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Block of sodium channels by psychotropic drugs in single guinea-pig cardiac myocytes

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1 Effects of imipramine and haloperidol on voltage-gated sodium channels were investigated in guinea-pig isolated ventricular myocytes by the whole-cell patch clamp technique. Some additional experiments were also performed with chlorpromazine for the purpose of comparison.

2 All test drugs in micromolar concentrations suppressed the amplitude of peak sodium current associated with step depolarization from a holding potential of −140 mV in a reversible manner. The order of potency was chlorpromazine > imipramine > haloperidol.

3 Dose-response curves obtained with a holding potential of −140 mV were best fitted by 2:1 stoichiometry in all three drugs and were shifted in the direction of lower concentrations when a holding potential of −90 mV was used.

4 The drug-induced block was not associated with any change in the time courses of sodium current activation and inactivation.

5 Steady-state sodium channel inactivation curve was shifted in the direction of more negative potentials by the drugs.

6 All three drugs also produced marked use-dependent block as demonstrated by a cumulative increase in the block during a train of depolarizing pulses.

7 The use dependence was due to a higher affinity of the drugs for the inactivated state of sodium channels than the resting state and to a very slow repriming of the drug-bound sodium channels from inactivation.

8 The steady-state and use-dependent block of voltage-gated sodium channels by psychotropic drugs may contribute to their cardiotoxic and perhaps antiarrhythmic effect.

Introduction

Tricyclic antidepressants are used in the treatment of affective disorders, major depression in particular. Neuroleptic or antipsychotic drugs are widely used in the treatment of psychiatric disorders. Their antidepressant and antischizophrenic actions are thought to involve changes in amine function in the brain (Matthysse & Lipinski, 1975; Seeman, 1981). One of the major side effects of tricyclic antidepressants and neuroleptic drugs is cardiotoxicity. Cholinolytic, sympatholytic, and direct 'quinidine-like' membrane actions (Baldessarini, 1985; Risch *et al.*, 1981a,b; Stimmel, 1979) appear to interplay in the heart. Increased heart rate is believed to be due primarily to the antiacetylcholine action, whereas electrocardiographic changes and conduction disturbances largely result from the direct membrane effect (Frommer *et al.*, 1987).

The quinidine-like effect is thought to be caused by slowing of Na^+ flux into cells, resulting in altered configuration of action potential and slowing of conduction. However, the detailed cellular mechanism underlying the quinidine-like action remains to be elucidated. Since sodium channels play a pivotal role in causing various cardiac arrhythmias, the quinidine-like effects of tricyclic antidepressants and neuroleptic drugs on cardiac cells appear to be caused by their ability to block the sodium channels. In our previous study, it was indeed found that the neuroleptic chlorpromazine had a potent sodium channel blocking action (Ogata *et al.*, 1989). Since tricyclic antidepressants are chemically different from chlorpromazine, a phenothiazine neuroleptic, the

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quinidine-like effect of the former might be exerted by a mechanism different from that of chlorpromazine. In the present study, we investigated the action of imipramine, a tricyclic antidepressant, on the gating mechanism of sodium channels of cardiac myocytes by using the whole-cell patch clamp technique (Hamill *et al.*, 1981). The effect of haloperidol, a non-phenothiazine neuroleptic, was also studied for comparison. It was found that despite the considerable differences in chemical structure, imipramine and haloperidol blocked the sodium channels in a manner similar to that of chlorpromazine. These drugs had a greater affinity for the inactivated state of the sodium channel than the resting and activated states.

Methods

The materials and methods used in the present study were similar to those described in a previous paper (Ogata *et al.*, 1989). In brief, adult guinea-pigs of either sex (300–500 g) were anaesthetized with pentobarbitone (40 mg kg^{-1}, i.p.), and cardiac myocytes were isolated by a method modified from that described by Mitra & Morad (1985). The heart was excised and retrogradely perfused for 5 min with an oxygenated Ca^{2+}-free modified Tyrode solution with the following composition (mM): NaCl 135, KCl 5.4, $MgCl_2$ 1, NaH_2PO_4 0.33, HEPES 10, and glucose 11, with pH adjusted to 7.4 with NaOH.

The heart was then perfused for 7.5 min with the oxygenated, Ca^{2+}-free modified Tyrode solution containing 1.5 mg ml^{-1} collagenase type 1 (Sigma, St. Louise, MO), 0.2 mg ml^{-1} protease type 14 (Sigma), and 1 mg ml^{-1} bovine serum albumin (Sigma) at a temperature of 37 ± 1°C. Then the heart was perfused for 3 min with Krebs bicarbonate (KB) medium of the following composition (mM): KCl 25, KH_2PO_4 10, KOH 116, EGTA 0.5, glutamic acid 80, taurine 10, oxalic acid 14, glucose 11, and HEPES 10, with pH adjusted to 7.4 with KOH. The left ventricle was minced with fine scissors and cells were strained through a 200 μm nylon mesh and stored in the KB medium for 0.5 to 10 h. Only Ca^{2+}-tolerant, rod shaped cells with evenly spaced sarcomeres were selected for the experiment.

The external perfusate used was a low Na^+ HEPES buffered solution of the following composition (mM): tetramethylammonium chloride (TMA-Cl) 90, NaCl 50, $CaCl_2$ 1.8, CsCl 5, $MgCl_2$ 1, glucose 25, HEPES 5, and pH titrated to 7.4 with 1 M TMA hydrochloride. In some experiments, NaCl concentration was increased to 100 mM or reduced to 25 mM (substituted by TMA-Cl). The solution inside the suction-pipette contained (mM): CsF 130, NaF 20, HEPES 5, and pH titrated to 7.0 with 1 M CsOH. Test drugs were diluted to desired concentrations from a 10 mM stock solution.

Patch clamp electrodes were fire-polished borosilicate glass capillaries (0.8–1.1 mm i.d.; Kimble, Vineland, NJ, U.S.A.). Membrane currents were recorded by a current-to-voltage converter, and stored on disk using a PDP11/23 computer (Digital Equipment, Pittsburgh, PA). Each pulse protocol was applied at intervals longer than 30 s to avoid the use-dependent effects of drugs.

As described in our previous paper (Ogata *et al.*, 1989), the space- and voltage-clamp control was not satisfactory in the conditions that generated sodium currents larger than approximately 5 nA. In order to avoid such artifacts, we used patch electrodes with resistances less than 0.5 megohm and external Na^+ concentration at 50 or 25 mM. The experiments in which the peak current exceeded 5 nA were discarded.

The series resistance arising from the pipette tip and the cell interior was carefully compensated (Marty & Neher, 1983; Matteson & Armstrong, 1984). Capacitive and leakage currents were subtracted digitally by the P-P/4 procedure (Bezanilla & Armstrong, 1977). Exponential fits and fits to a simple Boltzmann distribution were determined by computer using a non-linear sum of the least squares fitting routine. The data were compensated for the liquid junction potential between internal and external solutions (about 3 mV). Experiments were carried out at room temperature (22°C). Results are expressed as the mean ± s.e.mean and Student's *t* test was used to estimate the significance of differences.

Results

Block of sodium current

At a concentration of 5 μM, imipramine suppressed the sodium current. Figure 1a illustrates changes in sodium current before (0 min) and during (1, 2 and 3 min) superfusion of the test solution. The peak sodium current decreased to approximately one-third of control value, and attained a steady state within 5 min. Washing with drug-free solution restored the sodium current, and a complete recovery was observed in 8–10 min. The sodium currents recorded with a faster time scale revealed no change in the time course of current during imipramine-induced suppression (Figure 1b). These results were confirmed by 30 experiments.

Similar results were obtained with chlorpromazine and haloperidol ($n = 10$ for each drug). Both chlorpromazine (2–5 μM) and haloperidol (5–10 μM) reversibly reduced the peak amplitude of sodium

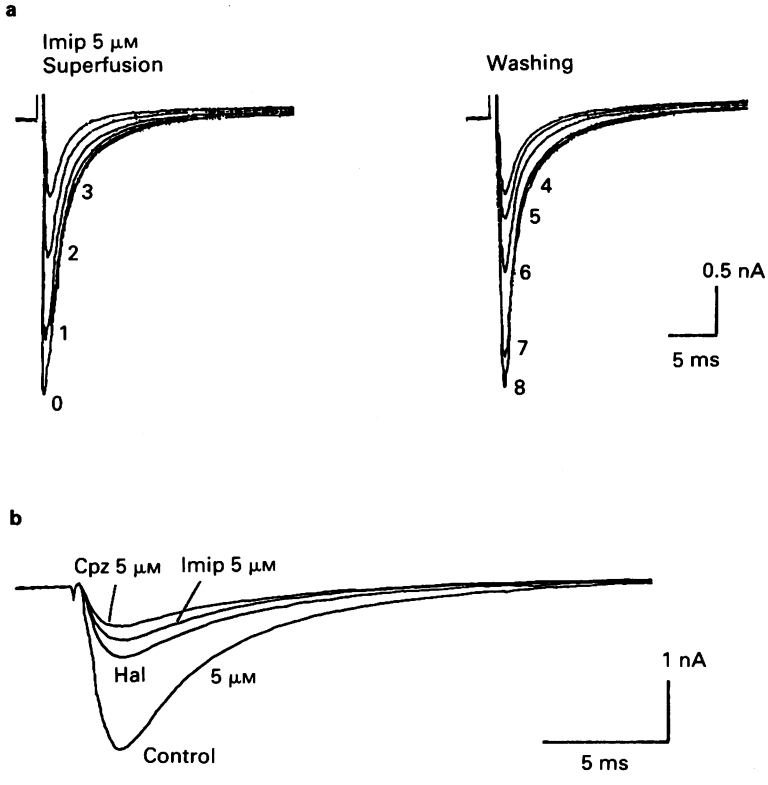

Figure 1 Effects of psychotropic drugs on sodium current in guinea-pig ventricular cells. (a) Sodium currents associated with step depolarizations to −10 mV from a holding potential of −140 mV before, during and after superfusion of 5 μM imipramine (Imip). The left panel illustrates successive recordings obtained 0, 1, 2 and 3 min after the start of superfusion of imipramine-containing solution. The right panel illustrates successive recordings obtained 4, 5, 6, 7 and 8 min after the start of superfusion with drug-free solution. (b) Sodium currents obtained in control, 5 μM imipramine, 5 μM chlorpromazine (Cpz) and 5 μM haloperidol (Hal) solutions.

current without affecting its time course (Figure 1b). The order of potency as measured in the same cell was chlorpromazine > imipramine > haloperidol. Detailed comparison of the potency of the three drugs in blocking sodium current will be given later.

The current-voltage relationships for the peak sodium current before and during application of 3 μM imipramine are shown in Figure 2. The membrane was held at −140 mV, and step depolarizing pulses were applied to various potential levels at a frequency of 0.05 Hz to record sodium currents. The current amplitude was suppressed by imipramine to the same extent at all membrane potentials tested. Thus there was no change in the voltage dependence of sodium channel activation. These results were confirmed by three experiments. Similar results were obtained with 7 μM haloperidol and 2 μM chlorpromazine (3 experiments for each drug).

The dose-response relationships for sodium current block caused by imipramine, haloperidol and chlorpromazine are illustrated in Figure 3. Step depolarizing pulses to −10 mV were applied at a frequency of less than 1 min^{-1} from a holding potential of −140 mV. The peak amplitude of sodium current was normalized to that of control sodium current, and is plotted against the drug concentration. The

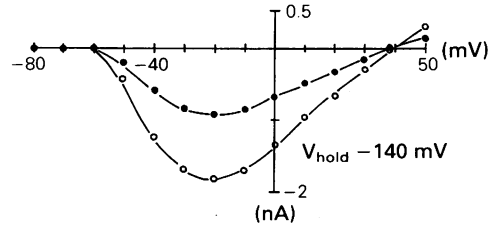

Figure 2 Current-voltage relationships of sodium current before (○) and after application of 3 μM imipramine (●).

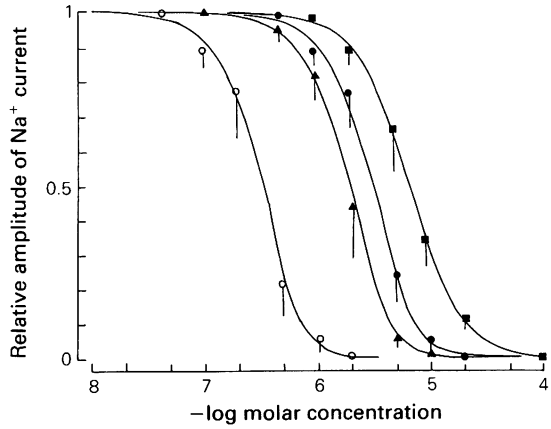

Figure 3 Dose-response relationships for the block of sodium current. The amplitude of peak sodium current elicited by a 20 ms depolarizing pulses to −10 mV from a holding potential of −140 mV in the presence of imipramine (●), chlorpromazine (▲) and haloperidol (■) and that from a holding potential of −90 mV in the presence of imipramine (○) were normalized to the control amplitude measured in the absence of drugs. Each point represents the mean (with s.e.mean shown by vertical lines) from six experiments. Theoretical curves are drawn by equation (1) for the value of $n = 2$.

measurements for each drug are fit by a sigmoid curve calculated by the following equation

$$I_{Na} = \frac{1}{1 + ([C]/K_d)^n} \quad (1)$$

in which I_{Na}, [C] and K_d represent sodium current amplitude, drug concentration, and the dissociation constant of drug binding reaction, and the exponent n is assumed to be 2. The exponent n = 1 and n = 3 gave less steep and steeper curves, respectively, than the measurements. Therefore, it was concluded that two drug molecules bind to one receptor in the sodium channel to exert the blocking action. The apparent dissociation constants for sodium current block were estimated to be 3.5 ± 0.74, 7.0 ± 0.86 and 2.1 ± 0.4 μM for imipramine, haloperidol and chlorpromazine, respectively ($n = 6$).

The degree of imipramine block was dependent upon the holding potential as is shown by the dose-response curves with holding potentials of −90 mV and −140 mV (Figure 3). At a holding potential of −90 mV, the apparent dissociation constant was estimated to be 0.35 ± 0.09 μM ($n = 3$), representing a 10 fold increase in the blocking potency compared with the data at a holding potential of −140 mV. The apparent dissociation constants for haloperidol and chlorpromazine were also decreased by changing the holding potential from −140 mV to −90 mV; to 0.65 ± 0.06 μM ($n = 3$) and 0.18 ± 0.03 μM ($n = 3$), respectively, representing an 11 fold increase in potency in both cases. Therefore, it was concluded that the block of sodium current by these three drugs is highly voltage-dependent, being augmented by membrane hyperpolarization.

Effects on sodium current kinetics

The currents illustrated in Figure 1b show that imipramine, haloperidol and chlorpromazine did not change the time course of sodium current. In order to substantiate the observation in a more quantitative manner, the time courses of sodium channel activation and inactivation were analyzed by Hodgkin-Huxley (1952) formulation as shown in Figure 4. The time course of sodium current activation is described by the equation

$$e^{-t/\tau_m} = 1 - (I(t)/I'(t))^{1/n} \quad (2)$$

where τ_m is the time constant of activation, and I(t) and I′(t) represent the recorded current amplitude and the current amplitude estimated by the extrapolation of the falling phase of current at time t, respectively, and n is the exponent.

The sodium currents recorded before and during imipramine (5 μM) application are superimposed in Figure 4a. The current in imipramine multiplied by 3.3 completely overlaps the control current. The extrapolation of the falling phase of sodium current is also shown. The time courses of activation as calculated by equation 2 in both control and imipramine fall on a straight line when n is assumed to be 3, indicating that the activation process is described by m^3 kinetics as it is in the sodium channel of squid giant axons (Hodgkin & Huxley, 1952). Imipramine (2–5 μM) had no effect on τ_m ($P > 0.05$, $n = 5$).

The analysis of the time course of sodium channel inactivation is shown in Figure 4b. The sodium current in the presence of 3 μM imipramine was suppressed to 50% of control and mimicked the control current when multiplied 2 fold. The time course of current decay is expressed by two exponential functions with time constants of 1.7 ms (τ_{fast}) and 12.3 ms (τ_{slow}) in both control and imipramine for the experiment shown in Figure 4b. The values for mean ± s.e.mean are 2.0 ± 0.9 ms and 13.7 ± 1.4 ms ($n = 6$) for the fast and slow time constants, respectively, in both control and imipramine (2–5 μM).

Steady-state sodium channel inactivation

The steady-state sodium channel inactivation curve was greatly shifted in the direction of hyperpolarization after application of 5 μM imipramine (Figure 5). As illustrated in the inset of the figure, 5 s after a control step depolarizing pulse (−10 mV, 20 ms), a

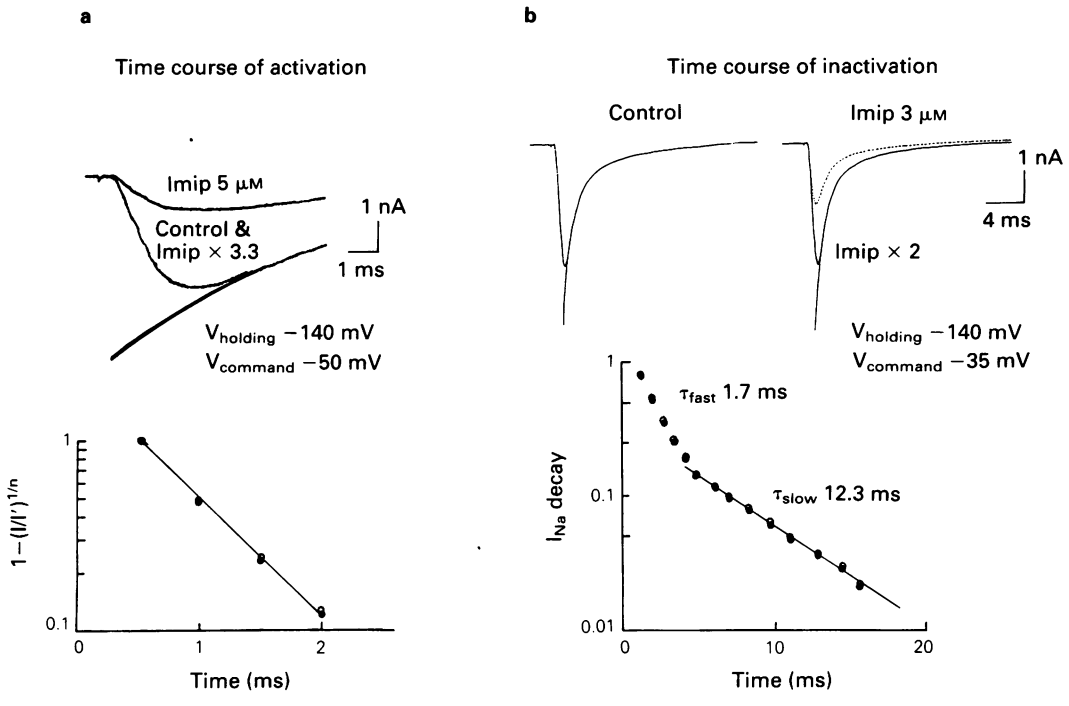

Figure 4 Effects of imipramine on the activation and inactivation of sodium current. (a) The activation time course. The sodium currents in control and imipramine (5 μM) are shown. When multiplied 3.3 fold, the current in imipramine completely overlaps the control current. The time course of sodium current activation was assessed by equation (2), and the measurements fall on a straight line with $n = 3$. (b) The time course of the falling phase of the sodium current. The current in 3 μM imipramine, when multiplied 2 fold, mimics the control current. The decay phases of currents before and during application of imipramine are plotted on a semi-logarithmic scale. In both (a) and (b): (●) control; (○) imipramine.

conditioning pulse (1 s duration) was applied to various potential levels, which in turn, with a 2 ms gap at the holding potential level (−120 mV), was followed by a test depolarizing pulse (−10 mV, 20 ms). The 2 ms interval allowed the capacitive current to decay without significant recovery of sodium current before the test pulse was applied. The sodium current associated with the test pulse, in a value relative to the current associated with the control pulse, is plotted as a function of the conditioning voltage. The sodium currents in imipramine were suppressed. When normalized to the control sodium currents obtained before application of imipramine, the inactivation curve is seen to be shifted by 19 mV in the direction of more negative potentials without change in the slope factor. The mean ± s.e.mean for the shift was estimated as 18.0 ± 2.4 mV ($n = 4$). Similar shifts were observed after application of haloperidol (7 μM) and chlorpromazine (2 μM) in amounts of 21.0 ± 0.5 mV ($n = 3$) and 17.5 ± 3.0 mV ($n = 4$), respectively. The slope factor was not affected by these two drugs. The results indicate that these drugs have a high affinity for the inactivated state of sodium channel.

Use-dependent block

The suppression of sodium current by imipramine was greatly enhanced by applying repetitive stimulations. An example of such an experiment is illustrated in Figure 6a. Step depolarizing pulses (−10 mV, 30 ms) were applied at an interval of 100 ms. Whereas the sodium current amplitude remained constant during repetitive stimuli in control experiments, drastic decreases were observed in the presence of imipramine. The time course of the use-dependent block is more clearly seen in Figure 6b in which the current amplitude associated with each pulse (I_n) is plotted as a function of pulse number. The use-dependent block was accelerated by shortening the pulse interval, and an interval of 5 s was required to avoid the use-dependent block in the presence of imipramine (not shown). Similar results were obtained in all ten cells examined.

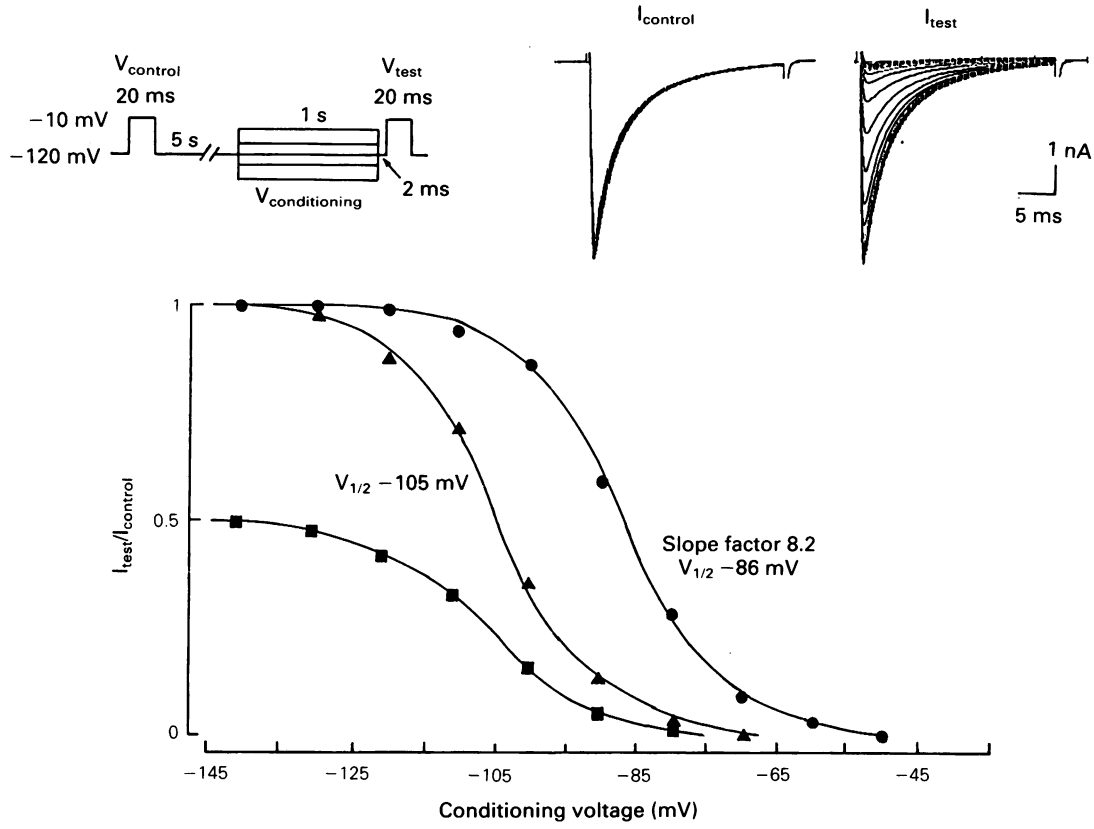

Figure 5 Steady-state inactivation curves for sodium current in the presence and absence of 5 μM imipramine. Measurements were made using a standard two-pulse protocol (see inset). The amplitude of peak current associated with a test pulse was normalized to the control current amplitude measured 5 s before the conditioning pulse, and is plotted as a function of the conditioning potential: (●) control; (■) imipramine 5 μM; (▲) imipramine normalized to control.

However, the use-dependent block was not observed with very brief pulse intervals (2–4 ms) in any of three cells tested during application of 5 μM imipramine. Similar use-dependent block was also observed in the presence of 7 μM haloperidol or 2 μM chlorpromazine (Figure 6b).

Dissociation of drugs from inactivated channels

Figure 7a illustrates the pulse protocol used for assessing the recovery from drug-induced block. The control sodium current was evoked by a 20 ms depolarizing pulse to −10 mV 10 s before the conditioning pulse. The conditioning depolarizing pulse (5 s) to −10 mV was followed by various recovery periods, and then by a test pulse to −10 mV. Each pulse sequence was given at a 30 s interval. Figure 7b illustrates a series of superimposed traces of control and test currents in the absence or presence of 1 μM imipramine. The peak current for each test pulse was normalized to that for the control pulse, and is plotted as a function of the recovery period in Figure 7c. The test currents in drug-free solution recovered within 1 s. In the presence of 100 nM or 1 μM imipramine, however, it took more than 2 s for complete recovery. As shown in Figure 7d, the recovery time course in control solution is expressed by two exponential functions (time constants of 43 ms and 192 ms for the fast and slow components, respectively). In the presence of 100 nM imipramine, the time course of recovery was markedly slowed, and a time longer than 2 s was required for complete recovery. The recovery time course is again expressed by two exponential functions (time constants of 210 ms and 1.6 s for the fast and slow components, respectively). The fast time constant approximated the slow component in the control. Thus, it appears that the slow component of the sodium current recovery in imi-

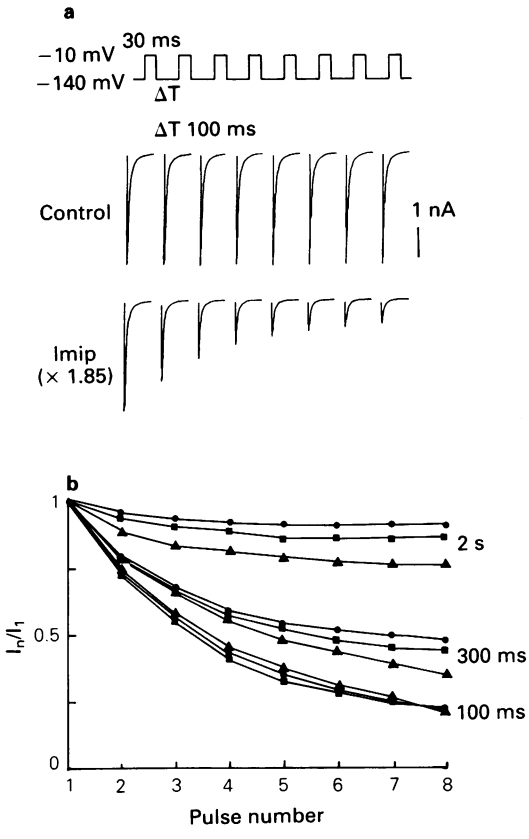

Figure 6 Use-dependent block of sodium current by 3 μM imipramine (■), 2 μM chlorpromazine (●) and 7 μM haloperidol (▲). Eight consecutive pulses to −10 mV were delivered at 100 ms, 300 ms and 2 s intervals from a holding potential of −140 mV. (a) Pulse protocol and successive current traces obtained in the control and imipramine (Imip)-containing solutions. The first current in imipramine was normalized to that of control. (b) The peak current amplitude for each pulse (I_n) in the train was normalized to that of the first pulse (I_1), and is plotted as a function of the pulse number.

pramine reflects the time course of drug dissociation from the inactivated sodium channel, whereas the fast component reflects the recovery of drug-unbound channels from inactivation. The extremely slow recovery of the drug-bound channels from inactivation is consistent with the observation that imipramine produced profound use-dependent block in a wide range of frequencies used (Figure 6). The recovery time constants after applications of imipramine (1 μM), chlorpromazine (1 μM) and haloperidol (3 μM) were 201 ± 37, 185 ± 42, and 220 ± 31 ms, respectively, for the fast components, and 1.8 ± 0.27, 1.7 ± 0.39, and 2.4 ± 0.23 s, respectively, for the slow components.

Discussion

Despite the considerable differences in chemical structure among imipramine, haloperidol and chlorpromazine, the characteristics of sodium channel block are very similar to each other. The present results with imipramine and haloperidol are in general agreement with those for chlorpromazine (Ogata *et al.*, 1989) in many respects. The sodium current is blocked without any change in the activation or inactivation kinetics. The resting or steady-state block is voltage-dependent, and intensified by shifting the holding potential to less negative values. The drugs have high affinities for the inactivated state of sodium channels as the steady-state sodium channel inactivation curve is shifted in the hyperpolarizing direction (Hondeghem & Katzung, 1977). There is a use-dependent component of block, as repetitive depolarizing pulses greatly accelerate the block. The recovery from the drug-induced block is very slow, indicating a slow dissociation of drug molecules from the inactivated sodium channels.

The apparent dissociation constant for imipramine block of sodium current is estimated to be 0.35 μM when measured at a holding potential of −90 mV which is close to the normal resting potential of cardiac cell. The plasma concentration for therapeutic antidepressant effects is in the range of 0.35 to 0.7 μM (Baldessarini, 1985). Therefore, the observed sodium channel block by imipramine is likely to cause alterations of cardiac function, including direct depression of the myocardium and amelioration of arrythmias. The potency will be high due to cardiac beat which will augment the use-dependent block.

The use-dependent block of sodium channels is important in interpreting the action of psychotropic drugs, because the sodium channels of the cardiac myocyte are continuously modulated by rhythmic activity which is intrinsic to the cell or even by incoming synaptic bombardments, and also because rhythmic activity of the heart is modulated by various pathological conditions.

A single or a train of brief conditioning pulses (2–4 ms), which were long enough for the sodium channels to open but short enough to avoid inactivation, produced little or no use-dependent block by imipramine. Therefore, in contrast to the relatively high affinity for the resting and inactivated channels, the drug appears to have only minimal effects on the sodium channel in the activated state. The absence of drug effect on the time course of sodium current decay (Figure 4b) is consistent with this notion, since drugs that bind to the open state of the channel have

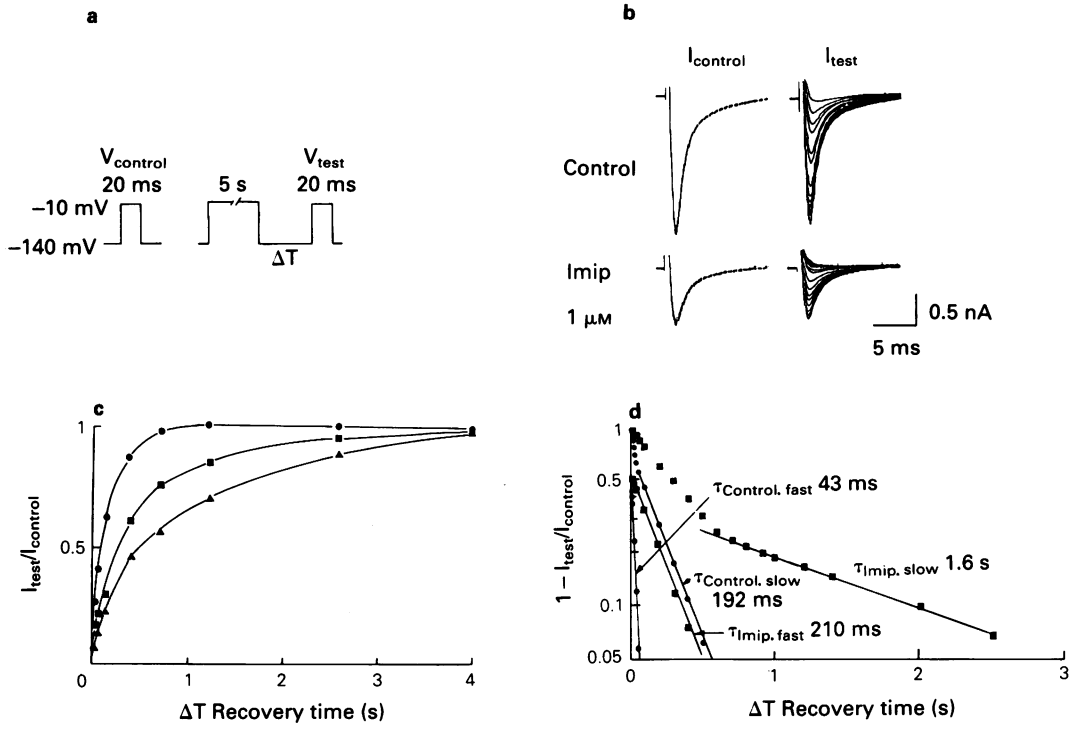

Figure 7 Recovery from the imipramine block as assessed by using the protocol shown in (a). (b) Sodium currents associated with the control pulse and the test pulse before and during application of 1 μM imipramine (Imip). (c) Recovery from the block caused by a 5 s conditioning pulse before (●) and during application of 100 nM (■) and 1 μM (▲) imipramine. The peak current for each test pulse was normalized to the current associated with control pulse, and is plotted as a function of the recovery time. (d) The recovery time courses plotted on a semilogarithmic scale for control (●) and 100 nM imipramine (■) data.

been shown to accelerate the falling phase of current (Colquhoun & Hawkes, 1983). The observation that imipramine had no effect on the current-voltage relationship for sodium channel activation (Figure 2) further rules out the possibility of the open-channel block. Drug binding to the inactivated state is probably much slower than channel gating (opening and closing).

As in the case of chlorpromazine (Ogata *et al.*, 1989), imipramine and haloperidol require the cooperation of two drug molecules for one channel site (Figure 3), whereas the binding of antiarrhythmic agents so far examined are well described by 1:1 stoichiometry (e.g. Bean *et al.*, 1983; Yatani & Akaike, 1984). This indicates that the dose-response relation will be steeper for the psychotropic drugs than for the antiarrhythmic drugs. Therefore, administration of these psychotropic drugs may tend to lead to 'overdose' intoxication. The dose may be high enough to cause toxic action through cardiac sodium channels. It is possible that the use-dependent effect of the psychotropic drugs and their binding stoichiometry are useful for the treatment of cardiac arrhythmias when properly used. In fact, tricyclic antidepressants are known to ameliorate considerably paroxysmal ventricular tachycardia (Manoach *et al.*, 1979; Frommer *et al.*, 1987).

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References

BALDESSARINI, R.J. (1985). Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics*. ed. Gilman, A.G., Goodman, L.S., Rall, T.W. & Murad, F. pp. 387–445. New York: Macmillan Publ. Co.

BEAN, B.P., COHEN, C.J. & TSIEN, R.W. (1983). Lidocaine block of cardiac sodium channels. *J. Gen. Physiol.*, **81**, 613–642.

BEZANILLA, F. & ARMSTRONG, C. (1977). Inactivation of the sodium channel. I. Sodium current experiments. *J. Gen. Physiol.*, **70**, 549–566.

COLQUHOUN, D. & HAWKES, A.G. (1983). The principles of the stochastic interpretation of ion-channel mechanisms. In *Single-channel Recording*, ed. Sakmann, B. & Neher, B. pp. 135–175. New York: Plenum Press.

FROMMER, D.A., KULIG, K.W., MARX, J.A. & RUMACK, B. (1987). Tricyclic antidepressant overdose. *J. Am. Med. Assoc.*, **257**, 521–526.

HAMILL, O.P., MARTY, A., NEHER, E., SAKMANN, B. & SIGWORTH, F.J. (1981). Improved patch-clamp techniques for high resolution current recording from cells and cell-free membrane patches. *Pflügers Arch.*, **391**, 85–100.

HODGKIN, A.L. & HUXLEY, A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.*, **117**, 500–544.

HONDEGHEM, L.M. & KATZUNG, B.G. (1977). Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. *Biochim. Biophys. Acta*, **472**, 373–398.

MANOACH, M., KAULI, N., NETZ, H., BEKER, B. & ASSAEL, M. (1979). Dibenzepin as an antifibrillatory agent for spontaneously terminating electrically induced ventricular fibrillation. *Isr. J. Med. Sci.*, **15**, 443–447.

MARTY, A. & NEHER, E. (1983). Tight-seal whole-cell recording. In *Single-channel Recording*. ed. Sakmann, B. & Neher, E. pp. 107–122. New York: Plenum Press.

MATTESON, D.R. & ARMSTRONG, C.M. (1984). Na and Ca channels in a transformed line of anterior pituitary cells. *J. Gen. Physiol.*, **83**, 371–394.

MATTHYSSE, S. & LIPINSKI, J.F. (1975). Biochemical aspects of schizophrenia. *Ann. Rev. Med.*, **26**, 551–565.

MITRA, R. & MORAD, M. (1985). A uniform enzymatic method for dissociation of myocytes from hearts and stomachs of vertebrates. *Am. J. Physiol.*, **249**, H1056–1060.

OGATA, N., NISHIMURA, M. & NARAHASHI, T. (1989). Kinetics of chlorpromazine block of sodium channels in single guinea pig cardiac myocytes. *J. Pharmacol. Exp. Ther.*, **248**, 605–613.

RISCH, S.C., GROOM, G.P. & JANOWSKY, D.S. (1981a). Interfaces of psychopharmacology and cardiology – Part one. *J. Clin. Psychiatry*, **42**, 23–34.

RISCH, S.C., GROOM, G.P. & JANOWSKY, D.S. (1981b). Interfaces of psychopharmacology and cardiology – Part two. *J. Clin. Psychiatry*, **42**, 47–59.

SEEMAN, P. (1981). Brain dopamine receptors. *Pharmacol. Rev.*, **32**, 229–313.

STIMMEL, B. (1979). *Cardiovascular Effects of Mood Altering Drugs*. New York: Raven Press.

YATANI, A. & AKAIKE, N. (1984). Effects of a new antiarrhythmic compound SUN 1165 [N-(2,6-dimethylphenyl)-8-pyrrolizidineacetamide hydrochloride] on the sodium currents in isolated single rat ventricular cells. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **326**, 163–168.

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