The effect of aliphatic alcohols on the transient potassium current in hippocampal neurones

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- 1 The transient potassium current was recorded in single hippocampal CA₁ neurones from the rat by use of the whole-cell patch clamp technique. The effects on this current of a homologous series of aliphatic alcohols, ranging from butanol to octanol, were investigated.
- 2 The predominant effect of octanol (and the other alcohols) was to cause an increase in the initial rate of decay of the transient potassium current together with a slight decrease in the rate of decay of later phases of the current, such that the current decay became markedly non-monotonic. The alcohols also caused a decrease in peak current amplitude which could not be accounted for solely by the change in current decay kinetics.
- 3 The effect of the alcohols was concentration-dependent and readily reversible. Increasing chain length increased the potency of each alcohol by about 3 fold for each methylene group added. Other than a difference in potency, there appeared to be little difference in the action of aliphatic alcohols of different chain length on the transient current.
- 4 The alcohols did not appreciably change the voltage-dependence of steady state inactivation or activation of the transient potassium current.
- 5 The rate of inactivation of the transient current in these cells was only weakly voltage-dependent. This weak voltage-dependence was not changed by the presence of aliphatic alcohols, neither was the effect of the alcohols themselves voltage-dependent.
- 6 The potencies of each of the aliphatic alcohols were well correlated with their respective membrane/buffer partition coefficients, a finding which implies a hydrophobic locus of action.

Keywords: Transient potassium current; anaesthetics; alcohols; neurone

Introduction

Although aliphatic alcohols are not used clinically as anaesthetics, they nevertheless share many properties with what may be called 'true' anaesthetics and they have been used in many systems to examine the way in which anaesthetic-like molecules change the properties of ionic currents (e.g. Armstrong & Binstock, 1964; Gage *et al.*, 1975; Haydon & Urban, 1983; Wachtel, 1984). They can be a useful tool in investigations of anaesthetic action since they provide a homologous series of molecules whose physico-chemical properties are well documented and vary predictably with chain length (Seeman, 1972). Although the aliphatic alcohols have been shown to affect such sodium channel properties as inactivation (e.g. Oxford & Swenson, 1979), the concentrations of alcohols and other anaesthetics which substantially affect sodium channel gating are generally quite high. Hence it appears unlikely that interference with the action potential generating mechanism is involved in the induction of anaesthesia.

Like sodium currents, transient potassium currents appear to be widely distributed among both neuronal (e.g. Linas, 1988) and non-neuronal tissues (e.g. Pelzer & Trautwein, 1987), and it has been suggested that they play a major role in the control of such cell properties as repetitive firing (Connor & Stevens, 1971) and action potential duration (Nakajima *et al.*, 1986). Therefore, if anaesthetics and similar molecules exert an action on the transient potassium current, one would expect that profound alterations of cell behaviour would result, possibly accounting for the anaesthetic action of these agents. In addition, information on the way in which these agents alter the transient current may elucidate the mechanisms which control the properties of the current itself.

The data presented here show that aliphatic alcohols affect the transient potassium current in hippocampal neurones by increasing the rate of decay of the current and causing a reduction in peak current amplitude. In addition, the potency of a series of alcohols in affecting the transient current

correlates well with their membrane/buffer partition coefficients, implying that these agents exert their effects by interaction with a hydrophobic environment. How these findings fit with contemporary ideas on the mechanism of inactivation of the transient potassium channel is discussed.

Methods

Cell preparation and solutions

Whole cell patch-clamp recordings were made from isolated neurones obtained from the CA₁ region of hippocampi from newborn rats (less than 12 h post-natal). Primary cultures were made by mechanical dissociation of the cells, which were then grown on coverslips coated with poly-L-lysine. The culture medium used was Minimum Essential Medium (Commonwealth Serum Laboratories) to which was added foetal calf serum (10%), glucose (6%), NaHCO₃ (1.5%), penicillin/streptomycin (2%) and fungizone (Flow Laboratories) (1%). Cells were kept in primary culture for 4 to 6 days before use. For experimentation, cells were transferred on a coverslip to a bath and superfused with solution of the following composition (mM): NaCl 150, KCl 3, CaCl₂ 2, HEPES 10, pH adjusted to 7.3 ± 0.05 with NaOH. Patch clamp electrodes were made from thick-walled borosilicate glass (Clarke Electromedical) and typically had resistances of 6 to 8 megohm when filled with intracellular solution of composition (mM): KCl 150, NaCl 4, CaCl₂ 0.5, EGTA 5, pH adjusted to 7.3 ± 0.05 with KOH. Experiments were done at room temperature (25 ± 2°C). Drug application was made with a rapid switching perfusion system, in which the perfusate entered the bath in the immediate vicinity of the cell. The solution bathing the cell could be changed in 1 to 2 s by this method.

Electrophysiology

Whole cell voltage clamp was performed with a List EPC 7 amplifier, with command potentials being generated by a PDP 11 microcomputer, which also digitized and stored the currents generated. Analysis of the records was performed on an IBM-compatible microcomputer with software specifically written for the purpose. Ohmic leak currents were nullified as well as possible 'on line' with an analogue subtraction circuit, any remaining leakage current being digitally subtracted at the data analysis stage. Transient currents arising from the capacitance of the pipette or cell membrane were cancelled by the circuitry employed in the List EPC7. Liquid junction potentials were not corrected for, and would be of the order of 4 to 5 mV (internal solution negative) (see Fenwick *et al.*, 1982). The 'G-series' control on the amplifier was set to minimize the capacitive transient but otherwise series resistance compensation was not generally used; the voltage error from this source would be of the order of 5% for the largest currents measured. The effect of series resistance on cell membrane charging time, even for the worst case estimate, would not be large enough to affect the currents described here.

Results

Cells selected on the basis of their appearance under phase contrast optics typically had membrane potentials more negative than -45 mV and, in current-clamp mode, responded to current injection with action potentials having an overshoot to about $+10$ mV. Input resistance of the cells was typically greater than 500 megohm. Decay of voltage transients in current-clamp mode was well fitted by a single exponential, indicating that the cells were electrotonically compact.

In voltage clamp mode the cells responded to depolarizing voltage steps from a holding potential of -50 mV with an outward, non-inactivating current (I_K). However, if the voltage command pulse was preceded by a hyperpolarizing pre-pulse to -120 mV, a large, rapidly inactivating outward current was evoked in addition. This transient current could be blocked by 4-aminopyridine (4-AP) at concentrations above 1 mM, and could not be evoked when internal KCl was replaced by CsCl. The transient current will be called I_A , due to its similarity to a current described in molluscan neurones by Connors & Stevens (1971). It was not possible to isolate I_A pharmacologically, since block of I_K by tetraethylammonium (TEA) was incomplete except at concentrations above 10 mM, a concentration which also blocked I_A by around 20%. It was also considered likely that there may be an interaction between the alcohols and pharmacological agents used to differentiate the currents, perhaps due to a change in the potency of the blocker in the presence of the alcohols. For these reasons I_K and I_A were isolated electrophysiologically, as described in Figure 1. The current evoked by a depolarization to $+80$ mV from a holding potential of -50 mV (at which potential I_A is entirely inactivated), was subtracted from the current evoked by the same depolarization following a pre-pulse to -120 mV. This procedure effectively produces a record of I_A alone, provided that one ensures that I_A is entirely inactivated at the holding potential used.

Calcium-dependent transient potassium currents have been described in guinea-pig hippocampal cells (Numann *et al.*, 1987). However, in the experiments described here, the addition of Cd^{2+} ($200 \mu\text{M}$) to the extracellular solution made no appreciable difference to the results (in 3 cells tested under both conditions); hence, there appears to be no calcium-dependent component to the currents examined in these experiments, possibly due to inter-species differences.

The effect of octanol on both I_K and I_A is illustrated in Figure 1. At the concentrations used throughout these experiments octanol caused a very small decrease in the magnitude

Figure 1 The effect of octanol on I_A and I_K . (a,b) Outward currents were elicited by a voltage step to $+80$ mV from a holding potential of -50 mV (lower current traces) or following a pre-pulse to -120 mV for 200 ms (current trace with large transient component). Panel (a) shows the currents recorded in control solutions; (b) shows currents recorded with 0.35 mM octanol added. (c,d) Show the result of subtracting the trace recorded with no pre-pulse from that recorded with a pre-pulse, to yield the transient component, or I_A .

of I_K , with no discernible effect on its kinetics. I_A was dramatically changed, however, showing a reduced peak height and increased initial rate of decay. In addition, there appeared to be a late, slowly inactivating component of the current in the presence of octanol, which was not discernible in the control currents.

Figure 2 illustrates the concentration-dependence of the effect of octanol. Each increment in concentration from zero to 1.26 mM caused a decline in the magnitude of the peak outward current. Upon cessation of application of octanol, the peak height recovered to near control values (data record truncated in the figure). These concentrations of octanol (and of the other alcohols described later) are comparable to those used by Haydon & Urban (1986) in a study of anesthetics on the potassium channels in the squid giant axon.

One explanation of the slowly inactivating component of the current revealed in the presence of octanol in Figure 1 could be that there is a contribution to the current from I_D , a slowly inactivating voltage-dependent potassium current described in these cells by Storm (1988), and that this is somehow enhanced by octanol. However, the decay of control records of I_A in these experiments was monotonic, a finding which suggests that I_D was not present. More persuasively, repetition of the experiments in the presence of $50 \mu\text{M}$ 4-AP, a concentration which has been shown to block I_D (Storm, 1988), did not alter the effects of the alcohols (tested in 5 cells, data not shown). This lack of I_D in the experiments described here may be due to the late post-natal development of I_D in neurones (Surmeier *et al.*, 1991), since previous reports of I_D have been in cells from adult animals (Storm, 1988).

Figure 3 shows the transient current in one cell (obtained by the subtraction procedure illustrated in Figure 1) plotted semi-logarithmically (Figure 3a) and linearly (Figure 3c) against time, each record fitted with a single exponential having a time constant of 58 ms. However, the current decay in the presence of octanol (0.3 mM) became markedly bi-phasic, with time constants of 37 ms for the initial decay (fitted between 0 and 40 ms) and 120 ms for the decay beyond 150 ms. Figure 3b and d show the current recorded

Figure 2 The effect of increasing concentrations of octanol on the transient potassium current. Currents were elicited by a voltage step to +80 mV from a pre-pulse of -140 mV (duration 200 ms). (a) The largest current record is the control; progressively smaller currents show the effect of adding increasing concentrations of octanol to the bathing solution (0.16, 0.31, 0.63 and 1.26 mM). After a period of washout, the size and character of the current returned to near the control trace (data not shown for clarity). (b) Cumulative dose-response curve to octanol. Peak current amplitude of the transient currents is shown plotted against time, the concentration of octanol in the bathing solution being increased in steps as in the left panel. A short period of washout, starting at 110 s, is shown at the end of the trace.

in the presence of octanol plotted logarithmically or linearly and fitted with two exponentials. This effect of octanol was consistently seen, although it was somewhat variable (in 6 cells control τ was 54 ± 6.5 (mean $\pm$ s.e.) which changed to 36 ± 4.7 for the initial decay and 117 ± 16 for the late decay). The increase in the initial rate of decay of the current in octanol was not sufficient to account entirely for the decrease in peak current amplitude, since extrapolation of the fits to the currents to 'zero time' (shown in Figure 3) did not result in a 'corrected' peak current in octanol of the same magnitude as control. (This procedure should correct for the effect of the increased rate of decay during the finite time necessary for the rising phase of the current.) Hence it appears that octanol may exert two independent effects, one to increase the initial rate of current decay, and one to reduce peak current amplitude.

This reduction in the peak current amplitude was not due to a change in the voltage-dependence of either the activation or steady state inactivation of the current (a change which has been shown to be induced in these cells by, for instance, GABA_B agonists (Saint *et al.*, 1990)), as shown in Figure 4, which shows data typical of that recorded in 5 cells. Concentrations of octanol which caused considerable changes in maximum conductance ($G_{\max}$) did not cause a large shift in the voltage-dependence of either activation or inactivation. A small shift to the right of both curves may have occurred

Figure 3 Octanol makes the current decay bi-phasic. Transient currents were elicited by a voltage step to +80 mV from a pre-pulse potential of -140 mV. Records for control current and current recorded in the presence of octanol (0.33 mM) are plotted semi-logarithmically against time in (a) and (b) and linearly in (c) and (d). Control currents were typically mono-exponential, as shown in (a), in which a single regression line with a slope equivalent to a time constant of 58 ms has been fitted to the record. The effect of octanol was to cause a marked increase in the rate of decay of the early phase of the current ($\tau = 35 \pm 4$ ms) along with a decrease in the rate of decay of the latter part ($\tau = 120 \pm 10$ ms). Correlation coefficients of the regressions were 0.99 for the initial decay (fitted between 0 and 40 ms) and between 0.8 and 0.9 for the late decay (fitted between 150 and 250 ms). The regression lines have been extrapolated for clarity. The currents shown are averages of 5 records for each trace. Records from the same cell as in Figure 2.

Figure 4 Steady state inactivation and activation curves for the transient current. Peak current amplitude for transient current records was converted to conductance by use of the equation $g = I / (V - V_k)$, where V = membrane potential (see below), V_k = reversal potential for the current (calculated as -100 mV for the potassium concentrations used and a pNa/pK of 0.04). Conductance is shown plotted against potential, where 'potential' represents either the potential of a pre-pulse lasting 200 ms immediately preceding the test pulse to +40 mV (inactivation curves, open symbols), or the potential of the test pulse following a pre-pulse to -140 mV (activation curves, closed symbols). The application of 0.31 mM or 0.62 mM octanol, while causing a substantial decrease in maximum conductance, did not substantially shift the voltage-dependence of either the inactivation or activation of the current. (○, ●) Control; (▽, ▼) 0.31 mM; (△, ▲) 0.62 mM. Filled symbols, activation data; open symbols, inactivation data.

with the higher concentration of octanol used, but this could not account for the change in peak current with the voltage protocol used. Hence the reduction in current amplitude, since it appears not to be due to a change in current kinetics, must be due to the reduction in $G_{\max}$.

A possible explanation of the effect of octanol in causing this decrease in the peak current magnitude and a concurrent increase in the rate of decay could simply be that, for some reason, smaller I_A currents have a faster rate of decay. In other words, the increase in rate of decay could be incidental to the decrease in current magnitude caused by octanol. This possibility was discounted by varying peak current amplitude by changing the degree of inactivation of the transient channels (by varying the potential of the pre-pulse). Little effect on the rate of decay was seen, even when the peak current amplitude was greatly attenuated, as shown in Figure 5a, indicating that transient currents decay at the same rate irrespective of their size. The same procedure carried out in the presence of octanol showed that octanol, although causing an overall depression of peak current, did not alter this lack of correlation between peak height and τ (Figure 5a, filled circles). However, when the same type of analysis was done for currents in which the peak height was varied by exposure to increasing concentrations of octanol, there was a strong correlation between τ and peak current, at least for reductions in current amplitude down to 1.5 nA (Figure 5b). Below this current amplitude (i.e. at higher concentrations of octanol) the relationship between τ and current amplitude seemed to degenerate, implying that the reduction in peak current and the reduction in τ are the product of different

Figure 5 Lack of correlation between peak current and τ for control currents and the effect of octanol. (a) Peak current amplitude was varied by changing the degree of inactivation current (by changing the potential of the pre-pulse over the range -140 to -90 mV). For each current record the peak height and the time constant of decay of the initial 40 ms of the current was measured. Over a range of peak current amplitudes from 0.6 nA to 2.3 nA there was very little change in τ (○). The effect of octanol (0.6 mM) was to reduce peak current amplitude and decrease τ , but there was no change in the lack of correlation between them (●). Lines show regression lines for the data. (b) When the same analysis as above was made for currents in which the peak current amplitude was reduced by increasing the concentration of octanol there was a strong correlation between peak height and τ , at least for reductions of peak height from 2 nA down to 1.25 nA. At smaller peak currents (i.e. for higher concentrations of octanol) the effect to reduce τ appeared to saturate.

processes, and that the effect of octanol in reducing τ saturates before the effect of reducing current amplitude.

The decay of I_A in these cells shows only a weak voltage-dependence (Numan *et al.*, 1987), as shown in Figure 6. Currents were elicited by voltage steps of varying size, from a fixed, hyperpolarizing potential. The time constant of decay of the initial phase (first 40 ms) of each current is shown plotted against the membrane potential at which it was elicited. In the cell illustrated, a weak voltage-dependence of the rate of decay was seen; currents at more depolarized potentials decayed somewhat more slowly. Exposure of the cell to octanol increased the rate of decay of the currents but did not alter this weak voltage-dependence. This result also indicates that the effect of octanol itself is not voltage-dependent, since the decrease in τ produced by octanol was the same at all voltages.

The effects of other aliphatic alcohols, down to a chain length of 4 (butanol), appeared to be qualitatively the same as the effects of octanol. Concentrations of octanol or butanol which caused a similar reduction in peak transient currents also caused a similar increase in the rate of current decay: i.e. the alcohols of different chain length did not produce discernibly different effects, other than a difference in potency. This is similar to the results of Armstrong & Binstock (1964), who also reported that chain length made little difference, other than in potency, to the action of alcohols on squid giant axon. However, it should be noted that Treisman & Wilson (1987) reported that the effects of alkanols on I_A in *Aplysia* did vary qualitatively with chain length, particularly with ethanol.

Aliphatic alcohols with carbon chains of 4, 5, 6 and 7, carbons, as well as octanol, were assessed for their potency in causing a reduction of peak current. Figure 7a shows that, on a logarithmic plot of peak current against concentration, each of the alcohols reduced the peak current height in a parallel manner (i.e. a doubling of the concentration of any one of the alcohols reduces peak height by a similar increment). There was a strong correlation between chain length and potency for the alcohols, the ED_{50} values being (in mM): C8 = 0.8, C7 = 3.5, C6 = 8.8, C5 = 26, C4 = 49. Hence the potency of the alcohols increased by about 3 fold for an increase in chain length of 1 carbon atom. A comparable result is obtained if one uses the reduction in τ as an index of potency, instead of reduction in peak current. These concentrations, and the change in potency with chain length, are similar to those reported for the effects of hexanol and octanol on I_A in *Helix* neurones (Winpenny *et al.*, 1990). A similar relationship between alcohol potency and chain length has also been described for effects upon potassium channels in the squid giant axon (Haydon & Urban, 1986).

Figure 6 Voltage-dependence of τ . Currents were evoked by a test pulse of varying potential following a fixed pre-pulse of -140 mV for 200 ms. The rate of decay of the current showed a slight voltage-dependence over the range of potentials from -30 mV to 40 mV (○). The addition of octanol (0.6 mM) caused an increase in the initial rate of current decay (decrease in τ), but the voltage-dependence of τ was not affected (●). Note that τ is plotted logarithmically.

Figure 7 Potency of other aliphatic alcohols. (a) The effect of increasing concentrations of each of the alcohols on the peak height of the transient current. Each data point is the mean of measurements in at least 4 cells. Lines are regression lines through the points, and points show data for octanol ($C=8$) ($\square$), $C=7$ ($\blacktriangle$), $C=6$ ($\triangle$), $C=5$ ($\bullet$) and $C=4$ ($\circ$). The standard error of the measurements of normalized peak height are of the order $\pm 5\%$ in all cases. (b) Correlation of the effect of the aliphatic alcohols with their membrane buffer partition coefficients. The potency of each of the alcohols from butanol to octanol (expressed as the concentration which produces 50% inhibition of the transient current) is shown plotted against the membrane/buffer partition coefficient (from Seeman, 1972). Both axes are logarithmic. The line through the points is a regression line.

Discussion

The results presented here show that the main effects of aliphatic alcohols on the transient potassium current are to cause a reduction in peak current and an increase in the initial rate of current decay, such that the current decay becomes markedly bi-phasic. There are two possible explanations for the increase in the rate of decay of the current: an increase in the rate of inactivation of the channels, or a 'channel blocking' action of the alcohols. The simplest way in which the behaviour of the transient potassium channel can be depicted is as follows:

In such a scheme the action of the alcohols would be to increase the rate of inactivation (K_1). A simple change in the rate constants of such a scheme by the alcohols is, however, incompatible with the data, since manipulation of the rate constants in such a model cannot yield a bi-phasic decay. This sort of model can be made to produce a bi-phasic decay with the addition of multiple inactivated (or non-conducting) states of the channel, and a differential effect of the alcohols upon the various rate constants. Such an action of the alcohols is possible, but seems somewhat implausible. It should perhaps be noted that if the alcohols act by increasing

the rate of inactivation then they do so without changing the voltage-dependence of steady state inactivation (see Figure 4), a result which also seems implausible.

An alternative explanation is that the alcohols act as channel blockers, i.e. an interaction of the alcohol molecule with the open channel to reduce (or abolish) its conductance, in the same way as the block of nicotinic channels produced by procaine (Adams, 1976). i.e.:

In this scheme the faster initial rate of decay of the current in the presence of the alcohols would be due to increased rate of conversion of the channels to a non-conducting form by interaction of the open channel with the alcohol molecule, the slower rate of decay at later times representing the channels becoming able to conduct again upon dissociation of the alcohol molecule (K_2), before finally inactivating.

The lack of voltage-dependence of the effect of the alcohols (illustrated in Figure 6) would then not be surprising, since one would not expect that uncharged molecules such as the alcohols would display a voltage-dependence in their interaction with the open channel.

However, if the only effect of the alcohols was a 'channel blocking' action, the reduction of the peak height of the current should be entirely accounted for by blockade of the channels as they are activated. As shown in Figure 2, extrapolation of the 'channel blocked' current in the presence of octanol does not yield an intercept of the same magnitude as control currents, indicating that some mechanism other than a channel block is responsible for at least some of the reduction in the peak current amplitude. Other evidence for a dual effect of octanol is provided by the data in Figure 5b, where the correlation between peak height and τ appears to break down at higher concentrations of octanol. This suggests two distinct effects of the alcohols with two sites in the channel protein, one which changes the kinetics of current decay, and one which affects ion conduction. A similar sort of 'dual action' of anaesthetics on potassium channels has been suggested by Haydon & Urban (1986), and 'one site' or 'two site' models of anaesthetic action have been discussed by Forman & Miller (1989) in the context of the nicotinic channel.

A further consideration to be taken into account in assessing whether a channel blocking mode of action of the alcohols can satisfactorily account for the data is the finding that the potency of the alcohols ranging from butanol to octanol correlates well with their respective membrane/buffer partition coefficients (from Seeman, 1972), as shown in Figure 7b. Such a correlation between potency and partition coefficient means, in effect, that the concentration of each alcohol is approximately the same in the membrane lipid phase when the current is reduced by the same amount, although the 'aqueous' concentration is very different. Such a finding implies a hydrophobic locus of action of the alcohols, either with a hydrophobic region of the channel protein, or the lipid environment around it. The same sort of relationship has been described for the effect of alcohols upon the decay of miniature endplate currents by Gage *et al.* (1975), and these authors advanced the same explanation. Similar results have also been shown for alcohol effects on squid giant axon, for both sodium and potassium channels (Haydon & Urban, 1983; 1986). Although one would imagine that a channel blocking agent should be active in the aqueous phase, Murrell *et al.* (1991) recently suggested that the action of n-alcohols in blocking the nicotinic channel was due to interaction at a hydrophobic site. Hence, the data presented here are not inconsistent with a channel blocking model for the action of the alcohols on the transient potassium current.

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(Received September 10, 1991

Revised May 29, 1992

Accepted June 5, 1992)