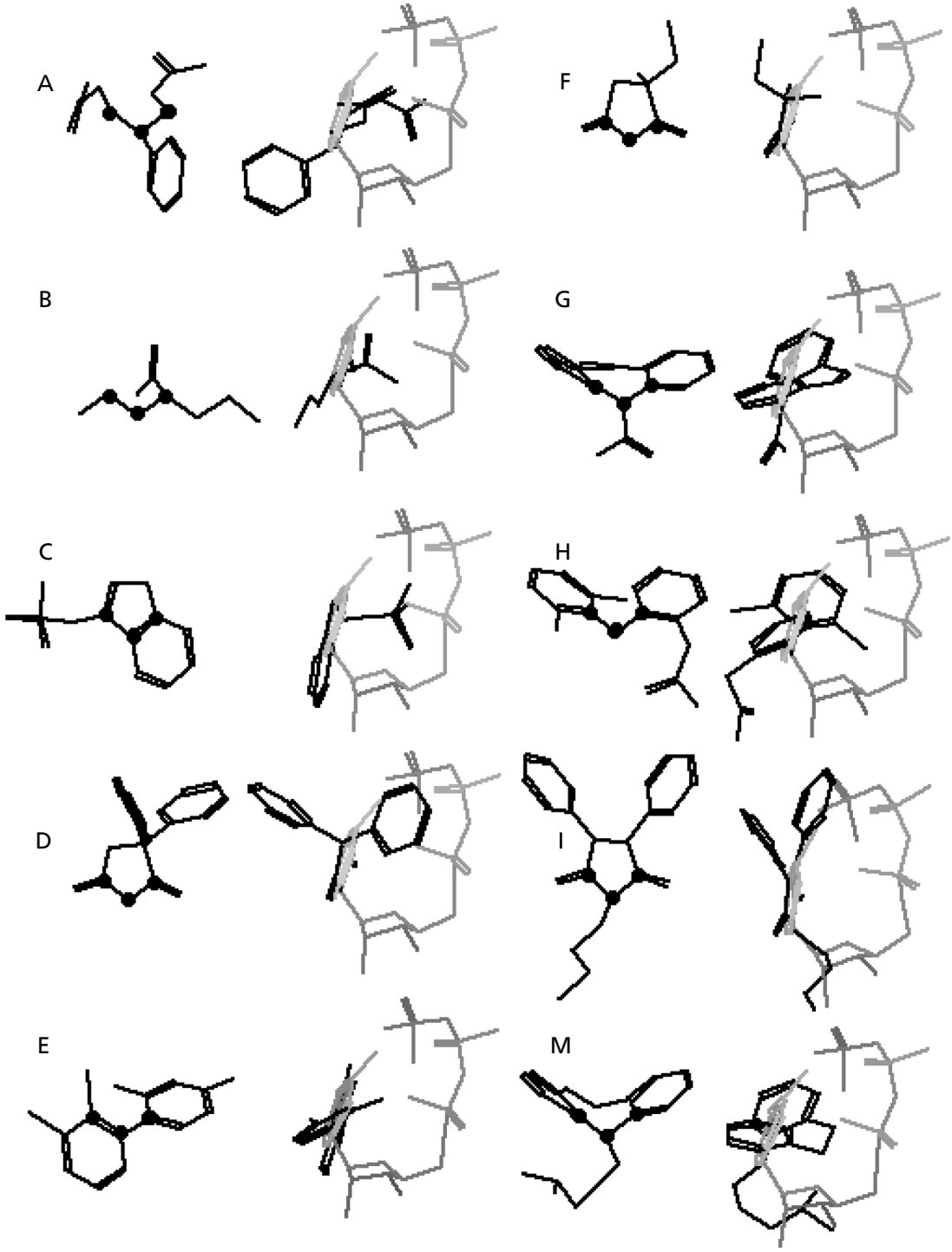

Figure 2 Common motif in drug structure (black) fits to the adenine ring (columns 1 and 3) and ATP (grey, columns 2 and 4): felbamate (A), valproic acid (B), zonisamide (C), phenytoin (D), lamotrigine (E), ethosuximide (F), carbamazepine (G), diclofenac (H), phenylbutazone (I), imipramine (M).

the pharmacophore within one ring system give a better fit to ATP than those that do not. The drugs in the best fitting group include zonisamide, phenytoin, ethosuximide, diclofenac and phenylbutazone (sum of the three inter-atomic distances < 0.22 Å, RMS < 0.0060). The fitting values of felbamate, valproic acid, lamotrigine, carbamazepine and imipramine are < 0.50 Å (sum of inter-atomic distances) and < 0.0130 (RMS). Most VGNC-blocking drug structures, when fitted to ATP as described, partially occlude the intra-molecular space between the nucleoside base and the triphosphate chain moiety.

The same degree of occlusion is not evident for the non-VGNC blockers, ethosuximide and phenylbutazone. Imipramine represents the structures in the analogous drug group (Kuo et al 2000) that have the fitting motifs C6-N9-C5 (imipramine and tripelennamine) or C6-C9-C5 (diphenhydramine and benztropine) and fitting values of < 0.39 Å (sum of inter-atomic distances) and < 0.0180 (RMS).

Fit of the amide and ester groups of lidocaine, tetracaine and pethidine to the adenine ring results in occupancy of the intra-molecular space within the ATP conformer (Figure 3). Distribution of partial charges on the N-C-N motif in the adenine ring system approximates that of the amide and ester group atoms and differs from the anticonvulsant motif. Fitting values of the aforementioned drugs are < 0.22 Å (sum of inter-atomic distances) and < 0.0200 (RMS). Imipramine represents the structures in the analogous drug group, which have the fitting motifs N9-C6-C7 (imipramine and tripelennamine) or O9-C6-C7 (diphenhydramine and benztropine) and fitting values of < 0.35 Å (sum of inter-atomic distances) and < 0.0125 (RMS). For the same conformers, the fitting of a second pharmacophore group of more widely dispersed atoms (protonated amine group and two aromatic ring car-

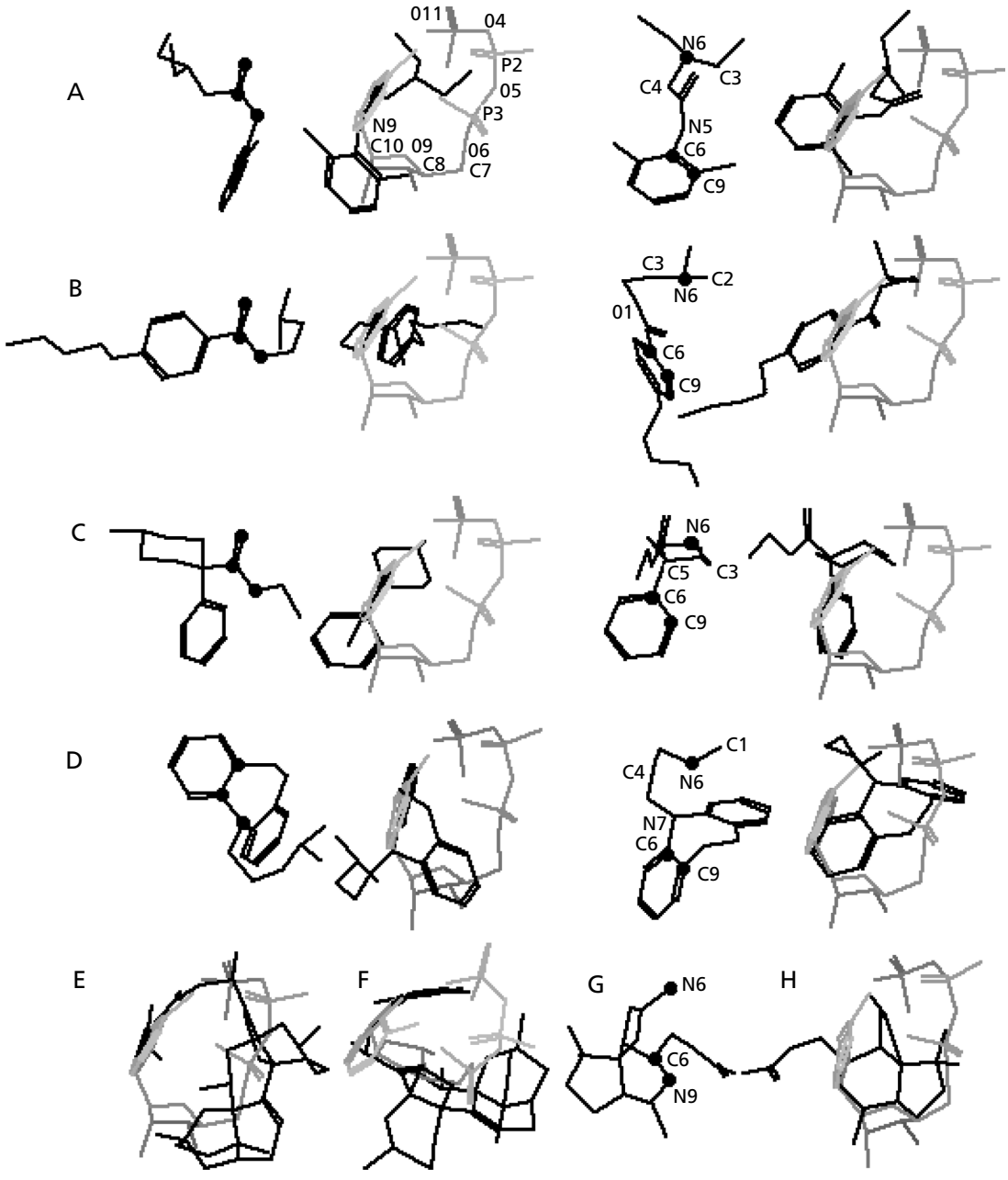

Figure 3 Common motif in drug structure (black) fits to the adenine ring of ATP (grey) based on amide/ester motifs (columns 1 and 2) or protonated amine group (columns 3 and 4): lidocaine (A), tetracaine (B), pethidine (C), imipramine (D), batrachotoxin (E and F), saxitoxin (G and H).

Table 1 Conformational data for structures fitted to ATP

	Inter-atomic distances (Å)				Torsion angles (°)
ATP	N9(C9)	N6	C6	RMS	C6N9C10O9 64, N9C10O9C8 −142, C10O9C8C7 162, O9C8C7O6 −40, C8C7O6P3 95, C7O6P3O5 158, O6P3O5P2 154, P3O5P2O4 −132, O5P2O4P1 67, P2O4P1O11 −178
Lidocaine	0.11	0.080	0.05	0.0012	C9C6N5C5 99, C6N5C5C4 −1, N5C5C4N6 −148, C5C4N6C3 84, C4N6C3C2 −156
Tetracaine	0.26	0.21	0.10	0.0236	C9C6C5O1 −169, C6C5O1C4 −166, C5O1C4C3 −53, O1C4C3N6 −32, C4C3N6C2 175
Pethidine	0.07	0.24	0.17	0.0405	C9C6C5C4 12, C6C5C4C3 69
Imipramine	0.09	0.15	0.06	0.0245	C6N7C5C4 −166, N7C5C4C3 55, C5C4C3N6 −62 C4C3N6C1 −76
Saxitoxin	0.16	0.09	0.11	0.0229	

Data for the fitting of drug conformers to ATP using the equivalent atoms identified in Figure 3 (drug conformers — column 3) and Figure 1 (ATP). RMS values for the fits are calculated by the Nemesis program from atom pairs selected from left to right.

bons) occludes the space between the nucleoside and triphosphate moiety of ATP. In the analogous drug group, tripelennamine and diphenhydramine share the same fitting motif as imipramine, whereas benztropine fits to an alternative atom in the adenine ring (N7 replaces C6). Conformational data for the structures in Figure 3 are given in Table 1, as their fitting geometries are not dependent on fixed adjacent atoms. The fits of the channel activator batrachotoxin to ATP make use of dimethylpyrrole and ester groups (sum of inter-atomic distances < 0.18 Å, RMS < 0.0140). In the dimethylpyrrole fit (E), much of the batrachotoxin structure is confined to the region of the triphosphate chain with little occlusion of intra-molecular space. The alternative ester group fit (F — viewed looking down onto the amine group of the adenine ring) shows batrachotoxin encircling the ATP structure. In contrast, the VGNC blocker saxitoxin sits within the intra-molecular space of ATP.

Discussion

The established regulatory effects of ATP on VGNC function initiated the current search for a pharmacophore common to ATP within the disparate array of Na^+-channel-blocking drugs. Although local anaesthetic, anticonvulsant and anti-arrhythmic drugs bind to overlapping receptor sites located in the inner cavity of the sodium channel pore (Ragsdale et al 1996), the likelihood of a common pharmacophore is lessened by the existence of more than one binding site for some classes of channel-blocking drug. In this study, the fitting of local anaesthetic structures to ATP is based on polar ester and amide groups. The polar groups of the anticonvulsant class could have been used in the same way but these show much greater diversity. One training set of 13 structures for identifying anticonvulsant pharmacophores contains 7 different polar groups, which range from carboxyl to triazine moieties (Tasso et al 2004). In this study, the anticonvulsant fitting motif is based on an alternative group of adjacent atoms within the hydantoin moiety of phenytoin (positions 2, 3, 4) and ATP, with commonality to other anticonvulsant structures. The pharmacological potency of phenytoin is reduced by alteration of the hydantoin moiety through methylation, cyanoguanidino substitution at position 2 and conversion into succinimide or pyrrolidine rings (Poupaert et al 1984; Lambert et al 1996), whereas a tertiary amine chain at position 3 changes the drug profile to a quinidine-like preference for activated channels (Ciechanowicz-Rutowska et al 2000).

Charged and uncharged forms of lidocaine participate, respectively, in rapid voltage-dependent open channel block, and block of the inactivated channel on a 1000-fold slower time scale (Zamponi & French 1993). The distinct kinetic activity of local anaesthetics may depend on modulation of the slow inactivated state (Fukuda et al 2005). Separate binding sites for these blocking actions have been proposed, with the hydrophobic and amine groups of lidocaine serving as a molecular gate (Zaponi & French 1994). Pharmacophores for the protonated and non-protonated molecular species identified in the adenine ring of ATP may relate to the slow and fast blocking Na^+ channel sites. Simple molecular species like diethylamide and phenol, respectively, mimic the fast and slow block of lidocaine, and illustrate the potential for a shift in the mode of action of a drug existing in different charged forms (Zamponi & French 1993). However, the effects of diethylamide and phenol are tissue specific, as there are differences in the Na^+ channel state behaviour of various tissues (Haeseler et al 2002). Furthermore, irrespective of the in-vitro potency of Na^+-channel blockers, clinical activity is defined by tissue drug levels (Kuo et al 2000).

Drugs in the analogous group are characterised in this study by a lack of specificity for the anticonvulsant and local anaesthetic motifs in the structure of ATP. With respect to their pharmacological properties, diclofenac binding to VGNC is mutually excluded by carbamazepine (Yang & Kuo 2005). Imipramine has local anaesthetic kinetic properties in Na^+-channel studies, and demonstrates anticonvulsant activity in-vivo (Kleinrok et al 1991). The mixed properties of imipramine are demonstrated in this study in respect of molecular structure. Pethidine is characterised as a local anaesthetic agent with less potency than lidocaine in phasic block (Wagner et al 1999) and is not included in the analogous drug group.

Previously, Kuo et al (2000) have emphasised the importance of the spatial distribution of diphenyl groups as key ligands of the drugs interacting with the Na^+ channel. In this study, drug aryl and alkyl moieties that do not participate in fitting are related to the intra-molecular space between the nucleoside and triphosphate chain. Drug structures fitted to atom motifs in the adenine ring partially occlude this intra-molecular

space, except for phenylbutazone and ethosuximide, which have negligible effects on the Na^+ current (Kuo et al 2000). Occlusion of the intra-molecular space is particularly good for saxitoxin, which contrasts with that of the channel activator batrachotoxin. Saxitoxin enhances the proportion of Na^+ channels in the slow inactivated state and prolongs blockade by local anaesthetics and tricyclic antidepressants (Barnet et al 2004). In this study, saxitoxin shares the same fitting profile as lidocaine and imipramine.

The batrachotoxin structure contains the fitting motifs of the local anaesthetic and anticonvulsant agents, which equates with the interaction of these drugs at the Na^+-channel binding site of the alkaloid (Linford et al 1998; Nicholson et al 2002; Cronin et al 2003). The fit of batrachotoxin to the anticonvulsant motif in ATP makes use of the dimethylpyrrolidone group employed in the binding model of Linford et al (1998), substitution of which reduces batrachotoxin potency one-thousand fold (Schow et al 1997). Tikhonov & Zhorov (2005) suggest that batrachotoxin actually binds inside the channel pore, retaining a hydrophilic ion pathway between the selectivity filter and gate, thus stabilising the open channel state. This 4-Å ion pathway is equivalent to the estimate of distance between the inactivation gate and the charged amine binding site of phenyltrimethylammonium (Zamponi & French 1994). The β-scorpiotoxins represent another neurotoxin class with a specific action on Na^+ channels. In their paper, El-Sherif et al (2001) point to similarity in the electrophysiologic and binding profiles of β-scorpiotoxins and ATP. The omission of β-scorpiotoxins may be perceived as a limitation of this study, although these peptide structures differ substantially from those of the other investigated small-molecular-weight Na^+-channel ligands.

Nucleotide modulation of ion-channel function is not restricted to VGNC. Run down of the rat epithelial amiloride-sensitive Na^+-channel activity is prevented by replenishment of the cytosol with ATP (Ishikawa et al 2003). Park et al (2004) draw a parallel between the nucleotide modulation of VGSC and K_{ATP} channels. The specificity of the nucleotide requirement identified by the authors cited varies from ATP or an ATP analogue (Ishikawa et al 2003) to ATP or GTP (El-Sherif 2001; Rola & Szulczyk 2004) to a range of di- and triphosphate nucleotides (Park et al 2004). El-Sherif et al (2001) suggest that ATP modulates Na^+ current through a charge screening effect at a high-affinity channel-binding site, whereas Park et al (2004) rule out a surface charge effect and P2 receptor involvement. Rola & Szulczyk (2004) infer from their study that nucleotide-depleted cells produce action potentials more effectively. The slower recovery from inactivation of nucleotide depleted cells results in a lower frequency of action potentials. The relevance of the latter findings and the observations from this study to VGNC function in normal and pathologic tissue will require further investigation.

In the context of previous studies, our findings suggest that polar functional groups and conformational flexibility may provide the adenine nucleotide with an endogenous channel gating role, which is modulated by Na^+-channel-binding drugs. Within the well-characterised gramicidin A channel, carbonyl oxygen atoms line the 4-Å pore and provide a suitable solvation environment for permeating monovalent cations (Roux 2002). In this respect, the capacity of tetrameric guanine nucleoside quartets to self assemble and provide a binding site for Na^+ in a 5-Å cavity at neutral pH (Wong & Wu 2003) may provide a suitable model for investigating the regulatory role of the adenine nucleotide on VGSC function.

Conclusion

This study shows that ligands with established functional effects on Na^+-channel current relate to molecular parameters of the adenine nucleotide in characteristic ways. Findings substantiate a role for ATP in modulating VGNC function, which is not currently defined in Na^+ channel drug receptor models.

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