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# Baclofen activates voltage-dependent and 4-aminopyridine sensitive $K^+$ conductance in guinea-pig hippocampal pyramidal cells maintained *in vitro*

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**1** The ionic mechanism underlying the effect of (−)-baclofen in the hippocampus was investigated using guinea-pig brain slices.

**2** (−)-Baclofen either perfused or applied directly by microiontophoresis hyperpolarized the membrane and decreased the membrane input resistance of pyramidal cells in a dose-dependent manner.

**3** The value of the reversal potential for the baclofen-induced hyperpolarization, as estimated from the current-voltage relationships, was about −95 mV.

**4** The reversal potential of the baclofen-induced hyperpolarization measured directly coincided with that for the post-burst hyperpolarization which is known to result from an activation of $Ca^{2+}$-activated $K^+$ conductance.

**5** The amplitude of the baclofen-induced hyperpolarization was increased in low $K^+$ (1.24 mM) medium whereas the hyperpolarization was decreased or abolished in high $K^+$ (12.4 and 25 mM). Low $Cl^-$ (10.2 mM) medium had no noticeable effect on the baclofen-induced hyperpolarization.

**6** The effect of baclofen was antagonized by a low dose of 4-aminopyridine ($5 \times 10^{-6}$ M) whereas it was unaffected by picrotoxin ($2 \times 10^{-5}$ M).

**7** These results strongly suggest that the effect of baclofen is mediated by an increase in $K^+$ conductance.

## Introduction

Baclofen, a β-chlorophenyl derivative of γ-aminobutyric acid (GABA), can depress neuronal excitability in various parts of the central nervous system (e.g. Pierau & Zimmermann, 1973; Fox *et al.*, 1978). The site of action for this drug has been considered to be distinct from GABA recognition sites.

In addition to the classical GABA recognition site ($GABA_A$ site), a new class of GABA receptor ($GABA_B$ site) has been characterized on the basis of pharmacological criteria. It was shown that baclofen exerts its effect as a selective agonist for this novel GABA-receptor (Bowery *et al.*, 1980). The $GABA_B$ site is resistant to bicuculline, whereas the $GABA_A$ site is bicuculline-sensitive. A number of studies on both the peripheral (Bowery *et al.*, 1981) and central (Davies, 1981; Ault & Nadler, 1983) nervous systems indicate that $GABA_B$ sites are present on nerve terminals and when activated result in diminished transmitter release possibly through a reduction in $Ca^{2+}$-current (Bowery *et al.*, 1980; Dunlap, 1981).

It has also been shown that baclofen directly hyperpolarizes the membrane of central neurones (Misgeld *et al.*, 1982; Ogata & Abe, 1982), and this effect of baclofen was suggested to involve an increase in $K^+$ conductance (Gähwiler *et al.*, 1984; Newberry & Nicoll, 1984). In this paper, we have further investigated the ionic mechanism of the postsynaptic effect of baclofen in guinea-pig hippocampal neurones.

## Methods

The experiments were performed on transverse slices (400–600 μm thick) of the guinea-pig hippocampus. The procedures for incubation and recording were fundamentally the same as described previously (Abe & Ogata, 1982). The standard medium was of the following composition (mM): NaCl 124, $NaHCO_3$ 13,

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KCl 5, $CaCl_2$ 2.6, $KH_2PO_4$ 1.24, $MgSO_4$ 1.3, glucose 10. The slices were continuously perfused with the standard medium equilibrated with 97% $O_2$ and 3% $CO_2$ at 30–32°C.

Pyramidal cells were impaled with microelectrodes filled with 2 M potassium acetate (d.c. resistance, 50–100 MΩ). Unless otherwise stated, recordings were made from cells in the CA3 pyramidal layer. Drugs were applied either in fixed concentrations to the bathing solution or directly onto the cell by microiontophoresis. Membrane input resistance was routinely measured by passing hyperpolarizing current pulses (0.3 Hz, 0.6 s pulse duration) of known intensities through the recording electrode using a conventional bridge circuit.

The experimental data are presented as mean ± s.e.mean. The drugs used in this study were: (−)-baclofen (Ciba-Geigy), (+)-baclofen (Ciba-Geigy), GABA (Sigma), picrotoxin (Sigma), tetraethylammonium chloride (TEA; Tokyo Kasei), 4-aminopyridine (4-AP; Tokyo Kasei), procaine (Ishizu), tetrodotoxin (Sankyo).

## Results

The results presented here were obtained from about 450 stable intracellular recordings (mainly from CA3 cells). The resting membrane potential and the input resistance were −62.3 ± 1.0 mV and 20.9 ± 1.5 MΩ, respectively, when measured in 57 CA3 cells on which an intracellular recording could be made for more than 3 h. Although all the figures in this paper show data obtained from CA3 pyramidal cells, the results

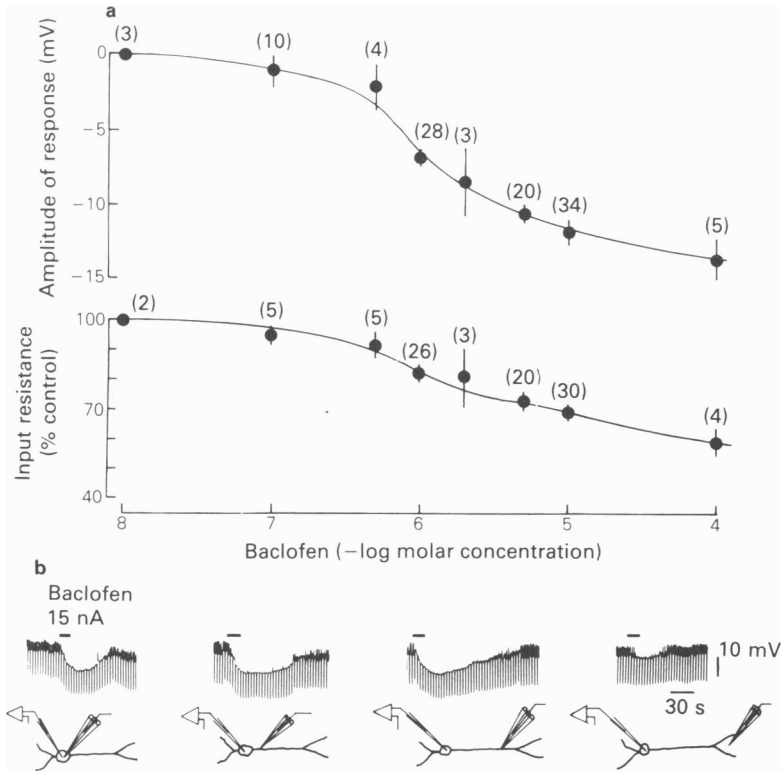


**Figure 1** Pharmacological actions of baclofen in hippocampal pyramidal cells. (a) Concentration-response curves for baclofen-induced hyperpolarization (upper graph) and decrease in input resistance (lower graph). Vertical lines show s.e.mean. Numbers in parentheses are the numbers of experiments. (b) The spatial responsiveness of the pyramidal cell to iontophoretically applied baclofen. The duration of the iontophoretic application of the drugs is indicated by solid lines. The recordings were made from pyramidal layer in all traces, while the tip of the iontophoretic electrode was moved successively along the apical dendrites towards the distal end. The diagram shown under each trace indicates the position of the iontophoretic electrode (0, 200, 400 and 600 μm from the mid line of the pyramidal layer). In this and subsequent Figures, recordings were made from CA3 pyramidal cells; repetitive negative deflections reflect the electrotonic potentials to inward current injections (0.3 Hz, 0.6 s pulse duration) of constant intensity for measurement of input resistance; upward deflection represents positive polarity; spikes were almost entirely eliminated from the traces due to the limited frequency band width of the pen-recorder.

were essentially the same in all the hippocampal subfields.

*General pharmacological effects of baclofen*

As has been demonstrated previously (Newberry & Nicoll, 1984), (−)-baclofen (referred to as baclofen hereafter) hyperpolarized the membrane and decreased the membrane input resistance of pyramidal cells in a stereospecific manner. (+)-Baclofen was about 270 times less potent than baclofen in producing hyperpolarization, as estimated from dose-response curves for these two drugs.

Baclofen produced consistent membrane hyperpolarization over a wide range of concentrations (see Figure 2). The concentration-response curves (Figure 1a), as measured by changes in amplitude of the hyperpolarization (upper graph) and in the input resistance (lower graph) showed the minimal effective concentration to be approximately $10^{-7}$ M. The concentration required to induce the half-maximal response was $1.1 \times 10^{-6}$ M, as estimated from the Lineweaver-Burk plot of the concentration-response curve in Figure 1a. Although concentrations above $10^{-4}$ M which are not included in the graph (up to $10^{-3}$ M) still produced concentration-dependent hyperpolarization, the effect of these high concentrations was irreversible.

Figure 1b illustrates the spatial responsiveness of the pyramidal cell to iontophoretically applied baclofen. Application in the dendritic region produced slightly larger and more prolonged hyperpolarization than the application in the somatic region in the 3 cells examined.

The membrane effects of baclofen were persistent during a perfusion of the medium in which $Ca^{2+}$ was totally removed and the concentration of $Mg^{2+}$ was raised to 12 mM in the 15 cells examined.

*Reversal potential of the baclofen-induced hyperpolarization*

Figure 2 shows the current-voltage relationships obtained in the same neurone at four different concentrations of baclofen. The current-voltage curve obtained in the control solution (solid line) intersects with those obtained during respective drug applications (broken lines) at around 30–35 mV below the original resting membrane potential. The membrane potential at which the two current-voltage curves intersect represents the potential at which the voltage effect of baclofen is cancelled, i.e. the reversal potential for the action of baclofen ($E_{baclofen}$). $E_{baclofen}$ thus estimated was $-95 \pm 4.4$ mV ($n = 3$).

Among the four current-voltage curves obtained during drug administration, the slope of the curve in the depolarized range apparently increased with concentrations $10^{-6}$ and $5 \times 10^{-6}$ M, and even at the highest concentration ($10^{-4}$ M), the decrease in input resistance was slight compared to the striking decrease noted in the hyperpolarized range. Such a paradoxical effect of low concentrations of baclofen was evident in 16 out of the 20 cells examined. The paradoxical increase of the input resistance observed at lower concentrations appeared to be caused indirectly by some conductance triggered by spikes which were elicited by depolarizing current pulses, since the paradoxical increase disappeared and the curve overlapped with that of the control when $Na^+$ and $Ca^{2+}$ spikes were blocked by the addition of tetrodotoxin and removal of $Ca^{2+}$ (compensated with 12 mM $Mg^{2+}$) in all the cells examined ($n=4$). The

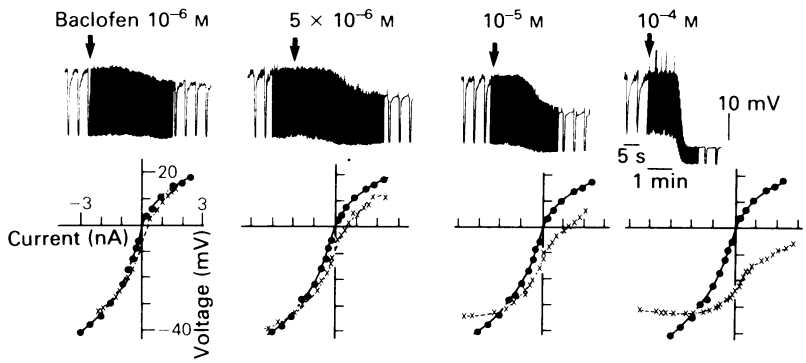


**Figure 2** The current-voltage relationships measured during application of various concentrations of baclofen. Upper traces illustrate recordings of the membrane potential and input resistance from which the current-voltage curves were compiled. All traces were recorded in the same neurone. Downward arrows represent the onset of superfusion of test solution. In this and subsequent Figures, the chart of the pen-recordings was intermittently run at a faster speed. In the graph shown under each trace, solid and broken lines represent the current-voltage curves in the control and test solutions, respectively. Abscissae represent transmembrane current (nA; duration, 600 ms); ordinates, steady-state membrane displacement (mV) produced by the current pulse.

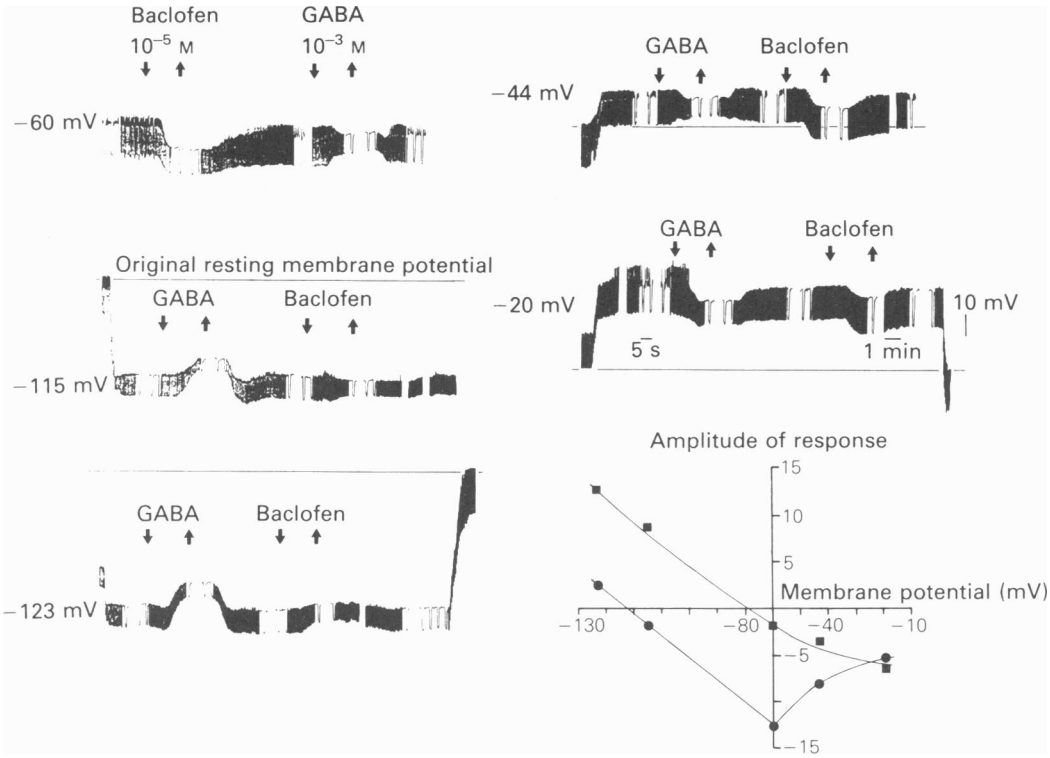


**Figure 3** Voltage-dependence of the membrane potential change induced by baclofen. Voltage-dependence of the action of γ-aminobutyric acid (GABA) is also illustrated for reference. The effect of baclofen was examined at various membrane potentials (−20, −44, −60, −115 and −123 mV) produced by inward and outward direct current (d.c.) injections. Gaps in the trace indicate an omitted period. In the graph, the amplitude of the hyperpolarization or depolarization (ordinates) induced by baclofen (●) or GABA (■) was plotted as a function of the membrane potential displacement (abscissae) produced by inward or outward d.c. injection.

current-voltage curves obtained in the presence of $10^{-4}$ M baclofen showed a small but definite negative slope at hyperpolarized levels in 2 out of 3 cells examined.

$E_{baclofen}$ was also measured directly. The effect of baclofen was compared with that of GABA at various membrane potential levels. An example is shown in Figure 3: $E_{baclofen}$ in this neurone was about −113 mV, whereas the reversal potential for GABA was about −68 mV.

$E_{baclofen}$ was also compared with the revesal potential for the hyperpolarization following the burst discharges triggered by the afferent fibre stimulation (the post-burst hyperpolarization) (Figure 4). Post-burst hyperpolarization was evoked by a perfusion of picrotoxin (which has no effect on the response to baclofen, see below). Again, $E_{baclofen}$ was very negative (about −129 mV). The value of $E_{baclofen}$ approximated that of the reversal potential for the post-burst hyperpolarization. In the 6 cells examined, the value of $E_{baclofen}$ measured directly was around −120 mV (−117.5 ± 3.5 mV), and in 3 cells the value of $E_{baclofen}$ approximated the reversal potential of the post-burst hyperpolarization.

*Effects of ions on the response to baclofen*

Figure 5 illustrates the effect of high external $K^+$ concentrations on the response to baclofen. The amplitude of the baclofen-induced hyperpolarization became progressively reduced when the external concentration of $K^+$ was raised from 6.24 mM (control) to 12.4 mM ($n = 9$) and 25 mM ($n = 4$). It should be noted that the baclofen-induced hyperpolarization was almost totally abolished in the presence of 25 mM $K^+$ even though the membrane potential was restored to the original level by passing a hyperpolarizing direct current (d.c.) (see Figure 5c). As shown in Figure 5d, the conductance change induced by baclofen became progressively reduced as the external $K^+$ concentration was increased. Figure 6 illustrates the effect of low external $K^+$ concentration on the response to

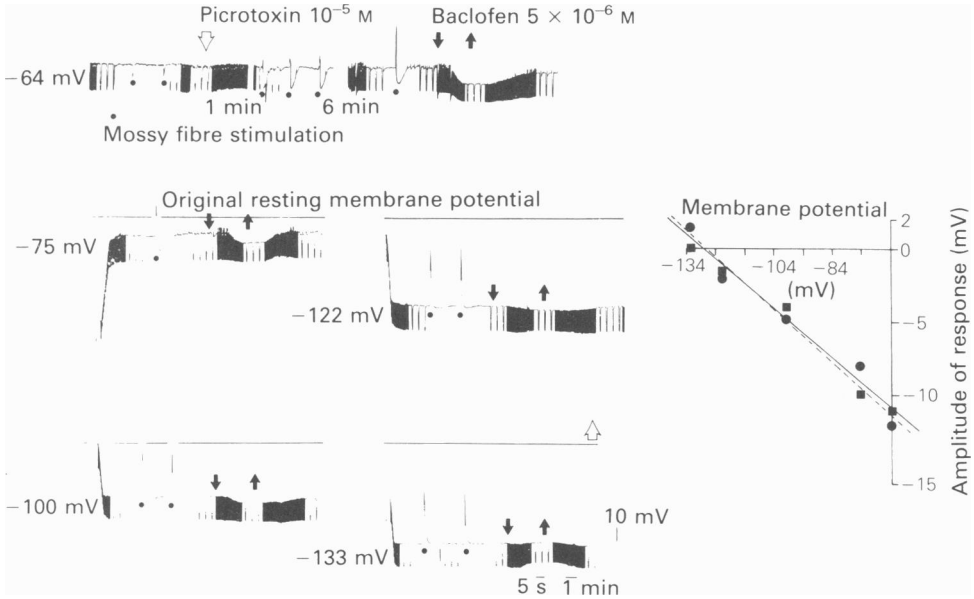


**Figure 4** Voltage-dependence of the membrane potential change induced by baclofen. Experimental protocol is identical to that of Figure 3, but here the voltage-dependence of the baclofen action was compared with that of the post-burst hyperpolarization. The post-burst hyperpolarization was triggered by mossy fibre stimulation (dot). The burst discharges were reflected on the pen-recordings as large positive deflections due to their slow time course. In the graph (●) represents responses to baclofen and (■) post-burst hyperpolarization. In this and subsequent Figures, time shown under gaps in the trace indicates an omitted period.

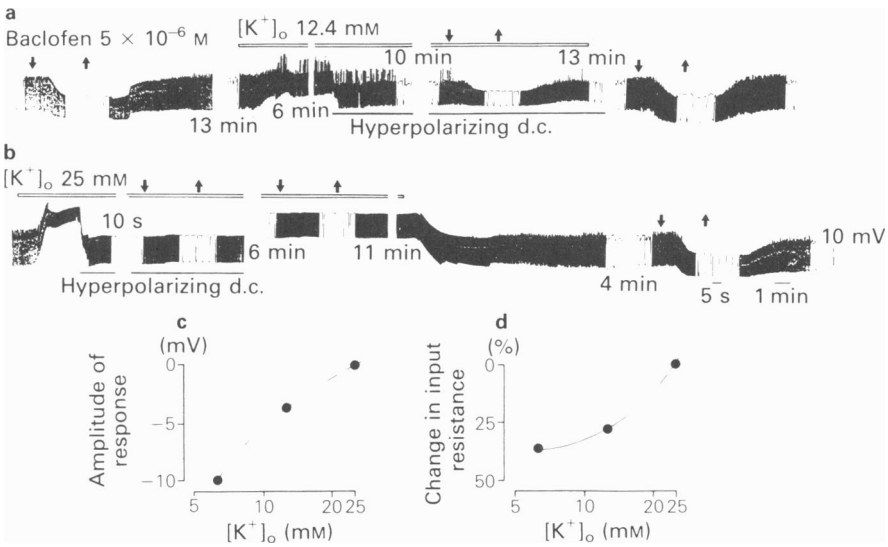


**Figure 5** Effects of high external $K^+$ concentrations on the response to baclofen. Baclofen was applied during perfusions with media containing 6.24 (control), 12.4 and 25 mM $K^+$. The concentration of $Cl^-$ was kept constant by reducing equimolar amounts of NaCl. During periods indicated by bars entitled 'Hyperpolarizing d.c.', the membrane potential was restored to the original level by inward d.c. current injection. (c) and (d) Show the amplitude of the hyperpolarization (c) and the input resistance change (d) induced by baclofen, as a function of external concentration of $K^+$.

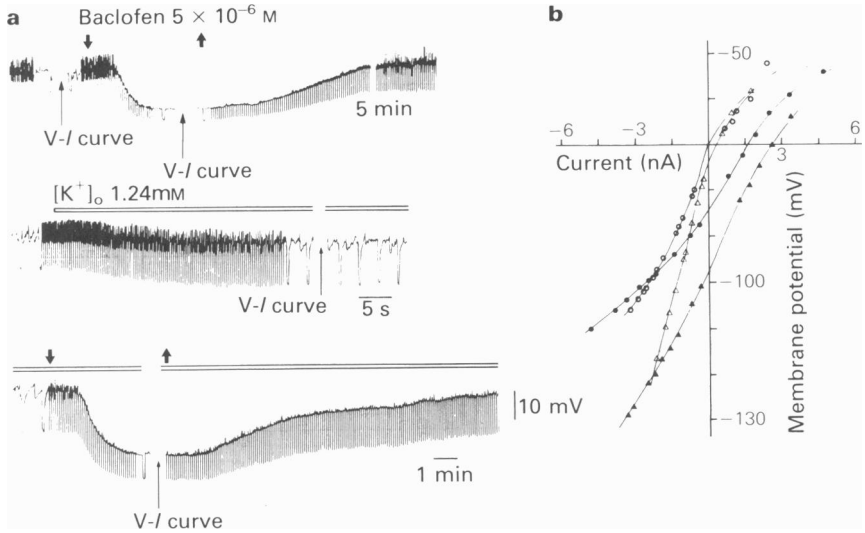


**Figure 6** Effects of low external $K^+$ concentration on the response to baclofen. Baclofen was applied during perfusions with media containing 6.24 (control) and 1.24 mM $K^+$. The concentration of $Cl^-$ was kept constant by adding equimolar amounts of NaCl. The current-voltage relationship was measured at four points indicated by arrows in the continuous pen-recordings, and the results were plotted in the graph (b). In (b), control V-*I* relationship in media containing 6.24 mM $K^+$ (○) and 1.24 mM $K^+$ (△) and the filled symbols (●,▲) represents the effects of baclofen in these two media.

baclofen. The amplitude of hyperpolarization produced by baclofen in the low $k^+$ medium was about 1.5 times greater than that in the standard medium ($n = 9$). $E_{baclofen}$ in the standard medium (about −98 mV) shifted towards the hyperpolarizing direction when measured in the low $K^+$ medium (−122 mV).

In contrast to the effect of modifying the $K^+$ concentration, substitution of total external NaCl with Na-isethionate produced no noticeable effect on the baclofen response in any of the 5 cells examined.

*Effects of drugs on the response to baclofen*

The effects of drugs thought to affect $K^+$ conductance on responses to baclofen were studied. Bath application of TEA (10 mM) or 4-AP ($5 \times 10^{-6}$ M) provoked spontaneous bursting discharges of pyramidal cells. Although TEA (10 mM) depolarized the membrane by 2–10 mV, 4-AP, $5 \times 10^{-6}$ M, did not produce an appreciable change in the membrane potential in any of 7 cells examined. The effect of baclofen was blocked during an application of a low concentration of 4-AP ($5 \times 10^{-6}$ M), whereas it was totally resistant to a very high concentration of TEA (10 mM) (Figure 7a). These results were reproducible in the 7 cells examined. Although the effect of 4-AP was fairly resistant to washing, the recovery of the response to baclofen was ascertained in 2 cells after a long period of washing (about 2 h). The hyperpolarization induced by GABA was not affected by 4-AP in any of 6 cells examined (Figure 7b).

The effect of baclofen was unaffected in a medium containing picrotoxin ($2 \times 10^{-5}$ M) in the 4 cells tested.

## Discussion

The intracellular recordings from hippocampal pyramidal cells demonstrate that baclofen exerts prominent membrane effects as has recently been reported (Newberry & Nicoll, 1984). Baclofen appears to have an additional property of inducing a change in the excitability of the neuronal membrane in addition to its well-known presynaptic action (e.g. Bowery *et al.*, 1980; Davies, 1981; Ault & Nadler, 1983). The finding that the effect of baclofen was persistent in the $Ca^+$-free medium further confirms its postsynaptic nature. Such a postsynaptic action of baclofen has also been observed in hypothalamic neurones (Ogata & Abe, 1982). The spatial responsiveness of the pyramidal cell to iontophoretically applied baclofen confirms the supposition that baclofen acts primarily in the dendrites (Newberry & Nicoll, 1984). The postsynaptic action of baclofen may be important for the pharmacological effect of this drug following its administration *in vivo*, since this effect appeared at relatively low concentrations (see Figure 1).

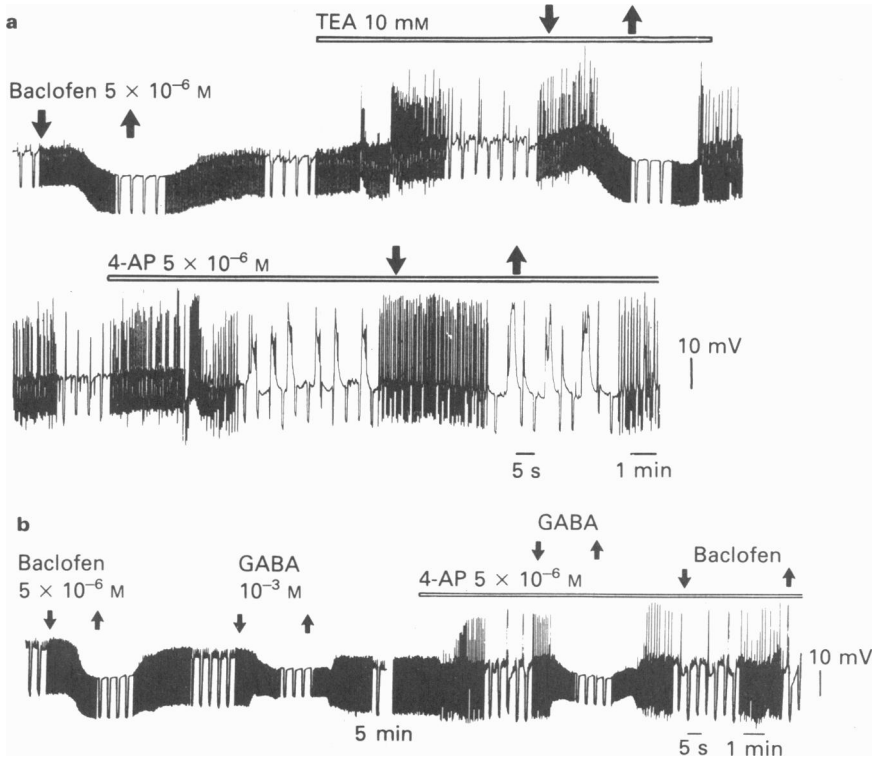


**Figure 7** (a) Effects of 4-aminopyridine (4-AP) and tetraethylammonium (TEA) on the response to baclofen. Effects of 4-AP on the response to γ-aminobutyric acid (GABA) is also illustrated for reference in (b). The medium containing 10 mM TEA or $5 \times 10^{-6}$ M 4-AP was superfused during the period indicated by a bar.

*Ionic basis for the effect of baclofen*

The value of $E_{baclofen}$, estimated from the current-voltage relationships, approximated that of the $K^+$ equilibrium potential (Figure 2) suggesting that the effect of baclofen results from an increase in $K^+$ permeability. Furthermore, the reversal potential estimated from the current-voltage relationship was shifted towards the hyperpolarized direction when the $K^+$ concentration in the medium was reduced to 1.24 mM (Figure 6).

The $E_{baclofen}$ measured directly was much more negative than the reversal point of the GABA-induced hyperpolarization (Figure 3) and coincided with the reversal point of the post-burst hyperpolarization (Figure 4). Since the post-burst afterhyperpolarization appears to be due to a $Ca^{2+}$-activated $K^+$ current (e.g. Alger & Nicoll, 1980; Hotson & Prince, 1980; Brown & Griffith, 1983), it is further suggested that the baclofen-induced hyperpolarization is brought about by an increase in $K^+$ conductance.

The response to baclofen was sensitive to changes in external $K^+$ concentration (Figures 5 and 6) but insensitive to a reduced external $Cl^-$ concentration. Furthermore, the effect of baclofen was absent during a perfusion of 4-AP which blocks a novel $K^+$ current, $I_A$, (Gustafsson *et al.*, 1982) (Figure 7). These observations further support the idea that the effect of baclofen in the hippocampus may be brought about by an activation of $K^+$ conductance.

The possibility of an involvement of $Cl^-$ permeability in the effect of baclofen may be excluded since neither the substitution of external $Cl^-$ with an impermeant anion nor the application of picrotoxin ($2 \times 10^{-5}$ M), which blocks GABA-mediated $Cl^-$ conductance in vertebrate neurones (Gallagher *et al.*, 1978; Brown & Galvan, 1979), produced any detectable change in the response to baclofen.

$E_{baclofen}$ measured directly was considerably (about 20 mV) more negative than that estimated from the current-voltage relationships. The reversal potential of the post-burst hyperpolarization which coincided with $E_{baclofen}$ measured directly in this study has been shown to be about −90 mV (e.g. Alger & Nicoll, 1980; Hotson & Prince, 1980). Therefore, the value of $E_{baclofen}$ measured directly in our study appears to have been distorted, most probably by some technical problem.

*Property of the baclofen-activated $K^+$ conductance*

The effect of baclofen was strikingly voltage-dependent, as shown in the current-voltage curves in Figure 2. It appears that membrane depolarization reduces the effectiveness of baclofen. The voltage-dependent nature of the effect of baclofen is also evident in Figure 3. Successive displacement of the resting membrane potential in the depolarized direction, which would further increase the electrochemical gradient for the permeant ions probably $K^+$, instead diminished the direct membrane effect of baclofen.

Such a prominent voltage-dependence of the effect of baclofen might also explain the complete absence of the response at 25 mM external $K^+$ (Figure 5); as, in contrast to the current injection from the soma which would polarize only a limited portion of the dendritic membrane, high external $K^+$ would evenly depolarize the entire dendritic tree. As shown in Figure 1b, the receptor for baclofen appears to be distributed widely throughout the dendritic tree of the neurone. Thus, it is possible that the $K^+$ channel linked to remote dendritic receptors, which could still open in response to baclofen even during a moderate depolarizing current injection from the soma, would no longer be responsive to baclofen in a high $K^+$ medium.

The $K^+$ conductance activated by baclofen was antagonized by a low concentration of 4-AP (Figure 7). On the other hand, it was resistant to depletion of $Ca^{2+}$ from the medium and unaffected by a high concentration of TEA which blocks delayed rectifier channels (Hille, 1967) and $Ca^{2+}$-activated $K^+$ channels in vertebrate neurones (Adams *et al.*, 1982). In addition, it revealed a prominent voltage-dependence (see above). These features of the $K^+$-conductance activated by baclofen resemble those of the novel $K^+$-current, $I_A$ (Gustafsson *et al.*, 1982), or the so-called A current in invertebrate neurones (Connor & Stevens, 1971). The former current was discovered in the guinea-pig hippocampal pyramidal cell, i.e. the cell impaled in our study. However, it is unlikely that the $K^+$ current activated by baclofen is $I_A$ itself, since $I_A$ is a transient current and activated by voltage. The possibility that baclofen prevented $I_A$ inactivation thereby inducing a persistent $K^+$ current may be excluded, since, in such a case, the direction of the voltage-dependent nature of the action of baclofen cannot be explained.

In conclusion, our results suggest that the postsynaptic effect of baclofen in the hippocampus is mediated by a highly voltage-dependent $K^+$ conductance which is sensitive to 4-AP.

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