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Importance of physico-chemical properties in determining the kinetics of the effects of Class I antiarrhythmic drugs on maximum rate of depolarization in guinea-pig ventricle

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1 The effects of Class I antiarrhythmic drugs on the maximum rate of depolarization ($\dot{V}max$) of guinea-pig ventricular action potentials were studied by standard microelectrode techniques.

2 The ability of seven different drugs to depress $\dot{V}max$ in unstimulated tissue ('resting block') was found to correlate poorly with the lipophilicity (log P) of the compounds and only a little better with their molecular weights.

3 Depression of $\dot{V}max$ in stimulated tissue was studied for 11 drugs and found, in all cases, to increase with stimulation frequency ('rate-dependent block').

4 The rapidity of onset of rate-dependent block (at approximately equipotent concentrations) varied markedly between drugs. It correlated well with molecular weight ($r = 0.83$; $P < 0.01$).

5 The time constant of recovery from rate-dependent block (τre) also correlated very well with molecular weight ($r = 0.94$; $P < 0.001$) for the seven drugs thus studied.

6 A simplified model for the interaction of Class I drugs with the fast sodium channel is proposed in which the drugs all act as 'inactivation enhancers' (as suggested by other workers) but in which their molecular weight plays a central role in determining the kinetics of this interaction.

Introduction

It is well-known that the ability of many antiarrhythmic drugs to depress the maximum rate of depolarization ($\dot{V}max$) of cardiac action potentials is enhanced by increased heart rate. This rate-dependence was first reported for quinidine by Johnson & McKinnon (1957) using guinea-pig papillary muscle. Since then, rate-dependence has been found in a large number of drugs with this 'Class I' activity (Vaughan Williams, 1970; 1975), and appears likely to be a property common to all such compounds (see, for example, Courtney, 1979; 1980a,b,c; 1981; Sada & Ban, 1980; 1981a; Frame & Hoffman, 1981; Campbell, 1982a,b).

Several studies of the structure-activity relationships of Class I drugs have been reported (Courtney, Kendig & Cohen, 1978a,b; Courtney, 1979; 1980a,b,c; 1981; Sada & Ban, 1980; 1981a,b,c). Their findings, briefly summarized, are as follows. The ability of these drugs to depress $\dot{V}max$ in unstimulated, quiescent myocardium (i.e. the degree of 'resting block') correlated well with lipophilicity (estimated from log P and pKa) but poorly with other physico-chemical parameters such as molecular weight. On the other hand, the speed with which the drugs would act in response to an abrupt increase of rate in a driven preparation, by producing an increase in rate-dependent depression of $\dot{V}max$ (the rapidity of onset of rate-dependent block, in other words) correlated well with molecular weight, and poorly with other factors, so that drugs with lower molecular weights produced faster onset of rate-dependent block. Finally, the rate of recovery from rate-dependent block on cessation of stimulation (or sudden reduction of stimulation frequency) correlated quite well with molecular weight and the correlation was significantly improved by taking log P and pKa (as a measure of the ratio of charged and uncharged forms) into account. (Permanently charged molecules were associated with very slow recovery, regardless of molecular weight.)

In the present study, 11 class I antiarrhythmic

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drugs were studied in terms of their ability to depress $\dot{V}max$ in resting and paced ventricular myocardium. The compounds studied were chosen because of their wide range of physico-chemical properties, in order to test as thoroughly as possible the correlations outlined above and possibly provide further insight into the interaction of Class I antiarrhythmic drugs and the fast sodium channel.

Methods

Guinea-pigs of either sex weighing 300–600 g were stunned and their hearts quickly removed. Strips were cut out from the right ventricular free wall and pinned to the base of a bath (volume 8 ml) with their endocardial aspect uppermost. The tissues were superfused at approximately 12 ml min^{-1} with modified Locke solution gassed with 95% O_2 and maintained at 36.5–37.0°C. The composition of the Locke solution was as follows (mM): NaCl 125, KCl 5.6, $CaCl_2$ 1.8, $NaHCO_3$ 25, $MgCl_2$ 1.0, NaH_2PO_4 0.8, glucose 11, and the pH was 7.5. Preparations were allowed to equilibrate for 1–2 h unstimulated. They were driven at 1 Hz for 30–60 min during which time a stable impalement was obtained. A further period of 15–20 min without stimulation preceded the recording of control values. The driving stimuli were provided from bipolar platinum electrodes producing square waves of 2 ms duration and sufficient intensity to produce a constant latency during a train of stimuli (Walton & Fozzard, 1979). Cumulative doses of drug were then added to the superfusate and at least 30 min exposure time allowed at each concentration before taking further readings. During this time, the preparation was not stimulated and remained quiescent. Action potentials were recorded by conventional 'floating' glass microelectrodes filled with 3 M KCl coupled to a high input impedance d.c. amplifier with variable capacity compensation. The upstroke of the action potential was electronically differentiated to give the maximum rate of rise of potential ($\dot{V}max$), and this signal was fed to a sample-hold peak detector (modified after Hondeghem & Cotner, 1978). The output of this instrument was simultaneously displayed on a storage oscilloscope and also recorded on FM tape from which it was later replayed at slow speed onto an X-Y plotter for analysis. To eliminate variation between cells within a preparation each experiment reported was performed during continuous impalement of a single cell.

To study rate-dependent effects, the preparations were driven by trains of stimuli at varying rates and of sufficient duration to achieve a stable level of effect. Rest periods were interposed between trains of stimuli to ensure full recovery from rate-dependent effects. The kinetics of this recovery were studied by applying single extra-stimuli at varying intervals after the end of a train, as previously described, (Campbell, 1982a).

Where applicable, results have been given as means ± s.e.mean and the significance of differences between means and of correlations, estimated by Student's paired *t* test or Student's *t* test.

Quinidine sulphate and procainamide HCl were obtained from Sigma Chemical Co. and lignocaine HCl from Ward Blenkinsop and Co. Ltd. The other drugs were kindly donated by the following companies: disopyramide phosphate (Searle Research and Development), encainide HCl (Bristol Myers), flecainide acetate (Riker Laboratories), lorcainide HCl (Janssen Pharmaceutical Ltd.), mexiletine HCl (Boehringer Ingelheim), tocainide HCl (Astra Pharmaceuticals), Org 6001 (3α - amino - 2β - hydroxy - 5α - androstan - 17 - one - hydrochloride, Organon Laboratories Ltd.), CCI 22277 (methyl 2β-ethoxy-3α - hydroxy - 11α - (3 - methylbutylamino) - 5α - androstane - 17β - carboxylate hydrochloride Glaxo Group Research Ltd.).

Table 1 gives the values of molecular weight (of free base), pKa and log P (log of octanol: water partition coefficient at pH 7.4) for these 11 drugs and the sources of these data.

Results

The results presented were obtained from a total of 64 ventricular muscle cells each from a different preparation. The baseline characteristics for these cells were: resting membrane potential = −86.6 ± 0.3 mV; action potential amplitude =

Table 1 Class I antiarrhythmic drugs used in this study

Drug	*Molecular weight*	*pKa*	*log P*
Mexiletine	179.0	9.3[a]	1.3[a]
Tocainide	190.0	7.8[a]	0.8[a]
Lignocaine	234.3	7.85[a]	2.9[a]
Procainamide	235.8	9.2[a]	0.8[a]
Org 6001	305.4	8.0[b]	3.93[c]
Quinidine	324.0	8.6[a]	3.6[a]
Disopyramide	339.0	8.4[d]	1.8[a]
Encainide	352.5	10.2[e]	0.91[e]
Lorcainide	371.0	9.44[f]	4.16[f]
Flecainide	408.0	9.3[g]	1.15[g]
CCI 22277	463.7	9.5[c]	7.19[c]

Key to sources of data: a = Courtney, 1980(c); b = Organon Laboratories Ltd; c = Glaxo Group Research Ltd; d = Searle Research and Development; e = Bristol Myer; f = Janssen Pharmaceutical Ltd; g = Riker Laboratories

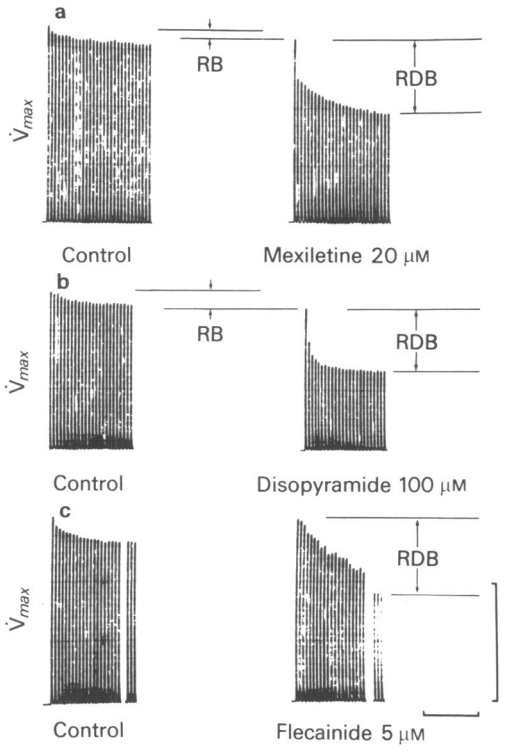

Figure 1 The effect on $\dot{V}max$ of a train of action potentials in previously quiescent tissue in control solution (left-hand panels) and in the presence of mexiletine 20 μM (a, right), disopyramide 100 μM (b, right), and flecainide 5 μM (c, right). The interstimulus interval in all cases is 300 ms. The spikes represent the $\dot{V}max$ of successive action potentials. There is minor rate-dependent depression of $\dot{V}max$ (RDB) in control solution in each case, and marked and approximately equal depression in the presence of each drug. RDB develops rapidly with mexiletine, slowly with flecainide (so that only the first 20 and last 3 beats of 60-beat trains are shown) and at an intermediate rate with disopyramide. There is also some resting depression of $\dot{V}max$ (resting block, RB), in the presence of mexiletine and disopyramide but very little in the case of flecainide. Vertical calibration: 200 $V\,s^{-1}$; horizontal calibration: 5 s. (Calibrations apply to all 3 panels).

125.1 ± 0.2 mV; $\dot{V}max = 276.5 \pm 8.2\ V\,s^{-1}$; action potential duration to 90% repolarization = 175 ± 1.2 ms. There were no significant differences in any of these parameters between the subgroups of cells exposed to the various drugs. None of the drugs significantly altered resting potential (in the concentrations used), and this parameter will not be discussed further. The effects of drugs on action potential duration could not be accurately assessed within the protocol used for these experiments (because of frequent changes of rate).

Time-independent depression of Vmax *('resting block')*

This aspect of antiarrhythmic action was studied in seven drugs. Figure 1 illustrates that fact that, even in high concentrations, some Class I antiarrhythmic drugs produced little or no depression of the $\dot{V}max$ of the first action potential of a train of impulses recorded in healthy tissue after a prolonged period of quiescence. Block observed after such a period of quiescence has been called time-independent or 'resting block' and is here expressed as percentage depression below control values.

Table 2 summarizes the data obtained from studying the resting block produced by seven antiarrhythmic drugs at various concentrations. The ability of the seven drugs to produce resting block correlated poorly with their lipophilicity (measured as log P; $r = -0.19$), but somewhat better with molecular weight ($r = -0.60$), though neither reached statistical significance. The correlation with lipophilicity was not improved by plotting log Q ($= \log P - \log[1 + 10^{pKa-pH}]$), against resting block, thus taking ionization state into account (see Courtney, 1980c). The new correlation coefficient was +0.08.

Rate-dependent depression of Vmax

Figure 1 shows that, in addition to the relatively small amounts of resting block with the three drugs illustrated, repetitive stimulation produced further, much larger falls in $\dot{V}max$, to a new plateau (or equilibrium) level which persisted indefinitely so long as the rate remained constant. The difference between this

Table 2 Percentage resting block obtained with various concentrations of 7 antiarrhythmic drugs

Drug (n)	*Concentration (μM) with corresponding % resting block*		
Flecainide	2	5	10
(11)	0	4.8 ± 1.0%	11.3 ± 2.9%
Encainide	1	3	6
(5)	0	0	0
Lorcainide	0.25	2	5
(5)	0	4.8 ± 2.6%	9.8 ± 2.1%
Disopyramide	10	40	100
(5)	0	2.6 ± 1.7%	19.6 ± 4.0%
Mexiletine	5	20	50
(5)	3.7 ± 2.3%	14.5 ± 3.4%	26.3 ± 7.2%
CCI 22277	2	4	
(6)	2.4 ± 2.4%	9.7 ± 1.5%	
Org 6001	30	60	
(7)	16.6 ± 1.9%	39.4 ± 3.3%	

Exposure time at each dose = 30 min. Values are mean ± s.e.mean.

new plateau level and the $\dot{V}max$ of the first beat of the train was expressed as a percentage decrease, and used as a measure of this rate-dependent block (RDB).

For every compound studied, the value of this RDB increased with increasing stimulation frequency over a wide range of inter-stimulus intervals (ISI) (Campbell, 1982a,b; 1983). At a given ISI, RDB also increased with drug concentration. The data which follow for kinetics of onset of RDB were all obtained at ISI = 300 ms, largely because this drive rate was used in a similar study in the literature (Courtney 1980a,c). The differences found between drugs at this rate, persisted at slower rates.

Kinetics of onset of rate-dependent block

While mexilitine, disopyramide and flecainide, in the concentrations illustrated in Figure 1, all ultimately produced similar degrees of RDB, it can be seen that there are marked differences between drugs, in the speed at which $\dot{V}max$ fell to the new plateau level. In the case of both disopyramide and flecainide, the approach to this plateau was well fitted by a single exponential. This allowed expression of the rate of onset of RDB in terms of the slope of that exponential (see Courtney, 1979). For disopyramide 100 μM, this slope (at ISI = 300 ms) was -0.113 ± 0.007 per action potential but for flecainide 5 μM, which ultimately produced an equal amount of RDB, the rate of onset was only -0.029 ± 0.002 per action potential. (These values for rate of onset of RDB could equally well have been expressed in units of s^{-1} without qualitatively altering any of the results.)

In the case of mexiletine, the rate of onset of RDB was too rapid to be accurately estimated by this technique. During trains at ISI = 300 ms; mexiletine 20 μM produced $61.1 \pm 3.9\%$ of its final rate-dependent fall in $\dot{V}max$ by the second beat.

Table 3 presents these data together with the data obtained from the other eight drugs studied, in the concentrations which ultimately produced approximately 50% RDB at ISI = 300 ms (except CCI 22277 which produced 68% RDB at ISI = 300 ms in the lowest concentration studied). Equipotent rather than equimolar concentrations were chosen so that the rate of approach to a given equilibrium effect could be studied for each drug. The great variation between drugs, in 'therapeutic' concentration ranges precluded detailed comparisons at equimolar concentrations without interference from toxic effects such as depolarization. However, the differences in onset rates could not simply be ascribed to concentration differences as can be seen for instance from the fact that mexiletine 5, 10 and 20 μM, and lignocaine 10 and 50 μM all produced faster rates of onset of RDB than did disopyramide 100 μM or procainamide 180 μM. (Data not included in Table 3: mexiletine 5 and 10 μM produced respectively $53.4 \pm 35\%$ and $63.3 \pm 6.5\%$ of the equilibrium effect by the second beat of the train; $n = 5$. Corresponding figures for lignocaine 10 and 50 μM were $78.2 \pm 3.7\%$ and $91.2 \pm 2.7\%$; $n = 8$.)

The 11 drugs fell into three groups: those with very slow rate of onset of RDB (flecainide, encainide, lorcainide and CCI 22277); those with intermediate rates of onset (quinidine, procainamide, Org 6001, disopyramide); and those with very fast kinetics (lignocaine, mexiletine, tocainide).

There was a statistically significant correlation between increasing molecular weight and decreasing onset rate ($r = 0.83$; $P < 0.01$). There was no suggestion of a correlation between log P and onset rate.

Table 3 Rates on onset of rate-dependend block for 11 antiarrhythmic drugs estimated from trains of stimuli at an interstimulus interval (ISI) of 300 ms

Drug	*No. of cells* (n)	*Concentration* (μM)	*% rate-dependent depression of* $\dot{V}$max *at ISI = 300 ms*	*Rate of onset of block* (per action potential)
Lignocaine	8	200	40.4 ± 2.1	Very fast (>0.6)
Mexiletine	5	20	49.2 ± 7.7	Very fast
Tocainide	8	300	45.2 ± 3.6	0.277 ± 0.029
Disopyramide	5	100	50.9 ± 2.1	0.113 ± 0.007
Org 6001	6	30	57.7 ± 1.9	0.079 ± 0.004
Quinidine	6	20	52.5 ± 2.3	0.068 ± 0.005
Procainamide	8	180	41.0 ± 2.2	0.055 ± 0.003
Flecainide	11	5	50.7 ± 5.0	0.029 ± 0.002
Encainide	5	3	50.0 ± 3.5	0.025 ± 0.006
Lorcainide	5	2	45.0 ± 4.1	0.022 ± 0.004
CCI 22277	6	2	68.0 ± 3.6	0.014 ± 0.001

Values are means ± s.e.mean

Table 4 Time constants of recovery from rate-dependent block (τre) of seven anti-arrhythmic drugs

Drug	*No. of experiments*	τre
Mexiletine	5	471 ± 36.1 ms
Org 6001	10	4.6 ± 0.5 s
Disopyramide	7	12.2 ± 1.0 s
Lorcainide	5	13.2 ± 1.3 s
Flecainide	13	15.5 ± 0.5 s
Encainide	6	20.3 ± 0.9 s
CCI 22277	5	80.4 ± 7.4 s

Figures are means ± s.e.mean

Kinetics of recovery from rate-dependent block

The rate at which $\dot{V}max$ recovered towards the initial (resting block) level at the end of a train of stimuli was studied for seven drugs by adding a single extra-stimuli at varying intervals after a series of trains of stimuli at a constant frequency (Campbell, 1982a). To reduce interference from the effects of extracellular K^+ accumulation during rapid stimulation, the ISI of these conditioning trains was always $>$600 ms. The time-course of the recovery process was found, in all cases, to be well-fitted by a single exponential and (for ISI $>$ 600 ms) appeared to be independent of the frequency of the conditioning trains and of the concentration of the drug (over at least a four-fold range).

The time constants of recovery from RDB (τre) thus derived ranged from 471.2 ± 36.1 ms for mexiletine to 80.4 ± 7.4 s for CCI 22277 (Table 4). Control values for τre were not routinely estimated as these are well documented to be consistently $<$100 ms (Gettes & Reuter, 1974; Brown, Lee & Powell, 1981). To confirm this, however, this parameter was measured in three preparations (using the method of Gettes & Reuter, 1974), and found to be 26 ms, 32 ms and 65 ms.

As was found for RDB onset rates, there was a trend for τre to increase with increasing molecular weight, and this correlation was highly significant ($r = 0.94$); $P < 0.001$). There was no correlation between log P and τre.

Discussion

The main aim of the present work has been an investigation of the way in which Class I antiarrhythmic drugs interact with the sodium channel in myocardium, by studying the ways in which the physico-chemical properties of a series of such compounds might alter the kinetics of that interaction. A consideration of these properties for the 11 drugs studied (Table 1) suggests that they should be able to provide data which considerably extend our knowledge of this field. Thus, the molecular weights of the free base forms of drugs previously investigated in this way (see Introduction) ranged from 190 (tocainide) to approximately 350. Lipophilicity has also been generally low, though quinidine (log P = 3.6) and some of the β-blockers have been exceptions. Of the drugs included in the present study, mexilitine has a lower molecular weight (179), and encainide, flecainide, lorcainide and CCI 22277 higher, (352–463) than any of these. Further, in CCI 22277, we have a molecule which combines the properties of the highest molecular weight of the series (463) with the highest log P (7.19, Campbell & Vaughan Williams, 1982).

Resting block

In contrast with previous reports linking the ability to depress $\dot{V}max$ in the absence of stimulation, with high lipophilicity (Sada & Ban, 1981b), the seven drugs studied suggested better correlation between resting block and molecular weight, than resting block and log P. In particular, CCI 22277, with the highest log P of any Class I drug previously investigated in this manner, produced less resting block than any drug except encainide (log P = 0.9). CCI 22277, however, also has the highest molecular weight (463.7) of the group and it is possible that access to the receptor site in the resting sodium channel is reduced both by low lipophilicity and by high molecular weight, (as suggested by Courtney, 1980c).

It must be noted that all these (generally low) values for resting block given in Table 2 were obtained from cells with normal resting potentials. It has been demonstrated for all the drugs studied that the degree of resting block increases markedly with only modest reductions of resting membrane potential (Kus & Sasyniuk, 1978; Hohnloser, Weirich & Antoni, 1982; Campbell, 1982a,b).

Kinetics of onset of rate-dependent block

The rate of onset of RDB was estimated for 11 compounds. The onset rates (plotted logarithmically) for 9 of the 11 drugs studied in Part 2 correlated well with molecular weight ($r = -0.83$; $P < 0.01$). There was no correlation between onset rate and lipophilicity.

These findings are in agreement with previous reports and are consistent with proposed models in which depolarization of the sodium channel somehow allows access to the receptor from the aqueous

phase, whereas access at the normal resting potential is only possible for drug dissolved in the lipid phase (see Hille, 1978). Rapid access during stimulation may also be favoured by low molecular weight, possibly because of the small dimensions of the aqueous pathway available to the drug.

Kinetics of offset of RDB (τre)

The rate at which $\dot{V}max$ recovered towards its initial (resting) level at the end of a train of stimuli was estimated (as the time constant of recovery, τre) for seven drugs (Table 4). There was a highly significant positive correlation ($r = 0.94$; $P < 0.001$), between log τre and molecular weight for these compounds. Once again, there was no correlation with log P, and, in fact, the two drugs with the highest values for log P, CCI 22277 (log P = 7.19) and lorcainide (log P = 4.16), both had very long time constants of recovery.

The correlation between molecular weight and τre is in good agreement with previous reports in the literature though the apparent lack of importance of log P (at least in compounds of relatively high molecular weight) is a little surprising (Courtney, 1980a,b,c). The relative independence from drug concentration, exhibited by τre, has also been noted by others (Heistracher, 1971; Kojima & Ban, 1979; Courtney, 1980a,c; Oshita, Sada, Kojima & Ban, 1980; Sada & Ban, 1981a; Sada, Grant, Trantham, Brown & Strauss, 1982).

Interpretation of findings

On the basis of previous concepts (Strichartz, 1973; Courtney, 1975, 1980a,b,c; Hille, 1978) and the present data, the following model for the sodium channel, and its interaction with antiarrhythmic drugs, seems a reasonable basis for further discussion and experiment: the Class I antiarrhythmic drugs act on a site, possibly a single 'receptor' within, or functionally associated with the sodium channel, and access to that site can be from the cytosol or the lipid membrane, but not directly from the extracellular fluids. Furthermore, depolarization, whether rapid (and hence associated with opening of sodium channels) or gradual, greatly enhances the binding of drugs to the receptor. When the depolarization is rapid and repetitive, the increased binding is manifested as 'rate-dependent block', and when a steady depolarization is applied, it appears as increased 'resting block' (Campbell, 1982a,b). The two phenomena can thus be thought of as two different aspects of a single voltage-dependent process. The fact that destruction of the inactivation gating process, by pronase (or other techniques, which leave activation intact) largely eliminates this voltage-dependence, strongly suggests that the receptor is the inactivation gate or some structure closely associated with it (Cahalan, Shapiro & Almers 1980).

In the fully polarized, resting state, this receptor is partially 'hidden' from the cytosol and accessible mainly via the lipid phase of the membrane. This would explain the correlation between resting block and log P found in some studies (see Introduction) although it seems possible from the present data that large molecular weight may impose an independent constraint as well. This could be because of some physical barrier to large molecules or because of their slower diffusion rates. However, there is another possible contributing factor which is that the larger molecular weight drugs tend to be more potent at producing RDB and therefore tend to be studied in lower concentrations. (This is discussed further below.)

It is reasonable to suppose that depolarization produces conformational changes in the inactivation gate which 'exposes' the receptor site to the cytosol so that binding is greatly facilitated. Once bound to the receptor, the drug molecule somehow stops the inactivation gate from swinging open again. Reactivation in response to repolarization is only possible if the drug dissociates from the receptor. The rate at which this dissociation occurs should be accurately reflected by τre, since this parameter is measured at normal resting potential (i.e. under conditions in which little, if any, further drug association is occurring). If this is the case, and τre is an index of the unbinding rate constant for the drug, then the reason for its independence of drug concentration becomes clear.

Furthermore, it is well known that within a series of related compounds binding to a common receptor, increasing molecular weight tends to be associated with increasing affinity for the receptor and increasing persistence of action (Paton, 1961; Barlow, 1980). This is usually attributed to increased Van Der Waal's and other short-range forces, between drug and receptor molecules (Paton, 1961). It seems possible then that this phenomenon could at least partially explain the close correlation between molecular weight and τre without the need to postulate physical, or other, barriers to large molecules, though the reason for the closer correlation with log re than with τre is not immediately apparent. This is not to deny the great importance of other factors, such as ionic charge (permanently charged analogues of antiarrhythmic drugs have very long values for τre regardless of molecular weight). Stereospecificity is also important. Yeh (1980) has shown widely differing values for τre between stereoisomeric pairs of local anaesthetics acting on nerve sodium channels.

The observation that drugs with 'fast' offset kinetics also have 'fast' onset kinetics and drugs with 'slow' offset kinetics have 'slow' onset kinetics

(Courtney, 1980a,b,c; Campbell, 1982a,b), is exactly what would be expected from such a model. Thus, at equilibrium at a given stimulation frequency in the presence of a Class I drug, the number of sodium channels recovering from 'block' (dissociating from drug) during each diastolic interval, must be exactly matched by an equal number of channels which become 'blocked' (drug associated) during the subsequent action potential. In the case of a drug such as CCI 22277 ($\tau re = 80$ s) with very little recovery occurring during the course of a 'normal' diastolic interval (<1000 ms), the number of additional channels becoming blocked per action potential will be correspondingly small. In the presence of mexilitine on the other hand ($\tau re = 471$ ms), most blocked channels will become unblocked during a diastolic interval of 1000 ms and thus, at equilibrium, the same number of channels must again become blocked during the next action potential. If, in the concentrations used, both drugs produce the same depression of $\dot{V}max$, implying the same number of sodium channels blocked at end-diastole, then the number of channels becoming blocked during each action potential must be far higher for mexiletine than for CCI 22277.

This argument can be generalized to the other drugs studied, assuming that the compounds have equal efficacy in blocking sodium channels, once bound to the receptor.

Thus in order to produce say 50% RDB at a given heart rate it is necessary to block far more sodium channels per action potential using a drug with a short τre than is necessary with a drug which has a long τre. It follows from this that the former compound will exhibit the faster onset of RDB and will achieve equilibrium in fewer heart beats. It also follows that the drug with the longer τre, because it can produce a steadily accumulating depression of $\dot{V}max$ without significant interference from diastolic recovery, is likely to be the more potent agent. That this tends to be the case is indicated by the concentrations of drug required to produce 50% RDB listed in Table 3. This is not to deny a possible role for other factors, such as differences in drug efficacy, faster diffusion of small molecular weight molecules and the possible presence of barriers to diffusion of larger molecules. There does, however, appear to be a trend for increased potency to be associated with slower kinetics and, as we have seen, slower kinetics correlate closely with increased molecular weight.

In conclusion, a simplified model for the interaction of Class I antiarrhythmic drugs is proposed in which the drugs all act as 'inactivation enhancers', but in which the molecular weight of a drug, by at least partially determining its offset kinetics and hence its onset kinetics and potency, plays an important role in influencing the nature of this interaction, and particularly its response to changes in heart rate.

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