Biochemical and Biophysical Research Communications 418 (2012) 161–166

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Pharmacophore modeling for hERG channel facilitation

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ARTICLE INFO

Article history:
Received 29 December 2011
Available online 8 January 2012

Keywords:
hERG channel
Facilitation
Pharmacology
Pharmacophore model

ABSTRACT

Human *ether-a-go-go*-related gene (hERG) channels play a critical role in cardiac action potential repolarization. The unintended block of hERG channels by compounds can prolong the cardiac action potential duration and induce arrhythmia. Several compounds not only block hERG channels but also enhance channel activation after the application of a depolarizing voltage step. This is referred to as facilitation. In this study, we tried to extract the property of compounds that induce hERG channel facilitation. We first examined the facilitation effects of structurally diverse hERG channel blockers in *Xenopus* oocytes. Ten of 13 assayed compounds allowed facilitation, suggesting that it is an effect common to most hERG channel blockers. We constructed a pharmacophore model for hERG channel facilitation. The model consisted of one positively ionizable feature and three hydrophobic features. Verification experiments suggest that the model well describes the structure–activity relationship for facilitation. Comparison of the pharmacophore for facilitation with that for hERG channel block showed that the spatial arrangement of features is clearly different. It is therefore conceivable that two different interactions of a compound with hERG channels exert two pharmacological effects, block and facilitation.

1. Introduction

The human *ether-a-go-go*-related gene (hERG) channel plays a critical role in cardiac action potential repolarization [1–3]. Modulation of hERG channel currents by compounds affects the cardiac action potential and can cause arrhythmia [2,4,5]. Therefore, compounds affecting hERG channels have been the focus of intensive study for over a decade. Facilitation is another effect of compounds that block hERG channels. This causes the enlargement of the hERG channel current amplitude at potentials close to the threshold for channel activation [6–9]. This phenomenon is triggered by the application of a depolarizing voltage step (prepulse), and is due to a modification of channel gating that shifts the voltage dependence of activation to more hyperpolarized membrane potentials; this suggests that facilitation is caused by a different compound-channel interaction than block [8]. To date, facilitation has been observed with several anti-arrhythmic drugs such as nifekalant, amiodarone, carvedilol, and quinidine, but not dofetilide [8,9]. The structural basis for hERG channel facilitation is not understood. Pharmacophore modeling is a method to analyze the common pharmacophoric features among a set of compounds with the same activity [10–12] and also provides structural insight into the mechanism of compound-channel interaction [13–15]. In the present study, we developed a pharmacophore model for hERG channel facilitation by analyzing three-dimensional quantitative structure–activity relationships (3D-QSAR).

The pharmacophore for hERG channel facilitation consists of one positively ionizable feature and three hydrophobic features. The same composition has been reported for a pharmacophore for hERG channel block [16,17]. But, the spatial arrangements of these features differ, suggesting that a compound that has both pharmacophore features may interact with the hERG channel in two different mechanism.

2. Materials and methods

Frogs (*Xenopus laevis*) were treated in accordance with the guidelines for the use of laboratory animals of Osaka University Graduate School of Medicine. Isolation and maintenance of the oocytes and injection with cRNA were performed as described previously [8]. hERG cDNA subcloned into the pSP64 vector was kindly provided by Dr. M.T. Keating and Dr. M.C. Sanguinetti [1]. The

Abbreviations: hERG, human *ether-a-go-go*-related gene; 3D-QSAR, three-dimensional-quantitative structure activity relationships; $V_{1/2}$, the half maximal of voltage dependence of activation; IC_{50}, the half maximal concentration for inhibition; EC_{50}, the half maximal concentration for facilitation.

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doi:10.1016/j.bbrc.2011.12.153

oocytes were injected with 5 ng of hERG cRNA, and incubated at 18 °C in ND96 solution (96 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, and 5 mM HEPES, pH 7.6 with NaOH) supplemented with 50 μg/ml gentamicin. Membrane currents were recorded using the two-electrode voltage-clamp technique and a GeneClamp 500 amplifier (Molecular Devices, Sunnyvale, CA) 4–7 days after cRNA injection. The electrical resistance of the glass electrodes was 0.4–1.5 MΩ when filled with 3 M KCl. Oocytes were bathed in a low-Cl^- solution (96 mM Na-[2-(*N*-morpholine) ethanesulfonic acid] (NaMes), 2 mM KMes, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 5 mM HEPES, pH 7.6 (with methanesulfonic acid)) to minimize interference from endogenous Cl^- currents. All experiments were conducted at ambient temperature (22–24 °C), and data were collected and analyzed using Clampfit 9.2 software (Molecular Devices).

In pharmacophore analysis, we used the EC_{50} value to reflect the activity for facilitation. The EC_{50} was obtained by a method described previously [9]. Briefly, the activation curve of the peak tail currents was fitted with the following Boltzmann function:

$$I/_{Imax} = F_{max}(1 - 1/(1 + \exp((V - V_{1/2})/k))).$$

Parameters were as described previously [9]. To obtain the current activation curve during facilitation, the current–voltage (I/V) relationships for the control hERG currents and a compound-bound and facilitated hERG current were recorded. For compound concentration–response curves, the peak currents were fitted with the Hill equation and EC_{50} values were obtained.

Chemical structures were drawn using the editor sketcher in Discovery Studio 3.0 (Accelrys) and diverse conformations of each compound were generated. Since the tested compounds possess diverse chemical properties, we examined several combinations of different pharmacophoric features. We set other parameters in Discovery Studio 3.0 that the maximum number of features generated was five, and the minimum was one. Statistical analysis was carried out using SAS 9.1 software (SAS Institute Inc., USA).

3. Results

3.1. Identification of new hERG channel facilitators among known hERG channel blockers

Five hERG channel blockers could also function as facilitators [8,9]. Considering the wide diversity of structures of these compounds, and in order to understand the structure–activity relationship of hERG channel facilitation, we extended our search for other hERG channel blockers that act as facilitators.hERG channel currents were recorded from hERG expressed in *Xenopus* oocytes using the two-electrode voltage-clamp technique. We assayed facilitation with a voltage-clamp protocol, which comprised a test pulse at −40 mV (4 s) from the holding potential of −90 mV, followed by a step to −80 mV (1 s) delivered at 15 s intervals, before and after the application of the +60 mV conditioning pulse (4 s). We calculated the values of the half-maximal voltage dependence of activation ($V_{1/2}$), slope factor (k), as well as the fraction of facilitated channels by fitting the activation curve to two Boltzmann functions [9].

The structures of 13 hERG channel blockers are shown in Fig. 1. Among them, ten compounds showed significant facilitation of the hERG channel currents (Fig. 1 upper panel), and the other three compounds show weak facilitation (Fig. 1 bottom panel). For example, the anti-psychotic drug haloperidol could markedly increase channel currents at low concentrations. 0.3 μM haloperidol increased the current by 1.7-fold at −40 mV with a prepulse (Fig. 2A), and 76.5% of unblocked channels were facilitated with the $V_{1/2}$ shifted by −20.5 mV (k = 9.2) (Fig. 2B). On the other hand, 300 μM sotalol, an anti-arrhythmic drug, had such a small effect on channel currents after a prepulse (Fig. 2A) that modulation of the activation curve was too small to fit by two Boltzmann functions (Fig. 2B) and we could not obtain values of $V_{1/2}$, k, and fraction of facilitated channels. The biophysical parameters for each of the 13 compounds are summarized in Table 1; they show that structurally diverse compounds can have different facilitation activity effects on hERG channel currents.

To quantify the activities of facilitation and block of the compounds, we estimated the concentration dependence of facilitation (EC_{50}) and block (IC_{50}) for each of them. The values of EC_{50} and IC_{50} for haloperidol and sotalol are shown in Fig. 2C, and these values for other compounds are summarized in Table 2. In the case of haloperidol, the EC_{50} and IC_{50} were 0.10 μM (Hill equation = 1.3) and 0.16 μM (Hill equation = 1.1), respectively. Therefore, the affinity for facilitation was similar to that for block. In some cases, the affinities for facilitation were lower than those for block. For example, amiodarone was shown to be a strong facilitator with an EC_{50} value of 0.55 μM (Hill equation = 1.1), which was markedly lower than the IC_{50} value of 4.02 μM (Hill equation = 1.0) [9]. Other compounds such as verapamil, chlorpheniramine, and propranolol also showed EC_{50} values lower than their IC_{50} values. These results suggest that the affinity for facilitation by a compound is not entirely determined by that for block.

3.2. Pharmacophore modeling of hERG channel facilitation

We divided the 13 compounds in this study into two groups according to their structures and their ability to induce facilitation (EC_{50}). One group was used for the construction of pharmacophore models. This included six compounds (haloperidol, chlorpheniramine, ICI118551, promethazine, metoprolol, and sotalol) from this study and four compounds (nifekalant, amiodarone, carvedilol, and quinidine) from previous studies [8,9]. The other group of compounds was used for validation testing of the generated model. This included seven compounds (verapamil, propranolol, fluoxetine, imipramine, nortriptyline, terfenadine, and atenolol).

In 3D-QSAR analysis, the EC_{50} values of compounds were used to reflect their facilitation activity. These values ranged from 0.16 to 89.61 μM. In the case of compounds for which we could not estimate an EC_{50} value, we set the activity parameter to 1000 μM since it is beneficial to have a wide range of activities to this analysis. For other parameters, see Section 2.

We obtained multiple pharmacophore models of hERG channel facilitation. These models consisted of combinations of diverse pharmacophoric features, which ranged from three to five hydrophobic features and zero to one positively ionizable feature. We showed the highest score of root–mean–square deviation (RMSD) of generated models in Fig. 3A. This model includes one positively ionizable feature (red) and three hydrophobic features (blue). All of the features are located within 9.1 Å, and the distances between each hydrophobic feature and the positively ionizable feature range from 4.5 to 7.0 Å.

Superimposition of the model and the structure of compounds with high or low facilitation activities are shown in Fig. 3B. The structures of compounds with high activities for facilitation, such as haloperidol and carvedilol, matched with all four features in the model. Their basic nitrogen center matched with the positively ionizable feature, and aromatic rings or carbons matched with the three hydrophobic features. The structures of chlorpheniramine, amiodarone, and quinidine matched with three features of the model, namely, the positively ionizable feature and two hydrophobic features. The structures of compounds with low facilitation activities (sotalol and metoprolol) matched with only two features of the model. Thus, compounds with high activities showed a

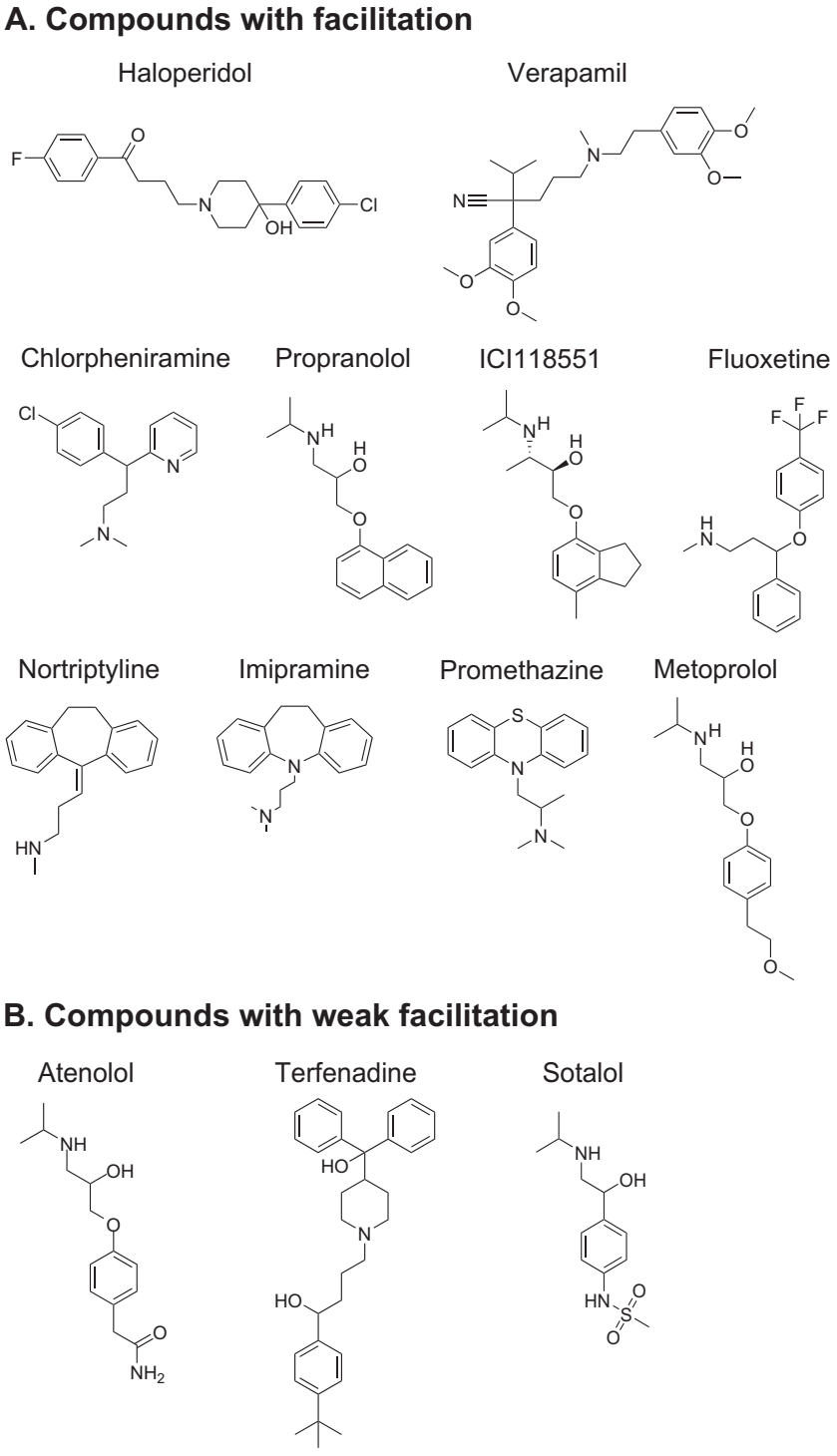

Fig. 1. The chemical structure of compounds examined in this study.

closer structural match to the pharmacophore model than compounds with low activity.

To validate this pharmacophore model, we calculated the correlation coefficient between the actual EC_{50} values and the predicted EC_{50} values that were obtained by matching compounds to the pharmacophore model (Fig. 3C). The correlation coefficient for compounds used to develop the model was 0.93. A more rigorous test was also conducted, which involved calculating the correlation coefficient using all of the compounds, including those that had not been used to construct the model. Among compounds in this latter group, the predicted EC_{50} value (2 μM) for terfenadine was quite different from the actual EC_{50} value. When we applied 2 μM terfenadine to oocytes, more than 80% of the channels must have been blocked, which could explain why we could not correctly evaluate the concentration dependence of facilitation for this compound. Therefore, in this study, we excluded terfenadine data as an outlier. Calculation of the correlation coefficient with the remaining 16 compounds gave the value of 0.80.

A final test of the generated model was to map some of the seven compounds that had not been used to develop the pharmaco-

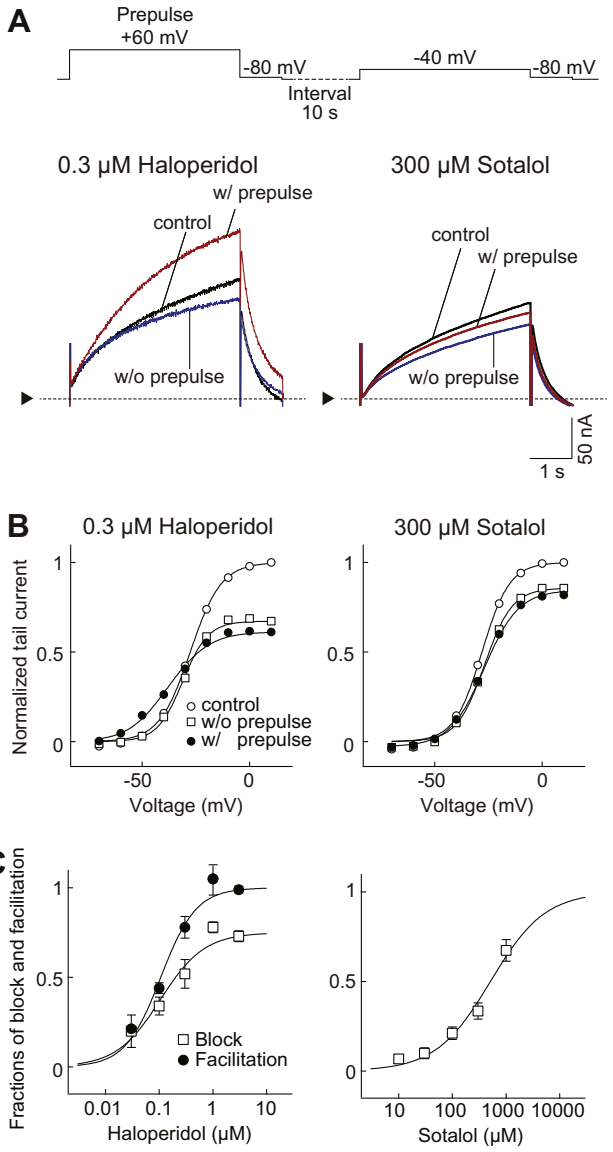

Fig. 2. Structurally diverse compounds facilitate hERG channel currents. (A) The effects of haloperidol and sotalol on hERG channel currents in *Xenopus* oocytes. The voltage-clamp protocol is shown in the inset at the top of the figure. Superimposed cell currents were recorded in the same oocytes before (control) and after perfusion of compounds (w/o prepulse) and then with prepulse (w/prepulse). Representative current traces during the voltage step to −40 mV are shown. (B) Voltage-dependent hERG channel activation curves. The hERG current–voltage (*I–V*) relationship was obtained by depolarizing voltage steps (4 s) from −70 to +10 mV in 10 mV increments followed by 1 s at −80 mV. Facilitation was elicited by a prepulse to +60 mV before each *I–V* test pulse. The amplitudes of hERG tail currents in the absence (open circles) and in the presence of 0.3 μM haloperidol or 300 μM sotalol (open squares) and then with prepulse (filled circles) are shown. Data were normalized to currents evoked by voltage steps to +10 mV in the absence of compounds. (C) The dose dependence of the fractions of hERG channel current block for each compound was obtained by dividing the current amplitude recorded during a voltage step to +10 mV in the presence of the compound by that recorded in its absence. For facilitation, the fractions of the total current corresponding to conventional and compound-associated facilitated hERG channels were obtained by fitting the activation curve to two Boltzmann functions. Data points represent means ± SEM.

phore to the model. The most (fluoxetine) and least (atenolol) potent facilitators were mapped to the model. Fluoxetine (10 μM) increased channel current by 1.4-fold compared with that of the control with a prepulse (Fig. 4A), and 53.0% of unblocked channels were facilitated and the $V_{1/2}$ shifted −20.9 mV (k = 7.9) (Fig. 4B). The structure of fluoxetine was mapped to the model (Fig. 4C left) where it matched one positively ionizable feature and two hydrophobic features. The central nitrogen of fluoxetine matched with the positively ionizable feature, three fluorines matched with one hydrophobic feature, and an aromatic ring matched with another hydrophobic feature. One hydrophobic feature was not matched to any structure. The model predicted that the EC_{50} value for fluoxetine was 11.8 μM, which was close to the actual EC_{50} value of 10.0 μM. In contrast, atenolol matched with only two of the pharmacophoric features (Fig. 4C right) and the predicted EC_{50}value was much higher than the actual value. These results suggest that the pharmacophore well describes the features related to facilitation of hERG channels.

4. Discussion

In the present study, we constructed a 3D-QSAR pharmacophore model for hERG channel facilitators in order to understand the structural basis of the action of these compounds. Verification experiments suggest that the model adequately depict the structure–activity relationship for facilitation.

Ten of the thirteen compounds assayed in this study elicited dual effects on hERG channels, facilitation and block. This is thought to be due to the pharmacophoric features for facilitation being similar to those for block. Thus, certain compounds possess pharmacophoric features for both facilitation and block. Inanobe et al. constructed a pharmacophore for block of hERG channels with the Catalyst program [17]. This model included one positively ionizable feature and three hydrophobic features. Using a different method, Cavalli et al. constructed an hERG channel-block pharmacophore with the CoMFA (comparative molecular field analysis) technique. Their model consisted of one basic nitrogen and three aromatic moieties [16]. The features of the two different block models serve the same function. The role of a positively ionizable feature can be played by the nitrogen, and the role of hydrophobic features can be played by aromatic moieties, implying that these block models are similar to each other. When we compared the pharmacophore model for facilitation with that for block, the chemical composition of the important features was shown to be the same, implying that the compounds examined in this study can have both pharmacophoric features and induce channel facilitation and channel block. However, the different arrangements of the four pharmacophoric features of the facilitation and block models mean that facilitation and block are determined by different mechanisms. This finding supports our previous hypothesis that hERG current facilitayion and hERG current block are based on two different configurations of interaction [9]. The different pharmacophoric characteristics of compounds may thus determine their affinities for facilitation and block.

We previously reported a docking simulation model of the interaction between a compound and hERG channel for facilitation. The docking simulation showed that nifekalant was situated in a pocket surrounded by Thr623 and Ser624 in a loop between the pore helix and the selectivity filter, and Tyr652 and Phe656 on the S6 helix [8]. The substitution of Tyr652 and Phe656 abolished facilitation by nifekalant [8]. The substitution of these residues also abolished facilitation by amiodarone (data not shown). In studies with hERG channel blockers, it was thought that Thr623/Ser624, Tyr652, and Phe656 interact with polar, ionized, and hydrophobic regions of the compounds, respectively [2,18,19]. For facilitators as well as blockers, their positively ionizable feature is likely to interact with Tyr652 by a cation-π interaction, and one of their hydrophobic features may interact with Phe656 by a π-stacking interaction. Furthermore, another hydrophobic feature may associate with Thr623 and Ser624. The distance from the positively ionizable feature to one of the hydrophobic features in the facilitation

Table 1
Biophysical parameters of drug-induced hERG channel facilitation.

Name	Concentration	$\Delta V_{1/2}$ (mV)	k	Fraction	n
Promethazine	10 μM	23.6 ± 0.5	5.8 ± 0.7	0.41 ± 0.04	5
Fluoxetine	10 μM	20.9 ± 2.8	7.9 ± 0.9	0.53 ± 0.10	4
Haloperidol	1 μM	20.5 ± 1.5	9.2 ± 1.3	0.78 ± 0.06	6
Metoprolol	100 μM	14.7 ± 3.2	6.4 ± 0.5	0.54 ± 0.06	6
Nortriptyline	10 μM	14.1 ± 2.1	6.1 ± 1.0	0.36 ± 0.02	4
ICI-118551	10 μM	13.4 ± 2.7	8.7 ± 0.6	0.46 ± 0.03	5
Verapamil	1 μM	13.0 ± 1.5	7.2 ± 0.6	0.66 ± 0.05	5
Chlorpheniramine	10 μM	12.9 ± 2.8	6.9 ± 1.1	0.75 ± 0.18	4
Propranolol	10 μM	12.3 ± 1.5	7.9 ± 0.2	0.45 ± 0.06	10
Imipramine	10 μM	10.3 ± 0.3	10.0 ± 0.5	0.34 ± 0.12	3
Atenolol	1 mM	N.E.	N.E.	N.E.	4
Terfenadine	0.3 μM	N.E.	N.E.	N.E.	4
Sotalol	300 μM	N.E.	N.E.	N.E.	10

Data are presented as mean ± SEM (n = number of observations). N.E., not estimated.

Table 2
Measured and predicted values for hERG channel block and facilitation.

Name	Actual EC_{50} (μM)	Actual IC_{50} (μM)	Predict EC_{50} (μM)
Haloperidol	0.16 ± 0.32	0.12 ± 0.03	0.11
Verapamil	0.78 ± 0.03	1.94 ± 0.02	22.37
Chlorpheniramine	1.59 ± 0.14	6.91 ± 2.21	1.62
Propranolol	2.89 ± 0.55	30.44 ± 4.54	4.10
ICI-118551	9.18 ± 1.75	40.24 ± 8.49	3.50
Fluoxetine	9.93 ± 2.23	8.52 ± 3.21	11.77
Promethazine	11.99 ± 0.11	29.01 ± 5.02	14.86
Imipramine	14.29 ± 0.30	19.52 ± 0.01	4.13
Nortriptyline	18.90 ± 4.73	31.57 ± 0.77	9.22
Metoprolol	89.61 ± 16.00	144.22 ± 7.31	190.96

Data are presented as mean ± SEM.

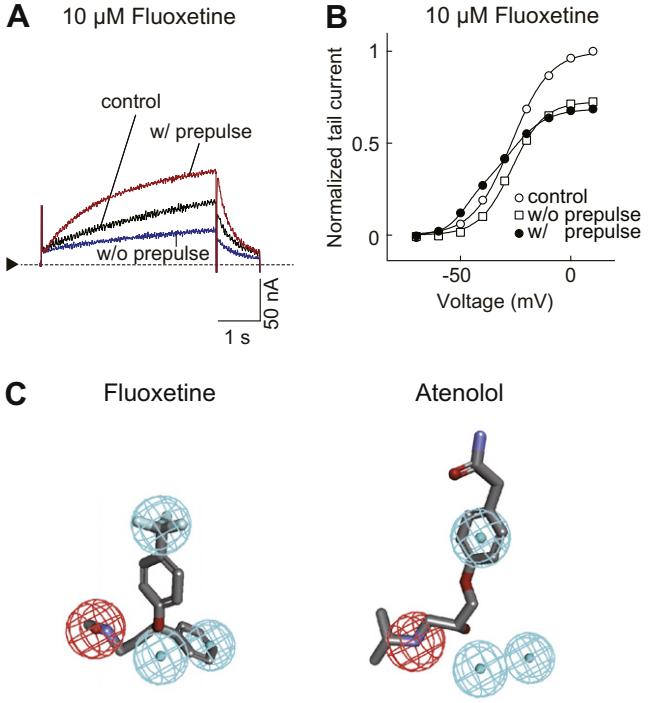

Fig. 4. Mapping compounds to the pharmacophore model. (A) Representative traces of the effects of 10 μM fluoxetine at −40 mV. Superimposed cell currents recorded in the same oocytes before (control) and after perfusion of 10 μM fluoxetine (w/o prepulse) and then with prepulse (w/prepulse). (B) The effect of fluoxetine upon voltage-dependent hERG channel activation. The *I–V* protocol was the same as in Fig. 1B. The amplitudes of hERG tail currents in the absence (open circles) and in the presence of 10 μM fluoxetine (open squares), and then with prepulse (filled circles). Data were normalized to currents evoked by voltage steps to +10 mV in the absence of 10 μM fluoxetine. (C) Superimposition of fluoxetine and atenolol on the pharmacophore model.

model is 7.0 Å. In a homology model of the hERG channel, the space between Tyr652 and Phe656 on the same subunit is ~8.0 Å [8,20]. This could allow pharmacophoric features for facilitation to be located inside a pocket surrounded by Tyr652 and Phe656.

In this study, sotalol and terfenadine showed very little facilitation of hERG current. It has been reported that sotalol sometimes induces lethal arrhythmia, including *torsades de points* [21–24]. In addition, terfenadine was withdrawn from the market because of its ventricular arrhythmic effect [25,26]. Compounds that show only weak facilitation could thus be associated with drug-induced arrhythmia, and the arrhythmia inducing side effects of compounds should be assessed in terms of both hERG channel facilitation and block.

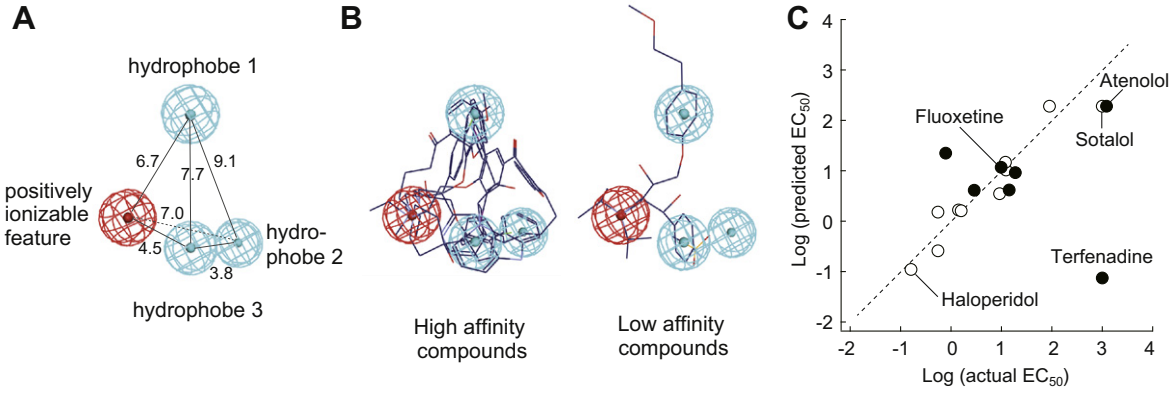

Fig. 3. The pharmacophore model for hERG channel facilitation. (A) The pharmacophore model for hERG channel facilitators. Pharmacophoric features are shown: positive ionizable feature (red) and hydrophobic features (blue). (B) Superimposition of the pharmacophore with high activity compounds or low activity compounds. C, The relationship between actual EC_{50} values versus predicted EC_{50} values. Compounds in the training set (open circles); compounds in the test set (filled circles). The correlation was calculated using Spearman's correlation coefficient.

Acknowledgments

We are grateful to Dr. Ian Findlay (Université François-Rabelais, Tours, France) for critical reading of this manuscript. This work was supported by Grants-in-Aid for the leading Project for Biosimulation "Development of models for disease and drug action"; for the Global COE Program "*In silico* Medicine" at Osaka University; Scientific Research (A) 20249012 (to Y.K.) and Scientific Research on Innovative Areas 22136002 (to Y.K.) from the Ministry of Education, Science, Sports and Culture of Japan, and also the Japan Society for the Promotion of Science.

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