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Characterization of pre- and postsynaptic actions of (−)-baclofen in the guinea-pig hippocampus *in vitro*

Masumi Inoue, Tadashi Matsuo & Nobukuni Ogata[1]

Department of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan

1 The effects of (−)-baclofen on evoked potentials in the hippocampus were examined through intracellular recordings from guinea-pig brain slices.

2 The evoked responses were recorded in two fibre connections within the hippocampus: the Schaffer collateral/commissural–CA1 pyramidal cell, and the mossy fibre–CA3 pyramidal cell.

3 The Schaffer collateral/commissural–CA1 response was suppressed by (−)-baclofen in concentrations over 2×10^{-5} M, whereas (+)-baclofen, an inactive isomer, in a concentration of 10^{-4} M had no effect on the response.

4 A compound action potential of Schaffer collateral/commissural axons was unaffected by (−)-baclofen even at 10^{-4} M, a concentration that almost completely depressed the evoked response in the CA1 pyramidal cell.

5 The mossy fibre–CA3 response was not inhibited by (−)-baclofen (10^{-4} M).

6 The depressant action of (−)-baclofen on the Schaffer collateral/commissural–CA1 response was unaffected by bicuculline (10^{-4} M), whereas the direct membrane effects of (−)-baclofen were antagonized by bicuculline (10^{-5} M).

7 It is suggested that (−)-baclofen may modulate neuronal transmission through presynaptic recognition sites possibly by decreasing transmitter release from nerve terminals and also may directly regulate the endogenous neuronal excitability through an activation of the postsynaptic recognition sites.

Introduction

γ-Aminobutyric acid (GABA) is a well-established inhibitory neurotransmitter in the mammalian central nervous system. Recently, 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 (Bowery *et al.*, 1980; 1981). The $GABA_B$ site is resistant to the $GABA_A$ antagonist, bicuculline. A number of studies (e.g., Bowery *et al.*, 1981; Davies, 1981; Ault & Nadler, 1983) indicate that $GABA_B$ sites are present on nerve terminals and that their activation results in diminished transmitter release probably through a blockade of Ca^{2+} channels.

(−)-Baclofen, a β-chlorophenyl derivative of GABA, is a selective agonist for $GABA_B$-receptors (Bowery *et al.*, 1980). This drug has a depressant action on neuronal excitability in various portions of the central nervous system including the hippocampus (Lanthorn & Cotman, 1981; Olpe *et al.*, 1982; Ault & Nadler, 1982; 1983). These depressent actions have generally been attributed to its presynaptic action through $GABA_B$ sites, on the basis of results from extracellular recordings. However, Newberry & Nicoll (1984b) have recently shown that (−)-baclofen exerts a prominent depressant action, which is apparently of postsynaptic nature, on rat hippocampal pyramidal cells, and have suggested the presence of postsynaptic $GABA_B$ sites in the hippocampus. This postsynaptic action of baclofen has been shown to be due to an increase in K^+ conductance (Inoue *et al.*, 1985). These findings warrant re-investigation of the reported presynaptic action of (−)-baclofen in this tissue through intracellular recordings. In this paper, we have studied the effect of (−)-baclofen on the evoked potentials in the hippocampus.

[1]Author for correspondence.

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Methods

The experiments were performed on transverse slices (400–600 μm thick) of 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, KCl 5, $CaCl_2$ 2.6, KH_2PO_4 1.24, $MgSO_4$ 1.3 and glucose 10. The slices were continuously perfused with the standard medium equilibrated with 97% O_2 and 3% CO_2 at 30–32°C.

Intracellular recordings were made from cells in the CA1 or CA3 pyramidal layer with microelectrodes filled with 2M potassium acetate (d.c. resistance, 50–100 MΩ). A single electrical pulse of 50 μs duration was applied to the mossy or the Schaffer collateral/commissural fibres through twisted tungsten needles (diameter, 50 μm) insulated except for the tips. Field potentials were recorded from the pyramidal cell layer in response to the fibre tract stimulation with glass microelectrodes filled with 0.9% NaCl (d.c. resistance, 1–3 MΩ).

Drugs were applied in fixed concentrations to the bathing solution. 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 drugs used in this study were: (−)- and (+)-baclofen (Ciba-Geigy); 4-aminopyridine (4-AP, Tokyo Kasei); tetrodotoxin (Sankyo); bicuculline (Sigma); bicuculline methiodide (Pierce Chemical). A stock solution of bicuculline (10^{-2} M) was prepared in 0.02 N HCl and was diluted immediately before use.

The experimental data are given as mean ± s.e.mean.

Results

Intracellular data presented here were obtained from 85 stable intracellular recordings. The resting membrane potential and the input resistance were −62.9 ± 2.5 mV and 17.8 ± 2.3 MΩ, respectively, when measured in 11 cells on which a stable intracellular recording could be maintained for more than 3 h.

It has been reported that (−)-baclofen preferentially depresses transmission at synapses made by axons of CA3 pyramidal cells (Ault & Nadler, 1982; 1983).

Therefore, we examined the effect of (−)-baclofen on the hippocampal evoked potentials in two synaptic connections within the hippocampus: firstly, the Schaffer collateral/commissural fibres (axons of the CA3 pyramidal cells) (Gottlieb & Cowan, 1973; Swanson *et al.*, 1978) and CA1 pyramidal cell; secondly, the mossy fibre (an axon of the dentate granule cell, i.e., non-CA3 pyramidal cell origin) (Blackstad *et al.*, 1970) and CA3 pyramidal cell.

Effects of (−)-baclofen on the Schaffer collateral/commissural–CA1 response

The upper traces of Figure 1a are continuous intracellular recordings from a CA1 pyramidal cell before, during and after an application of (−)-baclofen (10^{-5} M). (−)-Baclofen hyperpolarized the membrane, reduced the membrane input resistance and depressed the spontaneous firing. These postsynaptic actions of (−)-baclofen have been described in detail elsewhere (Inoue *et al.*, 1985).

Figure 1a, lower traces, illustrate the responses of the CA1 pyramidal cell to the Schaffer collateral/commissural stimulation examined at points indicated by dots in the upper traces of the figure. Stimulation of the hippocampal afferents evoked a sequence of events in pyramidal cells comprising (1) an excitatory postsynaptic potential (e.p.s.p.) which often provoked an action potential (see lower traces in a), (2) fast-hyperpolarizing inhibitory postsynaptic potential (i.p.s.p.) which peaked at a latency of about 50 ms (see lower traces in a), and (3) a slow i.p.s.p. (the late hyperpolarizing potential) which peaked at about 200 ms (see upper trace in a) (cf. Newberry & Nicoll, 1984a).

(−)-Baclofen at a concentration of 10^{-5} M augmented the amplitude of the e.p.s.p., whereas it totally suppressed the fast and slow i.p.s.ps (see the points of the second dots in upper and lower traces in Figure 1a). In contrast, as shown in Figure 1b, (−)-baclofen at a concentration of 10^{-4} M produced almost total suppression of the e.p.s.p. This was not due to membrane hyperpolarization, since the suppression was observed even when the membrane potential was restored to the original level by injecting outward d.c. current through the recording electrode. (+)-Baclofen had no detectable effect on the CA1 evoked response even at 10^{-4} M in any of the 3 cells tested.

Dose-response relationships obtained from 15 CA1 cells showed that the response of CA1 pyramidal cells to the Schaffer collateral/commissural stimulation was consistently depressed by (−)-baclofen at concentrations over 2×10^{-5} M, whereas the response was augmented at concentrations lower than 5×10^{-6} M. The concentration of 10^{-5} M was critical in that it enhanced the response in some cells and suppressed it in others.

Figure 2 shows a sequence of field potentials recorded from the CA1 pyramidal layer in response to the Schaffer collateral/commissural stimulation. (+)-Baclofen had no effect on the evoked potential even at a concentration of 10^{-4} M. Whereas (−)-baclofen at a concentration of 5×10^{-6} M exerted no detectable effect on the evoked potential, 10^{-5} and 10^{-4} M

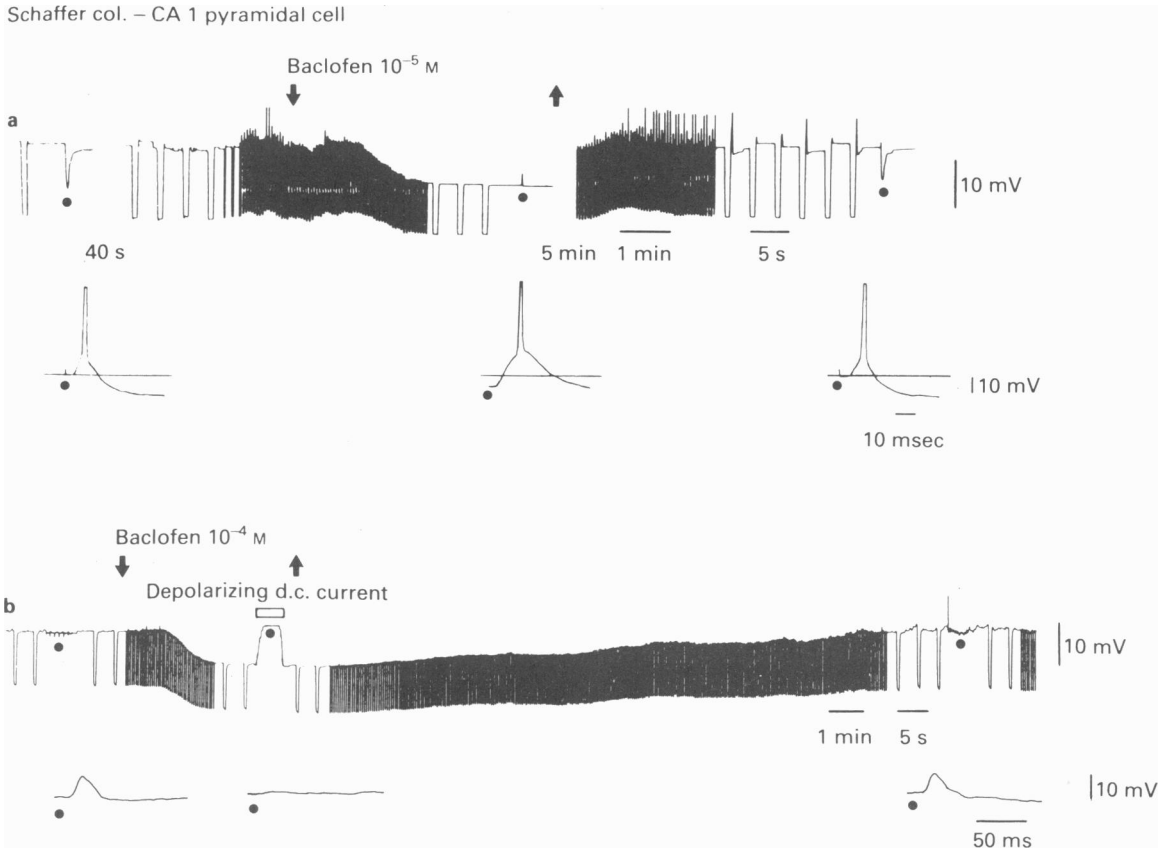

Figure 1 Effects of (−)-baclofen on the electrical activity of CA1 hippocampal neurones recorded with an intracellular electrode. In (a) and (b), upper and lower traces represent continuous intracellular recordings and evoked potentials in response to stimulation of the Schaffer collateral/commissural fibres, respectively. The stimulating electrode was placed in the CA1 stratum radiatum. In this and subsequent figures: downward and upward arrows represent the duration of superfusion of test solution; 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 lost in the continuous recordings due to limited frequency band width of pen-recordings, hence only the after-hyperpolarizations are registered; time shown under gaps in the trace indicates an omitted period. Note that in this and subsequent figures, the pen-recorder was intermittently run at a faster speed, giving rise to expanded time scale on the abscissae. Inset traces of the evoked potential were recorded on the storage oscilloscope and written on the X–Y recorder in which spikes were truncated; dots represent the afferent stimulation. The horizontal line drawn across the evoked responses in (a), lower traces, represents the level of the original resting membrane potential. At the period indicated by bar labelled 'Depolarizing d.c. current' in (b), the membrane potential was restored to the original level by passing d.c. current through the recording electrode.

produced concentration-dependent depression of the evoked potential. Bicuculline (10^{-5}–10^{-4} M) caused an oscillatory field potential in response to the Schaffer collateral/commissural stimulation. Bicuculline at these concentrations did not affect the depressant action of (−)-baclofen. An application of 4-AP (5×10^{-6} M) further augmented the evoked potential. (−)-Baclofen applied during a perfusion of 4-AP had no effect on the evoked potential. These observations were reproducible in all of 5 cases examined.

Effects of (−)-baclofen on the mossy fibre–CA3 response

The effect of various concentrations of (−)-baclofen on the potential evoked in CA3 pyramidal cells in

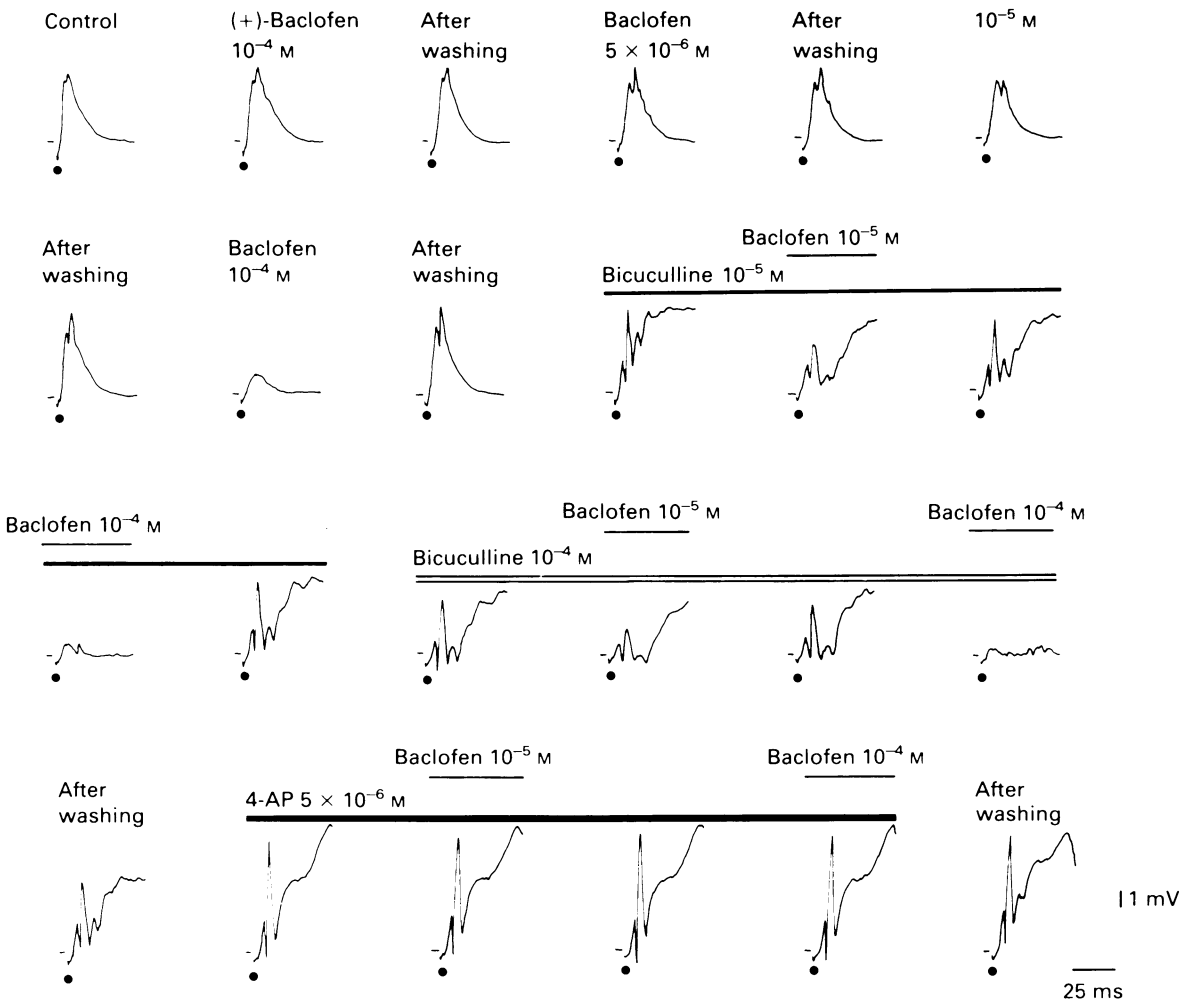

Figure 2 Effects of (−)-baclofen on the field potentials evoked by the Schaffer collateral/commissural stimulation. The stimulating electrode was placed on the CA1 stratum radiatum. The potential was picked up from the CA1 pyramidal layer, recorded on the storage oscilloscope, and written on the X–Y recorder. Dots represent stimulation.

response to mossy fibre stimulation was studied in 20 cells. As shown in Figure 3a, lower traces, the e.p.s.p. in the CA3 pyramidal cell evoked by stimulation of the mossy fibres (first trace) was potentiated by (−)-baclofen (10^{-6} M), and despite a membrane hyperpolarization, the e.p.s.p. provoked a single (second trace) or repetitive spike discharges (third trace). Likewise, a high concentration of (−)-baclofen (10^{-4} M) increased the amplitude of the e.p.s.p., and a spike superimposed on the e.p.s.p. was not blocked even during a marked hyperpolarization (Figure 3b). This augmentation of the e.p.s.p. was observed in all 20 cells examined. In contrast to the e.p.s.p., the fast and slow i.p.s.ps were consistently blocked.

In Figure 3c, the cell responded to the mossy fibre stimulation with a sequence of an e.p.s.p. and an i.p.s.p. in the control medium (left lower trace). When the membrane was hyperpolarized by (−)-baclofen, the i.p.s.p. was abolished and the e.p.s.p. became larger (not illustrated). Even when the membrane potential was restored to the original level by a depolarizing d.c. current during a perfusion of (−)-baclofen, the e.p.s.p. was still larger than the control and the i.p.s.p. remained absent (middle lower trace). These observations suggest that the increase in e.p.s.p. amplitude by (−)-baclofen may be due to the disappearance of the coexistent i.p.s.p.

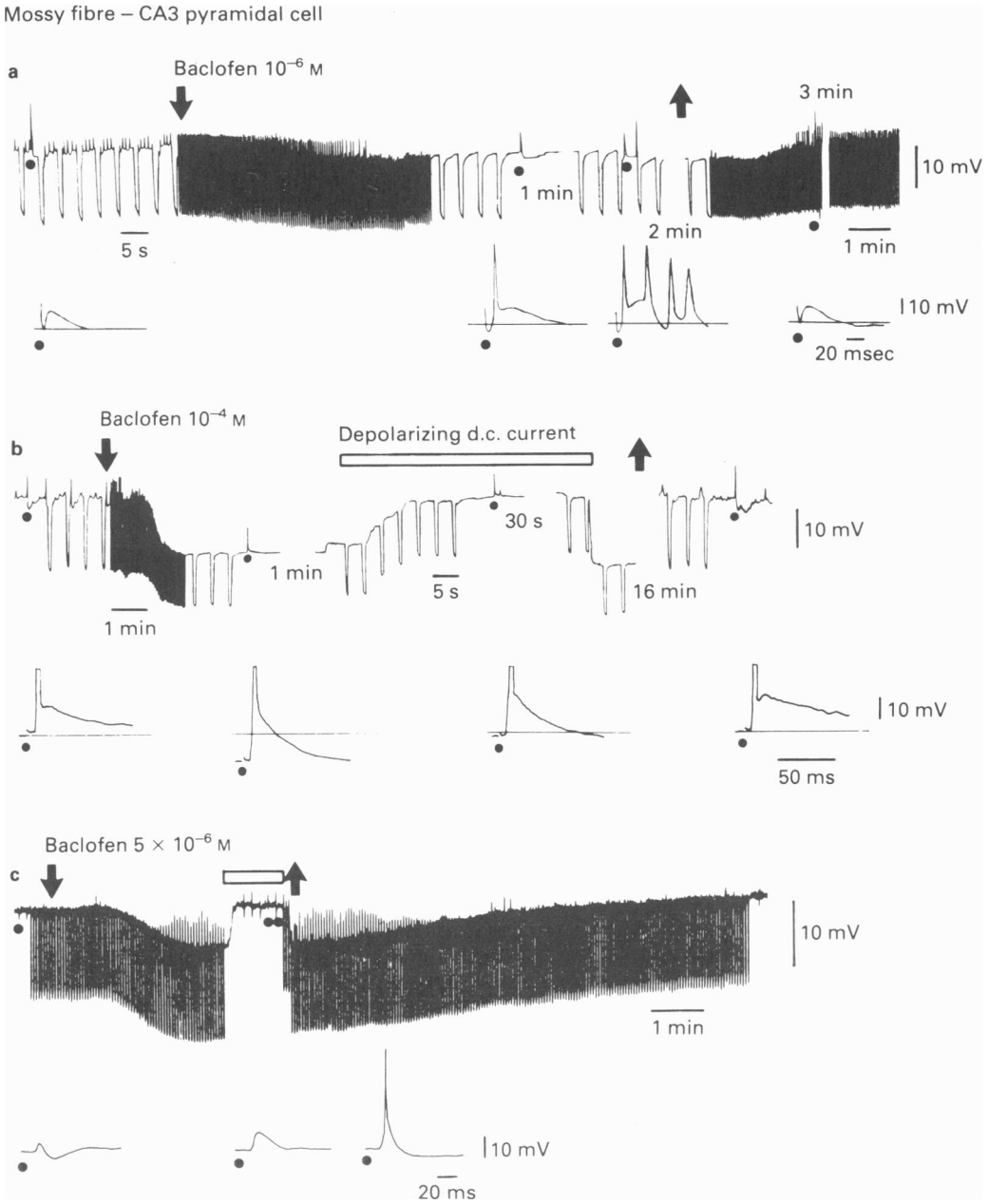

Figure 3 Effects of (−)-baclofen on the electrical activity of CA3 hippocampal neurones recorded with an intracellular electrode. Details, see legend to Figure 1.

Effects of (−)-baclofen on the presynaptic excitability

Figure 4 illustrates the effect of (−)-baclofen on the excitability of presynaptic fibres. The field potential recorded in the CA1 stratum radiatum in response to stimulation of the Schaffer collateral/commissural fibres (a) was markedly suppressed by (−)-baclofen (10^{-4} M) (b) and recovered after washing (c). The abolished portion in the response shown in (b) (dotted

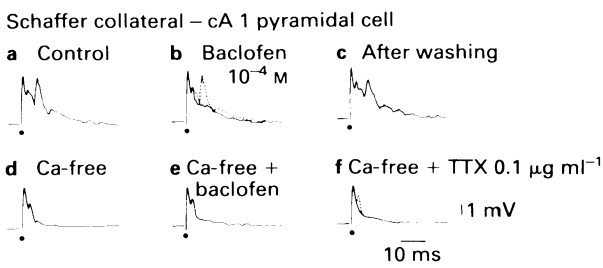

Figure 4 Effects of (−)-baclofen on the presynaptic population spike of the Schaffer collateral/commissural fibres. Details, see legend to Figure 2.

line) appears to represent the postsynaptic component of the response, since the response in (b) was much the same as that evoked in the medium in which Ca^{2+} was totally removed and Mg^{2+} was increased to 12 mM (d). (−)-Baclofen at 10^{-4} M exerted no detectable effect on the response in the Ca^{2+}-free condition (e). However, tetrodotoxin applied in the Ca^{2+}-free condition caused the suppression of an additional component of the response (f). Since the component suppressed by tetrodotoxin is assumed to be an extracellular manifestation of the presynaptic action potentials, the presynaptic action potentials appear to be retained during perfusion of 10^{-4} M (−)-baclofen. These results were confirmed in 4 additional experiments.

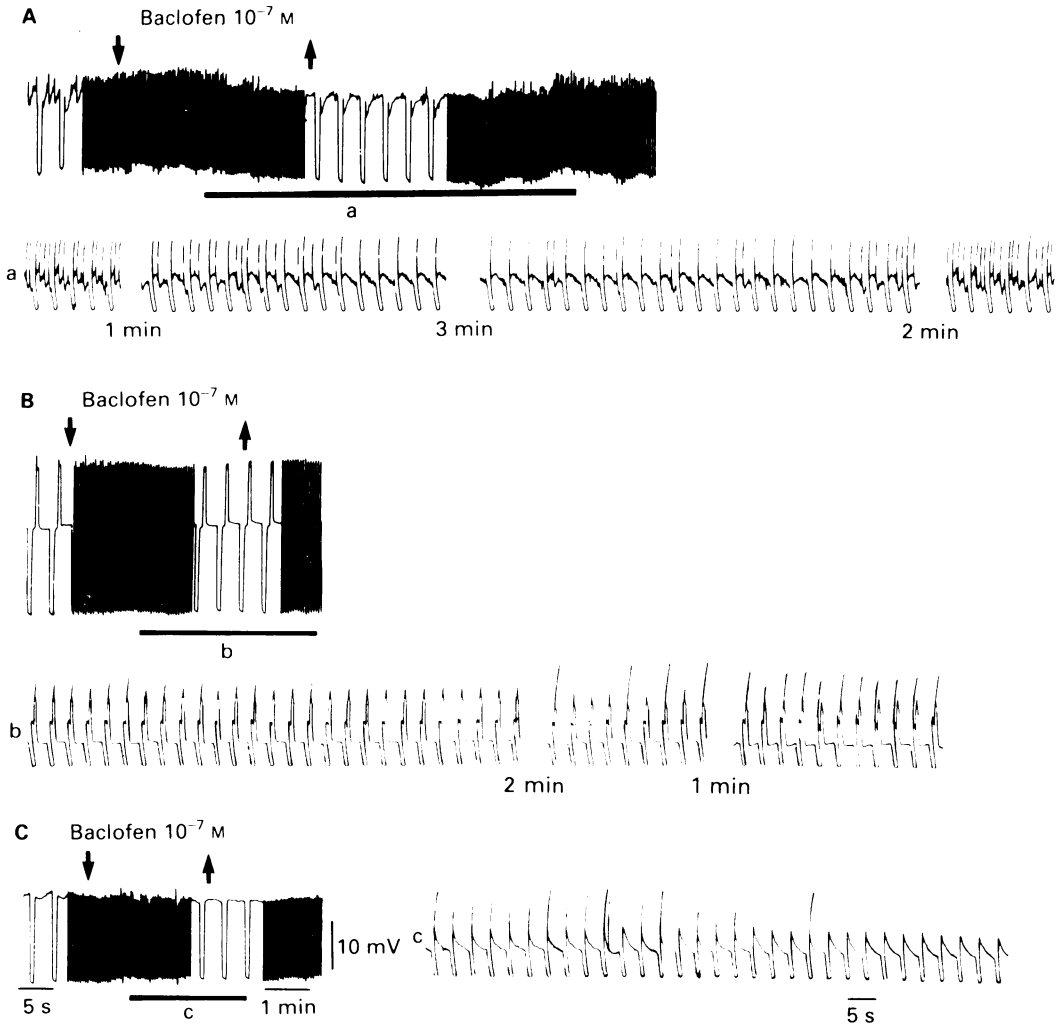

Figure 5 Effects of (−)-baclofen on the spontaneous or directly (nonsynaptically) activated spikes. Electrical activities at periods indicated by solid lines labelled (a) and (c) in the upper traces are presented in the additional pen-recording which has a relatively broader high-frequency band width but a non-linear amplification (lower traces). A, B and C were recorded from different cells.

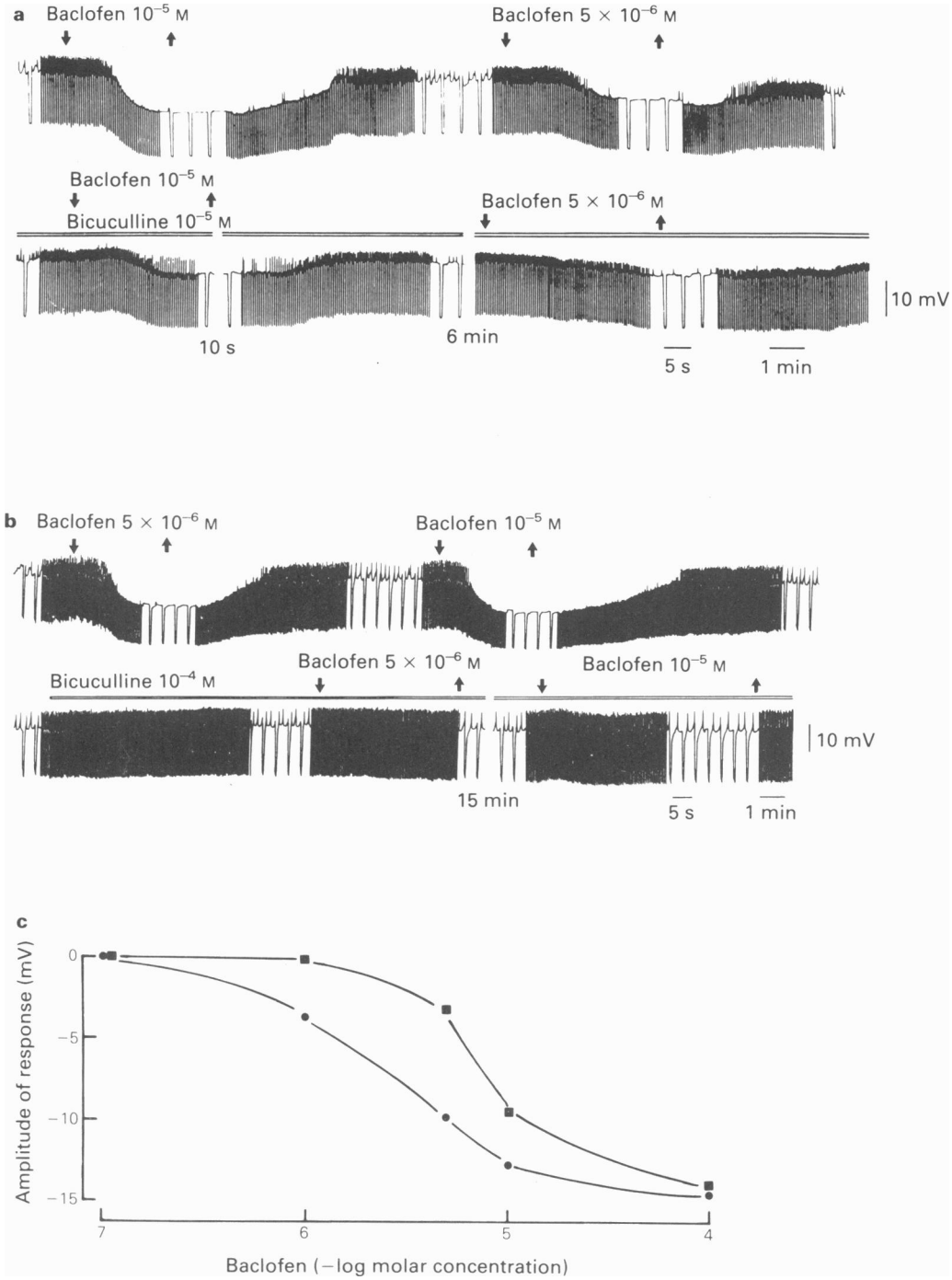

Figure 6 Antagonism of postsynaptic effects of (−)-baclofen by bicuculline. In (a) or (b), the medium containing 10^{-5} M (a) or 10^{-4} M (b) bicuculline was superfused during the period indicated by the bars; (c) shows concentration-response relationship for membrane hyperpolarization produced by (−)-baclofen in the presence (■) and absence (●) of 10^{-5} M bicuculline.

Effects of (−)-baclofen on the action potential generation

Although action potentials generated in CA3 by the afferent tract stimulation were resistant to or even facilitated by (−)-baclofen as described above (Figure 3), action potentials occurring spontaneously or evoked by direct membrane current injections were suppressed by (−)-baclofen. The spontaneous firing rate was decreased by (−)-baclofen (10^{-7} M) in 7 out of 10 cells examined (Figure 5a). Spikes evoked by direct depolarizing current pulses or by a hyperpolarizing current pulses (anode break excitation) were also blocked by baclofen (10^{-7}–10^{-6} M) in all of 6 cells examined (Figure 5b,c).

Antagonism between (−)-baclofen and bicuculline

Bicuculline antagonized the postsynaptic action of (−)-baclofen, the concentration-response curve being shifted to the right by 10^{-5}–10^{-4} M bicuculline (Figure 6). The antagonism between these two agents became progressively more noticeable with time (full antagonism was usually attained after a perfusion of bicuculline of at least 5–10 min prior to the testing of the antagonism). Bicuculline methiodide, a water-soluble analogue of bicuculline, had essentially the same effect as bicuculline when examined in 20 additional cells, although its potency was about one tenth that of bicuculline.

Discussion

Our findings, based on intracellular recording, that the evoked response in CA1 pyramidal cells to stimulation of the Schaffer collateral/commissural fibres was depressed by (−)-baclofen, whereas the response in CA3 pyramidal cells to stimulation of the mossy fibre was not affected confirm the finding based on the field potential recording that (−)-baclofen preferentially depresses transmission at synapses made by axons of CA3 pyramidal cells in the hippocampus (Ault & Nadler, 1982; 1983). Furthermore, the observation that the mossy fibre–CA3 response remained intact even when the postsynaptic membrane was markedly hyperpolarized by a high concentration of (−)-baclofen (10^{-4} M) strongly suggest that the depression of the evoked response in CA1 pyramidal cell is due to a presynaptic action of (−)-baclofen.

The relatively high concentration of (−)-baclofen required to produce the depressant action on the Schaffer collateral/commissural–CA1 response (over 10^{-5}–2×10^{-5} M) raised the possibility that this action may be due to a nonspecific depressant effect on the Schaffer collateral/commissural fibres. However, the action was stereospecific, (+)-baclofen being much less potent than (−)-baclofen, suggesting its receptor-operated nature. In addition, the compound action potential of Schaffer collateral/commissural axons was unaffected by (−)-baclofen even at 10^{-4} M, a concentration which almost completely depressed the postsynaptic response (Figure 4). This finding indicates that the depressant action of baclofen on the Schaffer collateral/commissural-CA1 response is not due to a blockade of presynaptic action potentials. Thus, the presynaptic action of (−)-baclofen in the CA1 pyramidal cell appears to be attributable to the blockade of transmitter release from the nerve terminals of Schaffer collateral/commissural axons.

The intracellular recordings shown in Figure 1a indicate that (−)-baclofen exerts a prominent postsynaptic action at particularly low concentrations; this is in agreement with our previous findings (Inoue *et al.*, 1985). The minimal effective concentration of the postsynaptic action was about 10^{-7} M (Inoue *et al.*, 1985), whereas that of the presynaptic action was 10^{-5}–2×10^{-5} M (present results). A possible postsynaptic site for a specific action of (−)-baclofen has already been reported in several regions of the central nervous system besides the hippocampus (Saito *et al.*, 1975; Henry, 1982; Ogata & Abe, 1982; Bowery *et al.*, 1983). Therefore, the postsynaptic action of (−)-baclofen may be important for the pharmacological effect of (−)-baclofen following its administration *in vivo*.

It has been shown that the postsynaptic action of baclofen is due to a selective increase in K^+ conductance of the membrane (Newberry & Nicoll, 1984b; Inoue *et al.*, 1985). A possible ionic mechanism for the presynaptic action of (−)-baclofen at the presynaptic recognition sites is also mediated by an increase in K^+ permeability, since this action was also antagonized by 4-AP (Figure 2). Whether the antagonism of the presynaptic action of (−)-baclofen by 4-AP is due to a blockade of K^+ channels or to the direct action of 4-AP on Ca^{2+} channels (Rogawski & Barker, 1983) remains to be elucidated.

The presynaptic action of (−)-baclofen was insensitive to a very high concentration (10^{-4} M) of the $GABA_A$-antagonist, bicuculline, confirming that action is mediated by bicuculline-insensitive $GABA_B$ receptors (Figure 2). On the other hand, the postsynaptic action of (−)-baclofen was sensitive to bicuculline (Figure 6). Although Newberry & Nicoll (1984b) originally reported that the postsynaptic action of (−)-baclofen is not antagonized by bicuculline, they have recently observed that bicuculline (10^{-5} M) can antagonize the postsynaptic action of (−)-baclofen (Nicoll, personal communication).

In conclusion, our results indicate that (−)-baclofen at relatively low concentrations activates postsynaptic receptors which are somewhat sensitive

to bicuculline and are distributed on the pyramidal cells ubiquitously within the hippocampus, while (−)-baclofen at higher concentrations also activates presynaptic receptors which appear to be relatively resistant to bicuculline. We suggest that activation of the postsynaptic receptors which results in an increase in K^+ permeability of the membrane may directly regulate the intrinsic neuronal excitability; activation of the presynaptic receptors may modulate neuronal transmission possibly by decreasing transmitter release from nerve terminals as has been shown by many investigators (Potashner, 1979; Bowery *et al.*, 1980; Johnston *et al.*, 1980; Collins *et al.*, 1982).

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