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POSTSYNAPTIC EFFECTS OF SOME CENTRAL STIMULANTS AT THE NEUROMUSCULAR JUNCTION

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1 Miniature endplate currents (m.e.p.cs) were recorded with extracellular electrodes from sartorius muscles of toads.

2 Central excitant analogues of amylobarbitone (3M2B) and halothane (DBE) decreased the amplitude and time constant of decay of m.e.p.cs and hence reduced the amplitude of miniature endplate potentials. The decay remained exponential with single time constant.

3 A central excitant analogue of ether (indoklon) reduced the amplitude of m.e.p.cs and made their decay biphasic. The decay could be fitted by the sum of two exponentials.

4 Bemegride, a central excitant, prolonged m.e.p.cs. Their decay remained exponential with single time constant. The effect was not due to inhibition of acetylcholinesterase.

5 All of the drugs tested, including amylobarbitone, reduced the temperature-sensitivity of the decay of m.e.p.cs.

6 The biphasic decay of m.e.p.cs caused by indoklon could not be explained simply by supposing that the drug blocked open endplate channels unless it was assumed that the normal rate of channel closing also increased and became much less temperature-sensitive than normal.

Introduction

Many general anaesthetics have been found to depress the amplitude of endplate potentials by increasing the rate of decay of endplate currents (for a review, see Gage & Hamill, 1981). The change in the time course of these currents is caused by a decrease in the open time of endplate channels (e.g. Gage, McBurney & Van Helden, 1978; Gage, Hamill & Van Helden, 1979). The effectiveness of the general anaesthetics in reducing the time constant of decay (τ_D) of endplate currents and channel lifetime correlates well with membrane-buffer partition coefficients (Gage & Hamill, 1976), as does their efficacy as anaesthetic agents (Seeman, 1972), and this has led to the suggestion that general anaesthetics may depress central excitatory synapses in a similar way (Gage & Hamill, 1976; Torda & Gage, 1977).

We have tested the effects on neuromuscular transmission of central stimulant analogues of the anaesthetics, amylobarbitone, ether and halothane, in order to see whether they have an opposite effect on endplate currents. In addition, we have examined the effects of bemegride which has been used as an analeptic in barbiturate poisoning.

Methods

In all experiments, the sartorius muscle of the cane toad (*Bufo marinus*) was used. Miniature endplate currents (m.e.p.cs) were recorded extracellularly. The methods of intracellular recording of miniature endplate potentials (m.e.p.p.s.), extracellular recording of m.e.p.cs and analysis of data have been described in detail previously (Gage & Hamill, 1976).

The 'control solution' contained (mmol/litre): NaCl 130, KCl 2.5, $CaCl_2$ 1.8, Na_2HPO_4/NaH_2PO_4 buffer 3. The pH was 7.1 to 7.2. The sodium ion concentration was raised to 180 mM in some experiments to increase the frequency of miniature endplate currents. The drugs, amylobarbitone, 5-ethyl-5-(3'-methyl-but-2'-enyl) barbituric acid (3M2B, a gift from Dr P.R. Andrews), hexafluorodiethyl ether (indoklon) and 1,2 dibromotetrafluoroethane (DBE) (gifts from ICI), and 4-ethyl-4-methyl-2,6-dioxopiperidine (bemegride) were dissolved directly in the normal Ringer to give appropriate concentrations.

Results

5-Ethyl-5-(3'-methyl-but-2'-enyl) barbituric acid (3M2B)

Many anaesthetic barbiturates have been shown to reduce the time constant of decay of endplate currents (Adams, 1974; 1976; Seyama & Narahashi, 1975; Torda & Gage, 1976). There have been re-

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ports that 5-ethyl-5-(3′-methyl-but-2′-enyl) barbituric acid (3M2B), an analogue of amylobarbitone, causes convulsions in whole animals (Taylor & Noble, 1949; Andrews, Jones & Lodge, 1979). We have found that 3M2B reduces the time constant of decay of miniature endplate currents (m.e.p.cs) and hence depresses miniature endplate potential (m.e.p.p.) amplitude. These effects of 3M3B (100 μM) are illustrated in Figure 1. An m.e.p.p. (upper trace) and the associated m.e.p.c. (lower trace) recorded in control solution can be seen in Figure 1a. After exposure to 3M2B (Figure 1b) the m.e.p.cs decayed at a faster rate than in control solution (see also Figure 2) resulting in a reduction in m.e.p.p. amplitude. There was no change in the peak amplitude of m.e.p.cs, nor in the resting potential of the muscle with this concentration of 3M2B. The effect of 3M2B on the decay of m.e.p.cs was fully reversible. The decay of m.e.p.cs, although faster in the presence of 3M2B, remained exponential with a single time constant (τ_D). This is illustrated in Figure 2. M.e.p.cs decayed more rapidly after 15 min in a solution containing 100 μM 3M2B (right trace, Figure 2a) than in control solution (left trace, Figure 2a). The decays of an averaged m.e.p.c. (average of 20 normalized m.e.p.cs) in control solution (circles) and in a solution containing 100 μM 3M2B (squares) are plotted semilogarithmically against time in Figure 2b. In this experiment, the average τ_D was 3.1 ms in control solution and 2.2 ms in the presence of 3M2B. In 10 similar experiments, the average reduction in τ_D caused by 100 μM 3M2B was 40%. M.e.p.cs with a biphasic decay were not seen at any concentration of 3M2B (range tested, 50 μM–1 mM).

At the normal endplate, τ_D decreases as the temperature is raised and the Q_{10} is 2–3 (Takeuchi & Takeuchi, 1959; Magleby & Stevens, 1972; Gage & McBurney, 1975). This temperature-sensitivity is thought to reflect the activation energy of the reaction that rate-limits the closing of channels. In order to characterize the reaction (or reactions) controlling m.e.p.c. decay in the presence of 3M2B, the temperature-sensitivity of m.e.p.c. decay in the presence of the drug was examined. The effect of temperature on the rate of decay of m.e.p.cs in control solution (circles) and in the presence of 100 μM 3M2B (squares) is illustrated in Arrhenius plots in Figure 3. It can be seen that in the presence of 3M2B, the relationship between $-\ln \tau_D$ and 1/T was linear and that the slope of relationship was less than in control solution. It can be concluded that the reaction rate-limiting the decay of m.e.p.cs in the presence of 3M2B is a single step reaction and that its activation energy is lower than normal. In this experiment the activation energy in normal Ringer solution was 81 kJ/mol and in the presence of 3M2B (100 μM) it was 59 kJ/mol. Results from a number of preparations showed a significant change ($P<0.05$, Student's t test) in the activation energy, from 75 ± 3 kJ/mol (mean ± s.e. mean) in control solution ($n=16$) to 52 ± 3 kJ/mol ($n=6$) in the presence of 3M2B.

Amylobarbitone

Amylobarbitone, the anaesthetic analogue of 3M2B, had effects similar to 3M2B. M.e.p.cs decayed more rapidly in the presence of the drug but the decay remained exponential with a single time constant. In 37 cells in control solution (20°C), τ_D was 2.7 ± 0.1 ms (mean ± s.e.mean) whereas in 11 cells in the presence of amylobarbitone (100 μM) τ_D was 1.8 ± 0.1 ms. Again, the effect was fully reversible.

Amylobarbitone also caused a reduction in the temperature-sensitivity of τ_D. In four cells exposed to a solution containing 100 μM amylobarbitone, the activation energy was 60 ± 6 kJ/mol.

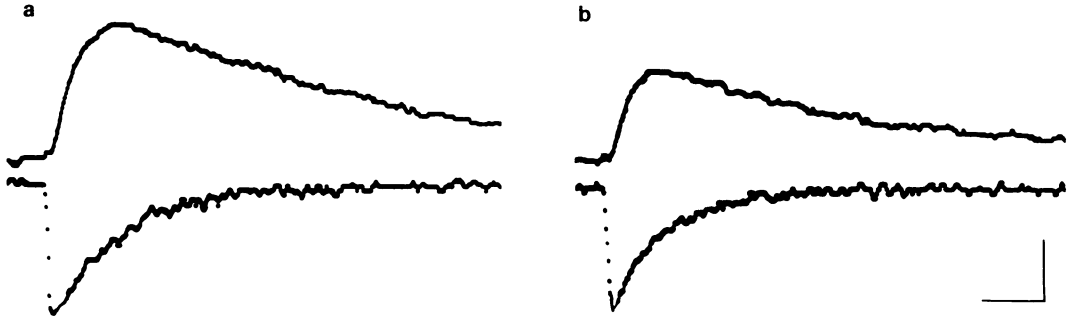

Figure 1 The effect of 3M2B on m.e.p.ps (upper traces) and m.e.p.cs (lower traces). Representative traces are shown in control solution (a) and in 100 μM 3M2B (b). 3M2B reduced the amplitude of m.e.p.ps and the time constant decay of m.e.p.cs. Calibrations: vertical, 0.4 mV for m.e.p.ps, 70 μV for m.e.p.cs; horizontal, 2.5 ms. Temperature 20°C.

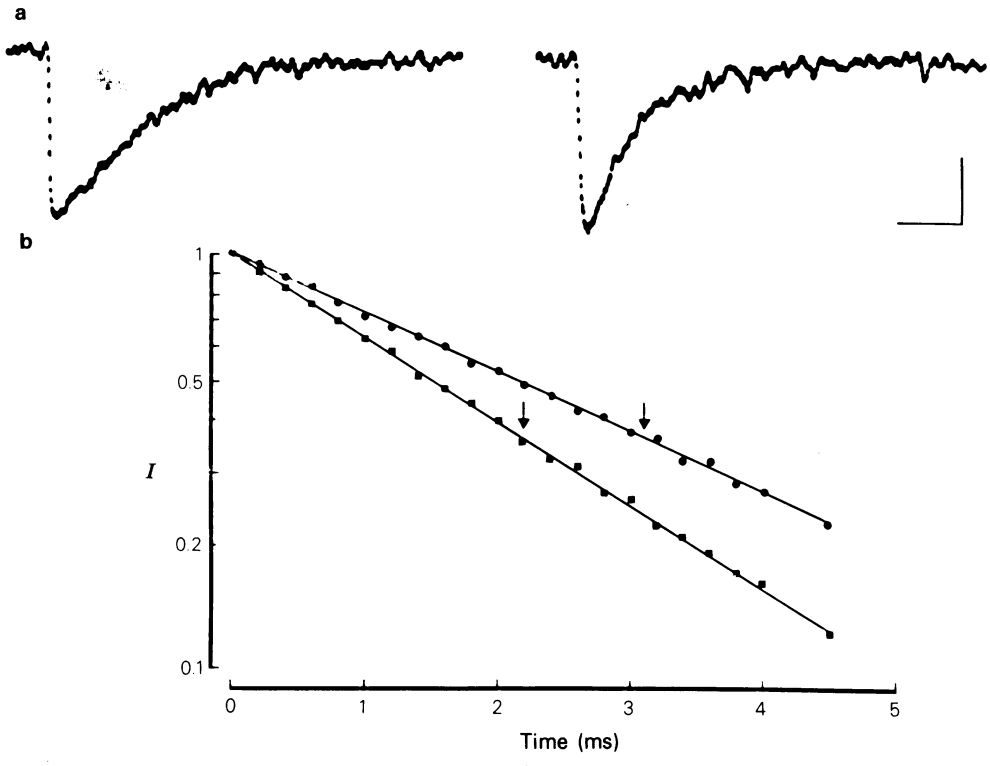

Figure 2 The rate of decay of m.e.p.cs is increased by 3M2B but remains exponential. (a) Representative m.e.p.cs in control solution (left trace) and after 15 min in 100 μM 3M2B (right trace). The decays of an average of 20 normalized m.e.p.cs in control solution (●) and in 3M2B (■) are plotted semilogarithmically in (b); (Ordinate: *I*, the fraction of the peak current). The straight line fits to the data illustrate that the decays are exponential with single time constant (τ_D, denoted by arrows). τ_Ds in control solution and in 3M2B were 3.1 ms and 2.2 ms respectively. Calibrations: vertical, 70 μV; horizontal, 2.5 ms. Temperature 20°C.

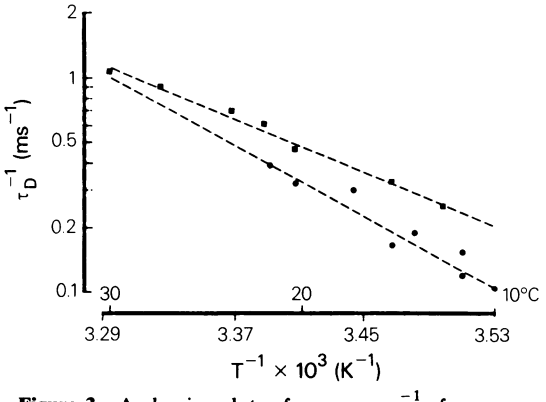

Figure 3 Arrhenius plots of average τ_D^{-1} of m.e.p.cs recorded in control solution (●) and in a solution containing 100 μM 3M2B (■). Each point represents the average τ_D from 15–20 normalized m.e.p.cs recorded at each temperature. The activation energy obtained from the linear regression lines of best fit (broken lines) was 80.6 kJ/mol in control solution and 58.5 kJ/mol in the solution containing 3M2B.

1,2 Dibromotetrafluoroethane (DBE)

Halothane increases the rate of decay of m.e.p.cs and at higher concentrations, produces biphasic m.e.p.cs (Gage & Hamill, 1976). A convulsant analogue of halothane, DBE, also increased the rate of decay of m.e.p.cs and reduced m.e.p.c. amplitude. These effects are illustrated in Figure 4. M.e.p.cs in the presence of 0.75 mM (Figure 4b) and 1.5 mM (Figure 4c) DBE decayed more rapidly than before exposure to the drug (Figure 4a) and the effect was reversible (Figure 4d). Their amplitude in the presence of 1.5 mM DBE was clearly reduced (Figure 4c). The decay of m.e.p.cs in the presence of DBE remained exponential with single time constant (Figure 4e). No biphasic m.e.p.cs were seen.

Hexafluorodiethyl ether

Diethyl ether depresses the postsynaptic response to acetylcholine at the neuromuscular junction by re-

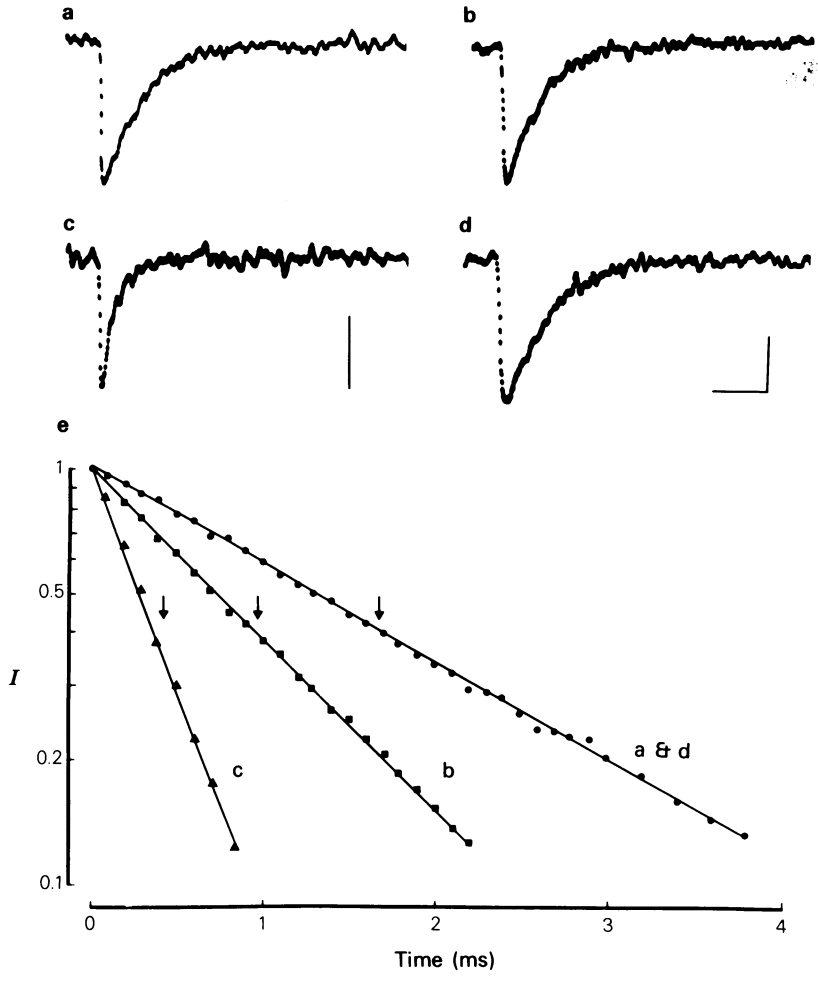

Figure 4 The effect of DBE on m.e.p.cs. Representative m.e.p.cs are shown in control solution (a), 0.75 mM DBE (b), 1.5 mM DBE (c) and after recovery (d); (e) semilogarithmic plots of the decay of an average of 15–20 m.e.p.cs in each of the above solutions. τ_Ds in control solution (●, a), 0.75 mM DBE (■, b), 1.5 mM DBE (▲, c) and after recovery in control solution (●, d) were 1.9, 1.0, 0.5 and 1.9 ms respectively. Calibrations: vertical 70 μV; horizontal, 2.5 ms. Temperature, 23°C.

ducing channel open time (Gage *et al.*, 1979). Hexafluorodiethyl ether (indoklon), a convulsant (Krantz, Truitt, Speers & Ling, 1958), has been reported to reduce the amplitude of m.e.p.ps at the frog neuromuscular junction (Richter, Landau & Cohen, 1977). It was suggested that this effect was due to a reduction in postsynaptic sensitivity to acetylcholine. We have found that indoklon affects both the amplitude and time course of m.e.p.cs. With low concentrations of indoklon (less than 1 mM), a small number of m.e.p.cs had a biphasic decay but most had a normal single-exponential decay. At higher concentrations (e.g. 3 mM) most m.e.p.cs had a biphasic decay and their peak amplitude was reduced. The effects of indoklon at a concentration of 3 mM are illustrated in Figure 5. An m.e.p.c. recorded in the presence of indoklon (Figure 5b) is smaller than in control solution (Figure 5a, note change in vertical calibration). Furthermore, in the presence of indoklon, the decay of most m.e.p.cs became biphasic. The semilogarithmic plot of the average of 20 normalized m.e.p.cs in indoklon (Figure 5c) shows more clearly the biphasic nature of the decay. The time constant of the first phase, τ_f, was 1.2 ms and the time constant of the second, slower phase, τ_s, was 2.8 ms. If this biphasic m.e.p.c. is assumed to consist of the sum of

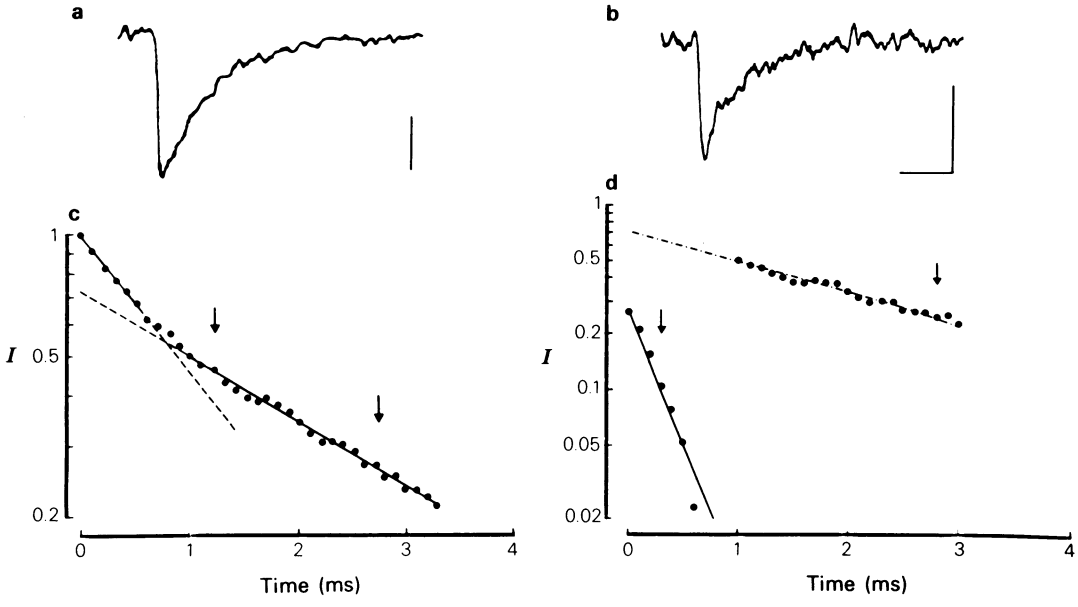

Figure 5 M.e.p.cs have a biphasic decay in the presence of indoklon. An m.e.p.c. recorded in control solution (a) has a τ_D of 2.7 ms. After exposure to indoklon (3 mM) the decay is biphasic (b). (c) A semilogarithmic plot of the decay of an average of 20 normalized m.e.p.cs recorded in the presence of indoklon is fitted by two straight lines which give the rates of decay of the initial fast phase ($\tau_f = 1.2$ ms) and the slow phase ($\tau_s = 2.8$ ms), denoted by arrows. (d) By assuming that the decay of the current can be described by $I(t) = A_s.\exp(-t/\tau_s) + A_f.\exp(-t/\tau_f^*)$ (where I is the fraction of the peak current) the decay of the average m.e.p.c. is divided into a slow component and a fast component with time constants $\tau_s = 2.8$ ms and $\tau_f^* = 0.3$ ms. Temperature 20°C. Calibrations: vertical, 80 μV, horizontal, 2.5 ms.

two exponentials, a 'true' fast phase can be extracted by subtracting out of the slow phase. The fast phase obtained in this way is shown in Figure 5d and its time constant, τ_f^*, was 0.3 ms. The slow phase had a time constant, as before, of 2.8 ms.

Changes in temperature had relatively little effect on the decay of m.e.p.cs in the presence of indoklon. M.e.p.cs recorded at 13°, 20° and 30°C in the presence of indoklon (3 mM) are shown in Figure 6a, b and c respectively (left traces). The semilogarithmic plots of the normalized average of 15–20 m.e.p.cs at the same temperature are shown on the right of each trace. Changing the temperature from 13°C to 30°C had very little effect on either τ_f^* or τ_s. In this experiment, τ_f^*'s at 13° and 30°C were 0.30 and 0.35 ms respectively. At the same temperatures, the τ_ss were 2.4 and 2.0 ms respectively. Results from an experiment in which m.e.p.cs were recorded over a range of temperatures are shown in Figure 7. Measurements were taken from averages of, 15–20 m.e.p.cs at each temperature. There was less than a twofold change in either τ_f^* (squares) or τ_s (circles) over a temperature range of 20°C. The Q_{10} for both τ_f^* and τ_s was 1.4 whereas the Q_{10} for τ_D in the same cell before exposure to indoklon (triangles) was 2.9. It can be seen that τ_s in indoklon was less than τ_D in control solution at temperatures of 20°C or below. Average Q_{10}s ($\pm$ 1 s.e.mean) measured in 9 similar experiments were 1.6 ± 0.1 for τ_f^* and 1.4 ± 0.1 for τ_s.

Bemegride

Bemegride (megimide, 4-ethyl-4-methyl-2,6-dioxopiperidine) has been used clinically to counteract the central effects of overdoses of barbiturates. Bemegride prolongs m.e.p.cs, an effect opposite to that of amylobarbitone and other similar barbiturates. This effect was relatively slow to develop (15–30 min) and could be fully reversed by washing out the drug. Neither the resting potential of the muscle fibre nor the peak amplitude of m.e.p.cs were changed significantly. The effects of bemegride on m.e.p.cs are illustrated in Figure 8. The traces in the upper half of Figure 8 are representative of m.e.p.cs in control solution (a), in 1 mM bemegride (b) and in 4 mM bemegride (c). Semi-logarithmic plots of the decay of m.e.p.cs show that the decay remained exponential as the concentration of bemegride was raised and the m.e.p.cs became longer (Figure 8d). In this experiment the time constants of decay in normal Ringer solution (circles), 1 mM bemegride (squares)

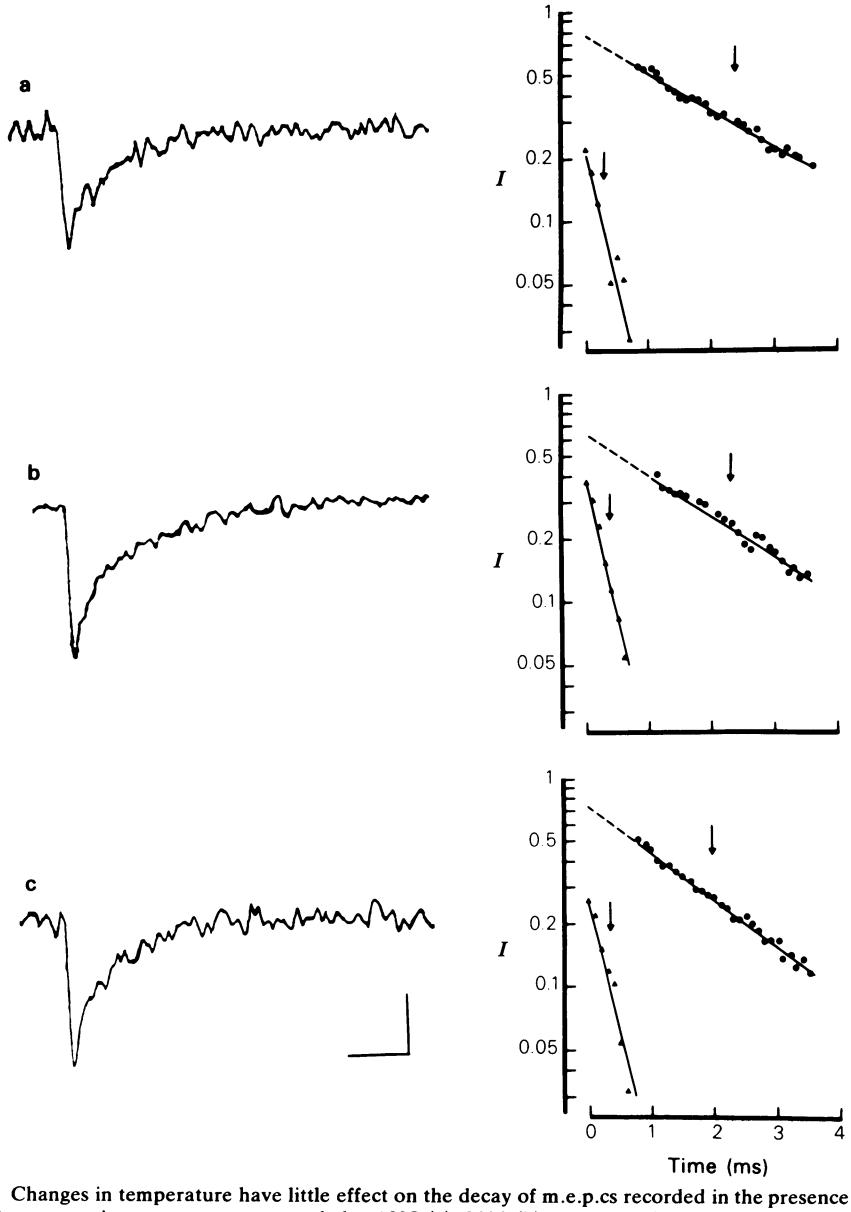

Figure 6 Changes in temperature have little effect on the decay of m.e.p.cs recorded in the presence of indoklon (3 mM). Representative m.e.p.cs were recorded at 13°C (a), 20°C (b) and 30°C (c). The semilogarithmic plot of the decay of an average of 15–20 normalized m.e.p.cs in indoklon at each of the above temperatures is shown to the right of each trace. The two components shown were separated as described for Figure 5d. The τ_f*s measured at 13°, 20° and 30°C were 0.3 ms, 0.35 ms and 0.35 ms respectively. τ_ss at the same temperature were 2.4 ms, 2.3 ms and 2.0 ms respectively. Calibrations: vertical 60 μV; horizontal, 2.5 ms.

and 4 mM bemegride (triangles) were 1.9, 2.7 and 7.0 ms respectively.

Bemegride could conceivably prolong m.e.p.cs by acting as an anticholinesterase. To test this possibility, several experiments were done in the presence of the anticholinesterase, prostigmine (5 μM). If bemegride were also acting as an anticholinesterase then its effectiveness should have been reduced in the presence of prostigmine. However, this was not seen: bemegride was equally effective in solutions containing prostigmine.

It was found that bemegride reduced the

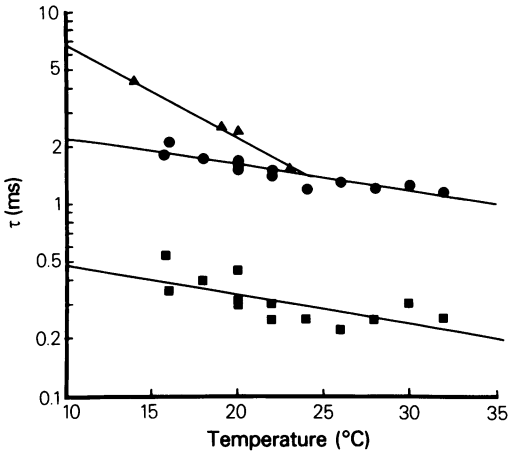

Figure 7 Temperature-sensitivity of τ_s (●) and τ_f^* (■) in the presence of indoklon is much less than the temperature dependence of τ_D (▲) recorded in the same cell before exposure to indoklon. The Q_{10}s obtained from the linear regression lines fitted to the points are 2.9 for τ_D, 1.4 for τ_s and 1.4 for τ_f^*.

temperature-sensitivity of τ_D. This is illustrated in Figure 9. The activation energy was 68 kJ/mol in control solution (circles) and 54.3 kJ/mol in a solution containing bemegride (1 mM, squares). When the results from 6 cells were pooled, the activation energy in control solution was 74 ± 8 kJ/mol and in bemegride it was 55 ± 3 kJ/mol ($P<0.05$, Student's t test).

Discussion

The central excitant analogues of amylobarbitone, halothane and ether all increased the rate of decay of endplate currents and reduced their amplitude, thus reducing the amount of charge transferred across endplate channels and hence the amplitude of endplate potentials. The similar postjunctional depressant effect of these central depressants and their excitant analogues contrasts with their opposite effects in whole animals. The neuromuscular junction is obviously not an ideal model for central synapses in this respect. The two classes of drugs may have different postsynaptic actions at central excitatory or inhibitory synapses. Alternatively, the anaesthetics and their convulsant analogues may have different effects on transmitter secretion. It is interesting that bemegride has an opposite postjunctional effect to amylobarbitone (and other central depressant barbiturates): the central effects of bemegride may depend on a similar excitant action.

It has been suggested that amylobarbitone increases the rate of decay of endplate currents by blocking open endplate channels (Adams, 1974; 1976). Such a mechanism might also account for the effects reported here. In terms of the blocking model, the reaction scheme during the decay of an m.e.p.c. can be represented in simple form as

$$C \underset{\alpha}{\leftarrow} A \underset{b}{\overset{fc}{\rightarrow}} B$$

where C are closed channels, A are activated (open) channels, B are blocked channels, α, f and b are rate constants and c represents the concentration of the blocking drug. It is assumed that endplate current amplitude is directly proportional to the number of open channels, A.

This model might provide an explanation for m.e.p.cs with decay time constants less than α^{-1} or m.e.p.cs with 'biphasic' decays, depending on the values of the rate constants f and b. The decay after the peak (amplitude I(0) at t = 0) is given by

$$I(t) = I(0).(r_f - r_s)^{-1}[(b - r_s)\exp(-r_s t) + (r_f - b)\exp(-r_f t)]$$

$$\text{where } r_f = (\alpha + b + fc) - \frac{\alpha b}{\alpha + b + fc} \quad (1)$$

$$\text{and } r_s = \frac{\alpha b}{\alpha + b + fc} \quad (2)$$

$$\text{as } \alpha b \ll (\alpha + b + fc)^2$$

Thus, in the presence of a blocking drug, the decay of m.e.p.cs would have two components, a 'fast' phase and a 'slow' phase, with initial amplitudes $I(0).(r_f - b)/(r_f - r_s)$ and $I(0).(b - r_s)/(r_f - r_s)$ and decay time constants of r_f^{-1} and r_s^{-1} respectively. When b, the rate of dissociation of the blocking drug, is relatively small, the amplitude of the 'slow' phase would be very small and m.e.p.cs might appear to decay exponentially with single time constant r_f^{-1}.

Assuming that biphasic m.e.p.cs in the presence of indoklon can be described as the sum of two exponentials i.e. $I(t) = I(0).[A_s.\exp(-t/\tau_s) + A_f.\exp(-t/\tau_f^*)]$ the values of τ_s, τ_f^*, A_s and A_f can be obtained from averaged m.e.p.cs. In terms of the simple blocking model the time constant of the slow phase of decay of an m.e.p.c., τ_s, equals r_s^{-1} and the time constant of the 'extracted' fast phase, τ_f^*, equals r_f^{-1}. From measurements of τ_D before exposure to a drug, and of τ_f^* and τ_s in the presence of the drug, the rate constants b and f can be calculated and the relative amplitude of the slow phase at t = 0 (A_s) can be predicted for comparison with the observed A_s from the equations,

$$b = \frac{r_s(r_f + r_s)}{\alpha} \quad (3)$$

$$f = (r_s + r_f - \alpha - b)/c \quad (4)$$

$$A_s = \frac{b - r_s}{r_f - r_s} \quad (5)$$

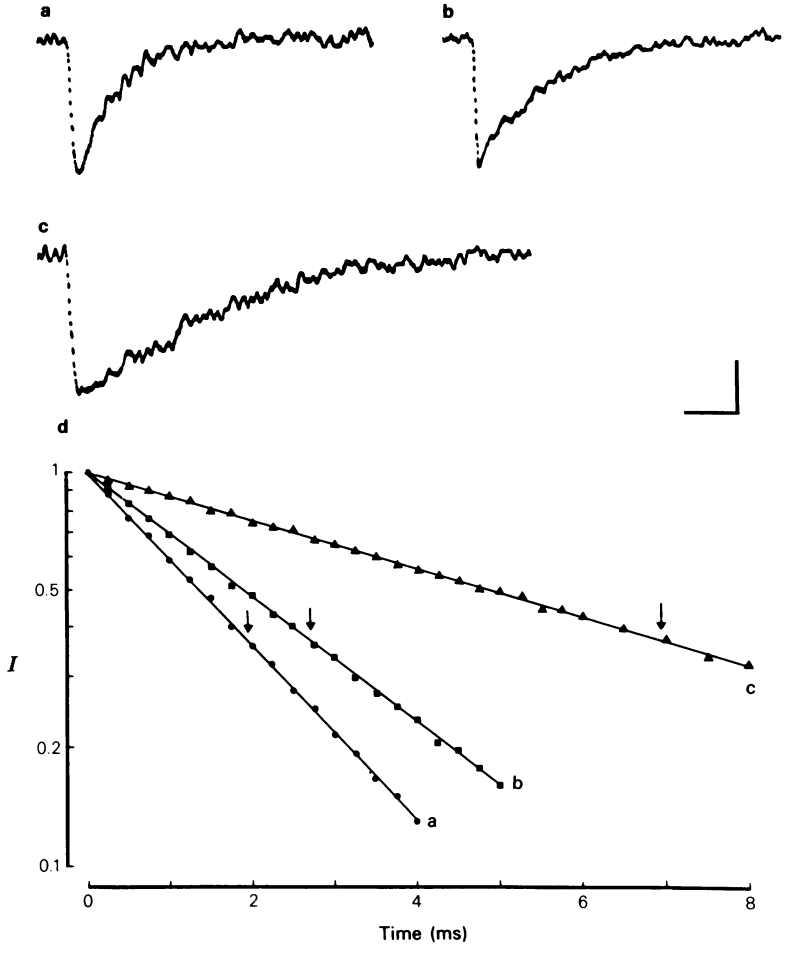

Figure 8 Bemegride decreases the rate of decay of m.e.p.cs. Representative m.e.p.cs in control solution (a), 1 mM bemegride (b) and 4 mM bemegride (c) are shown above. A semilogarithmic plot of the decay of an average of 15–20 normalized m.e.p.cs in each of the above solutions is shown in (d). τ_Ds (denoted by arrows) in control solution (●), 1 mM bemegride (■) and 4 mM bemegride (▲) were 1.9 ms, 2.7 ms and 7.0 ms respectively. Calibrations: vertical 70 μV; horizontal 2.5 ms.

It was found that this model, as it stands, cannot account for the characteristics of the biphasic m.e.p.cs recorded in the presence of indoklon. At temperatures below 20°C, τ_s was less than τ_D measured at the same temperature in control solution (Figure 6). This is inconsistent with the prediction from equation 2 that

$$\tau_s > \tau_D + \frac{1}{b} + \frac{fc}{\alpha b}$$

However, this observation can be accommodated if α, the rate of closing of channels, increases in the presence of indoklon. Some difficulties remain however, and these can be illustrated by results from one cell exposed to 3 mM indoklon (Table 1). In control solution at 20°C, the average τ_D was 2.4 ms. In 3 mM indoklon at the same temperature, τ_s was 2.3 ms and τ_f* 0.35 ms. The equations above predicted an impossible A_s of 1.2 if α^{-1} is equal to τ_D. However, arbitrarily decreasing α^{-1} to 1.4 ms gives an A_s of 0.65, close to the observed A_s of 0.63. When the temperature was changed to 13°C giving a τ_s of 2.4 ms, τ_f* of 0.33 and A_s of 0.78, a value of 1.7 ms for α^{-1} is needed to give an A_s close to that observed. A similar procedure gives an α^{-1} of 1.4 ms at 30°C. Thus α would have to be rather temperature-insensitive in the presence of indoklon for the model to be acceptable.

Average values for α^{-1}, f and b measured in 10 cells exposed to 3 mM indoklon at 20°C and in 7 of the same cells at 30°C, are given in Table 2. From these

Table 1 Rate constants α, f and b predicted, using the simple 'blocking' model, from biphasic m.e.p.cs recorded in the presence of 3 mM indoklon over a range of temperatures in the one cell.

	Observed				*Predicted*		
Temp (°C)	τ_s (ms)	τ_f*(ms)	A_s	τ_D (ms)	α^{-1} (ms)	$f(s^{-1}.M^{-1})$	$b(s^{-1})$
30	2.0	0.25	0.74	—	1.4	2.3×10^5	3.1×10^3
20	2.3	0.35	0.63	2.4	1.4	2.0×10^5	2.0×10^3
13	2.4	0.33	0.78	—	1.7	1.4×10^5	2.5×10^3

The τ_D at 20°C was recorded in control solution before exposure to indoklon.

Table 2 Average values (1 s.e.mean in parentheses) for α^{-1}, f and b calculated as described in the text, from τ_f*, τ_s and A_s, measured in 10 cells at 29°C and 7 of the same cells at 30°C in the presence of 3 mM indoklon

Temperature (°C)	α^{-1} (ms)	f $(s^{-1}.M^{-1})$	b (s^{-1})
20	1.3	1.6×10^5	2.4×10^3
	(0.1)	(0.2)	(0.1)
30	0.96	2.3×10^5	3.2×10^3
	(0.1)	(0.6)	(0.3)
Q_{10}	1.4	1.4	1.3

measurements, it is clear that it would be necessary to postulate that indoklon both increased α and decreased its temperature-sensitivity for the model to fit. Another possibility is that blocked channels may revert to closed channels without passing through an open conformation. However, this more complicated model is difficult to test.

Endplate currents normally decay exponentially with single time constant suggesting that the rate of decay is determined by a single step reaction of the first order with rate constant α. A change in α may underlie the effects of all of the drugs tested. Although this would not alone explain the biphasic m.e.p.cs produced by indoklon, such a mechanism could account for the changes in τ_D seen with the other agents. The rate constant α can be expressed in terms of entropy and enthalpy of activation (ΔS and ΔH) according to:

$$\alpha = \frac{kT}{h}\exp(\Delta S/R).\exp(-\Delta H/RT)$$

(see, for example, Moore, 1972) where the quantity ΔH may be assumed to be the same as the activation energy. The effects of the drugs which change α may be caused by changes in the entropy or enthalpy of activation of the channel-closing reaction. For example, the reduction in activation energy caused by 3M2B, amylobarbitone and bemegride could be due to a decrease in ΔH i.e. a decrease in the height of the energy barrier between open channels and a transition state. A decrease in ΔH would increase α, as was seen with 3M2B and amylobarbitone. The decrease in α caused by bemegride could be due to an added effect of increasing ΔS.

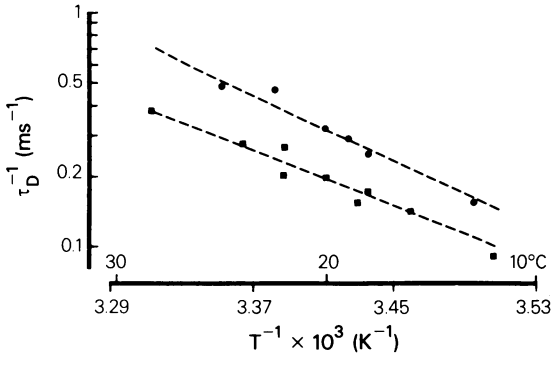

Figure 9 Arrhenius plots of τ_D^{-1} in control solution (●) and in the presence of 1 mM bemegride (■) in the same cell. Each point represents the average τ_D from 15–20 normalized m.e.p.cs recorded at each temperature. The activation energies obtained from the linear regression lines of best fit were 67.8 kJ/mol in control solution and 54.3 kJ/mol in the presence of bemegride.

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