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Anticonvulsant-like actions of baclofen in the rat hippocampal slice

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1 The effects of baclofen were tested on epileptiform discharge in the rat hippocampal slice. Slices were superfused with bicuculline methiodide (100 μM) and maximal periods of afterdischarge were evoked by stimulating the Schaffer collateral-commissural pathway in area CA1, mossy fibres in area CA3 or perforant path fibres in the fascia dentata or by antidromic stimulation of CA1 pyramidal cells.

2 (−)-Baclofen attenuated the afterdischarge evoked by stimulating all three sets of fibres in areas CA1 and CA3. In each case, a threshold effect was observed at a concentration of 0.25 or 0.5 μM, and complete suppression was usually attained with a concentration of 5 μM. EC_{50} values ranged between 1 and 2 μM. (−)-Baclofen attenuated hippocampal afterdischarge with 120 times the potency of (+)-baclofen. It did not, however, affect the repetitive firing of dentate granule cells in response to stimulation of perforant path fibres.

3 (−)-Baclofen also reduced the amplitude of the initial population spike evoked by stimulation of Schaffer collateral-commissural fibres, but did not affect the antidromic population spike nor the initial population spike evoked by stimulation of the mossy fibres.

4 Recurrent inhibition in area CA1 was abolished by 1 μM (−)-baclofen. Thus baclofen, unlike many anticonvulsants, does not suppress afterdischarge by potentiating GABAergic inhibition.

5 These results suggest that baclofen attenuates hippocampal afterdischarge by a combination of pre- and postsynaptic mechanisms.

Introduction

Baclofen [β-(*p*-chlorophenyl)-GABA, Lioresal], a γ-aminobutyric acid (GABA) analogue able to cross the blood-brain barrier, is used clinically as a centrally acting muscle relaxant. Baclofen acts by inhibiting excitatory transmission in the spinal cord, apparently by reducing the release of neurotransmitter from synaptic terminals (Davidoff & Sears, 1974; Fox, Krnjević, Morris, Puil & Werman, 1978; Curtis, Lodge, Bornstein & Peet, 1981; Ault & Evans, 1981). Indeed, biochemical studies have demonstrated its ability to depress the Ca^{2+}-dependent release of excitatory amino acids from various CNS preparations (Potashner, 1979; Johnston, Hailstone & Freeman, 1980; Collins, Anson & Kelly, 1982). It has been proposed that baclofen interacts with a novel GABA receptor that is insensitive to bicuculline (Bic) (Bowery, Hill, Hudson, Doble, Middlemiss, Shaw & Turnbull, 1980; Bowery, Doble, Hill, Hudson, Shaw, Turnbull & Warrington, 1981; Hill & Bowery, 1981) and is localized mainly on certain excitatory amino acid-releasing terminals.

We have shown that, in the hippocampal slice, baclofen selectively depresses excitatory transmission at synapses made by axons of CA3 pyramidal cells (Ault & Nadler, 1982a). This effect probably also arises from inhibition of excitatory amino acid transmitter release (Ault & Nadler, 1982a; Olpe, Baudry, Fagni & Lynch, 1982). While investigating the effects of baclofen on synaptically-induced firing in the hippocampal slice, we noted that submicromolar concentrations of the drug could attenuate 'burst firing' or afterdischarge evoked by single electrical stimuli in the presence of Bic. In the present study, we investigated this action in some detail, since hippocampal afterdischarges are associated with epileptic activity (Prince, 1978; Schwartzkroin & Prince, 1980; Traub & Wong, 1981; Gjerstad, Andersen, Langmoen, Lundervold & Hablitz, 1981). Portions of this work have been briefly presented (Ault & Nadler, 1982b).

Methods

Slice preparation

Adult female Sprague-Dawley rats were killed by cervical dislocation and the brains were removed. The hippocampi were dissected and cut into transverse slices of 500 μm thickness. Slices were then placed on small nylon nets in individual superfusion chambers of the type described by White, Nadler & Cotman (1978) and superfused with Elliott's (1969) medium (composition (mM): NaCl 122, $NaHCO_3$ 25, KCl 3.1, $CaCl_2$ 1.3, $MgCl_2$ 1.2, KH_2PO_4 0.4 and D-glucose 10, gassed continuously with 95% O_2 : 5% CO_2) at 30 ± 0.5°C. The medium was recirculated for 1.5–2 h before experimentation. During this period the fluid level was maintained just below the top surface of the slice.

Application of drugs

Slices were submerged during experimentation to facilitate the equilibration of drugs between the medium and the extracellular fluid within the slice. Media were introduced from pressurized flasks into the tissue chamber at a rate of 1.2–1.5 ml/min and were mainly removed by gravity through the bottom of the chamber. To maintain a constant fluid level in the chamber, excess medium was continuously aspirated with a glass pipette. Electrophysiological responses were recorded for 10–15 min before applying drugs, by which time they were of relatively constant amplitude.

When Bic (methiodide) was used, it was present continuously in both control and test media. Baclofen was dissolved in Elliott's medium, and the solution was either placed in one of the pressurized flasks or introduced into one of the superfusion lines by use of a three-way valve. The latter procedure proved most convenient for investigating dose-response relationships, and 5 ml of solution was found sufficient to produce a maximal effect. A six-way rotary valve was used to switch between control medium and one of the various drug-containing media. Responses to stimulation were recorded prior to and during application of baclofen until a maximal effect of the drug was obtained. Then the slice was washed with control medium to regain its initial response amplitude before the next drug application.

Stimulation and recording

Cathodal pulses of 40–100 μs duration were applied through the inner wire of a concentric bipolar electrode (inner Pt/Ir wire, 25 μm diameter; outer stainless steel cylinder, 100 μm diameter) at a frequency of 2/min. Field potentials were recorded in the pyramidal and granule cell body layers with glass micro-electrodes of 2–10 MΩ impedance filled with 4 M NaCl. When studying hippocampal afterdischarge, the stimulus current was adjusted to obtain a just-maximal response in the presence of Bic. Placement of stimulating and recording electrodes is shown in Figure 1.

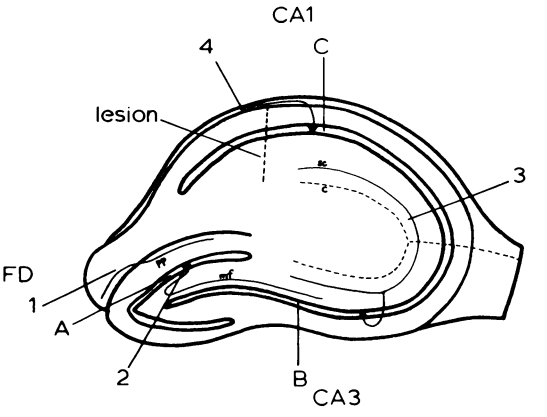

Figure 1 Stimulation and recording sites in the hippocampal slice. Pathways (abbreviation) (region, stimulating site, recording site): Perforant path (pp) (fascia dentata (FD), 1, A); mossy fibre (mf) (CA3, 2, B); Schaffer collateral-(sc)-commissural (c) (CA1, 3, C); antidromic firing of CA1 pyramidal cells (CA1, 4, c). When studying responses to antidromic stimulation of CA1 pyramidal cells, the alveus was isolated by cutting through area CA1 as shown (lesion).

Quantitation of responses to stimulation

The amplitudes of individual population spikes recorded on film were measured from the point of onset to peak negativity. Population spike amplitude serves as a measure of the number of cells brought to threshold by the stimulus (Andersen, Bliss & Skrede, 1971). Responses to stimulation of Schaffer collateral-commissural fibres were quantified by summing the amplitude of the initial population spike and the 3–5 large population spikes of the afterdischarge. Since the antidromic population spike in area CA1 and the initial orthodromic population spike evoked in area CA3 by stimulating the mossy fibres were unaffected by baclofen, these responses were excluded from the measurements. Responses to antidromic stimulation of CA1 pyramidal cells were quantified by summing the amplitudes of the 2–4 large population spikes of the afterdischarge.

Because individual population spikes in the afterdischarge evoked by mossy fibre stimulation were difficult to measure, the total duration of afterdischarge was determined. Total duration of afterdischarge was also employed to quantify the response to perforant path stimulation.

The degree to which baclofen inhibited hippocampal cell discharge was calculated as the maximum depression of the response expressed as a percentage of the mean of the three responses that immediately preceded introduction of the drug into the test chamber. EC_{50} values were computed from each dose-response curve by log-probit analysis. All values are expressed as means ± s.e. for n = number of experiments on separate preparations.

Recurrent inhibition

Population spikes of about half-maximal amplitude were evoked in area CA1 by stimulating the Schaffer collateral-commissural fibres, either 25 ms after an antidromic conditioning volley or without a conditioning stimulus. Antidromic stimulation of CA1 pyramidal cells evokes a disynaptic recurrent IPSP whose amplitude reaches a maximum in 25 ms (Dingledine, 1981). Orthodromic stimuli were delivered 30 s apart. The intensity of recurrent inhibition was calculated as the percentage difference between the mean amplitude of three conditioned orthodromic population spikes compared to the mean of three preceding unconditioned population spikes. The intensity of the antidromic volley was adjusted to give a submaximal recurrent inhibition. (−)-Baclofen was then introduced into the medium. After a period of at least 5 min, the stimulus current applied to the Schaffer collateral-commissural fibres was increased to evoke a population spike of the same amplitude as that evoked before the application of drug. The intensity of recurrent inhibition was then redetermined and compared to the control value.

Results

Pyramidal cell afterdischarge

Stimulation of the Schaffer collateral-commissural fibres to area CA1 in the presence of 100 μM Bic evoked a burst of 4–6 high-amplitude population spikes that were fired at a frequency of about 160/s and were superimposed on a positive wave (Figure 2). To determine whether this repetitive firing depended on antidromic activation of cell bodies in area CA3, the CA1 area of three slices was isolated by removing areas CA2 and CA3 with a razor blade before placing the slices in superfusion chambers. Isolation of area CA1 from the CA3 area failed to alter the response, in agreement with reports of Schwartzkroin & Prince (1978) and Gjerstad *et al.* (1981).

Because antidromic activation of CA1 pyramidal cells with a high stimulus current can also fire nearby afferent fibres in stratum oriens, a cut was placed

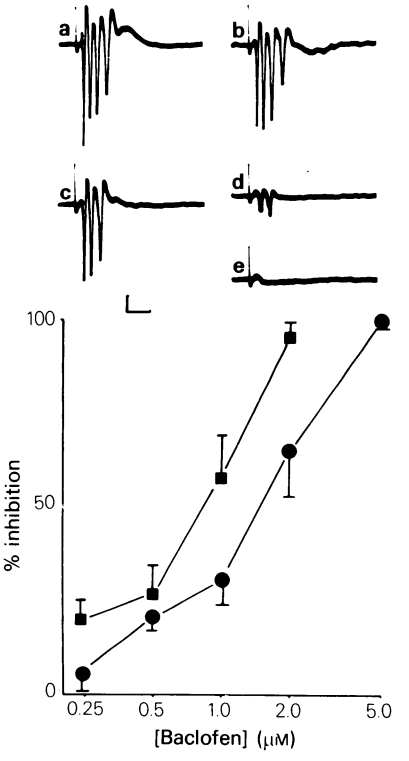

Figure 2 Depression induced by (−)-baclofen of CA1 pyramidal cell firing evoked by stimulation of Schaffer collateral-commissural fibres in the presence of 100 μM bicuculline. Recordings from a representative experiment illustrate the response in control medium (a) and the maximum depression induced by (−)-baclofen at concentrations of 0.5 μM (b), 1 μM (c), 2 μM (d) and 5 μM (e). Calibrations: vertical line, 0.5 mV; horizontal line, 20 ms. Inhibitions by (−)-baclofen of the initial population spike (●) and of the third spike of the afterdischarge (■) are plotted as means for 5 experiments; vertical lines indicate s.e.mean.

through stratum oriens before such stimuli were applied. When slices so treated were studied in normal Elliott's medium, stimulation of CA1 pyramidal cell axons in the alveus evoked a single antidromic spike in the cell body layer which did not appear to be followed by an extracellular e.p.s.p. After 100 μM Bic was added to the medium, the antidromic spike was followed by several smaller population spikes superimposed on a positive wave (Figure 3). The configuration and time course of this response closely resembled the response evoked by stimulation of Schaffer collateral-commissural fibres under the same conditions.

The mossy fibres were stimulated with an electrode placed in the granule cell layer of the fascia dentata. This placement assured that no other afferent fibres

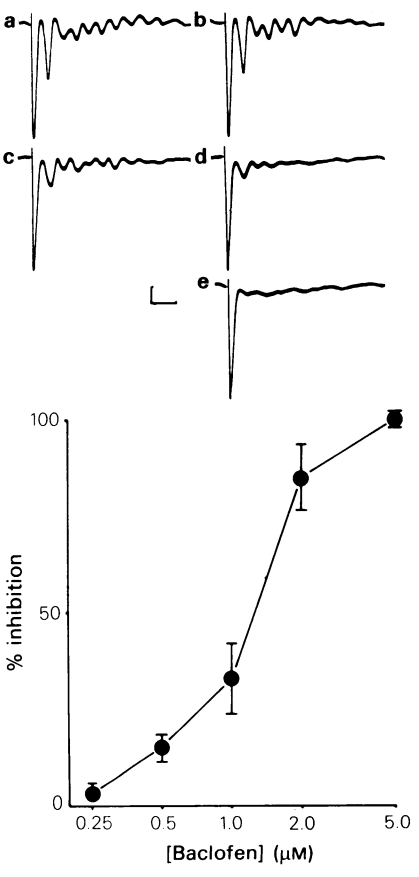

Figure 3 Inhibition by (−)-baclofen of CA1 pyramidal cell firing evoked by antidromic stimulation in the presence of 100 μM bicuculline. Recordings from a representative experiment illustrate the response in control medium (a) and the maximum depression induced by (−)-baclofen at concentrations of 0.5 μM (b), 1 μM (c), 2 μM (d) and 5 μM (e). Calibrations: vertical line, 0.5 mV; horizontal line, 10 ms. In 3 experiments the magnitude of afterdischarge was quantitated as described in Methods and is plotted as the mean reduction of the control magnitude; vertical lines indicate s.e. mean.

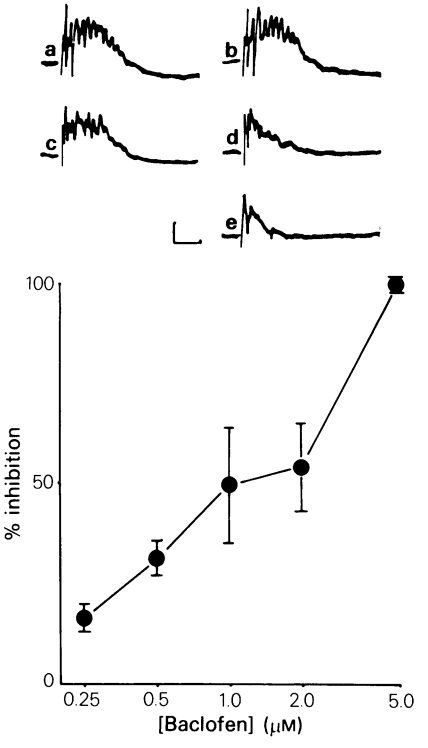

Figure 4 (−)-Baclofen-induced depression of CA3 pyramidal cell firing evoked by stimulation of the mossy fibres in the presence of 100 μM bicuculline. Recordings from a representative experiment illustrate the response in control medium (a) and the maximum depression induced by (−)-baclofen at concentrations of 0.5 μM (b), 1 μM (c), 2 μM (d) and 5 μM (e). Calibrations: vertical line, 0.5 mV; horizontal line, 20 ms. In 4 experiments the magnitude of afterdischarge was quantitated as described in Methods and is plotted as the mean reduction of the control magnitude; vertical lines show s.e. mean.

to area CA3 would be activated. In the presence of 100 μM Bic, the firing of CA3 pyramidal cells in response to mossy fibre stimulation consisted of numerous poorly synchronized population spikes superimposed on a positive wave (Figure 4). Individual population spikes of the afterdischarge were of low amplitude and short duration relative to those generated in area CA1.

Granule cell afterdischarge

Stimulation of the perforant path fibres where they pass through the subiculum normally evoked a single population spike whose amplitude increased with increasing stimulus current. In the presence of 100 μM Bic, a single stimulus continued to elicit a unitary population spike until the amplitude of the spike reached 1–2 mV. Any further increase in stimulus current evoked a burst of several large population spikes fired at a frequency of 200–300/s (Figure 5). These large spikes were usually followed by a series of smaller spikes, all superimposed on a positive wave of 1–2 mV amplitude.

Depressant effects of (−)-baclofen

(−)-Baclofen applied in 5 ml volumes at concentrations between 0.25 and 5 μM depressed repetitive firing of the CA1 pyramidal cell population evoked by

stimulation of Schaffer collateral-commissural fibres ($n = 6$) or by antidromic stimulation ($n = 5$) (Figures 2 and 3). In some slices the later spikes were strongly depressed at concentrations of (−)-baclofen that little affected the early spikes, but in others all the spikes were diminished concurrently. As previously reported (Ault & Nadler, 1982a, b; Olpe *et al.*, 1982), (−)-baclofen strongly depressed the initial population spike evoked by stimulation of Schaffer collateral-commissural fibres, but did not affect the antidromic population spike. At these concentrations, (−)-baclofen also inhibited repetitive firing of the CA3 pyramidal cell population evoked by mossy fibre stimulation ($n = 5$) (Figure 4). It did not affect the initial population spike, however. The concentration of (−)-baclofen necessary to produce a threshold depression ranged between 0.25 and 0.5 μM. Washing the slice with control medium for 10–20 min reversed all effects of the drug.

At a concentration of 5 μM, (−)-baclofen failed to inhibit the repetitive firing evoked in the fascia dentata by stimulation of perforant path fibres ($n = 5$). In contrast, 5 μM (−)-baclofen usually completely suppressed after discharge elicited by stimulation of the other pathways.

Dose-response relationships for the suppression of repetitive firing are shown in Figures 2–4. (−)-Baclofen depressed the response to stimulation of Schaffer collateral-commissural fibres with an EC_{50} of 1.3 ± 0.3 μM ($n = 5$), and EC_{50} values for inhibition of responses to antidromic stimulation of CA1 pyramidal cells and to mossy fibre stimulation were 1.3 ± 0.2 μM ($n = 3$) and 1.5 ± 0.2 μM ($n = 4$), respectively.

Stereospecificity

EC_{50} values for depression of cell discharge evoked by stimulation of Schaffer collateral-commissural fibres were determined for the (−) and (+)-isomers of baclofen in three experiments (Figure 6). (−)-Baclofen was found to be 120 ± 10 times as potent as the (+)-isomer.

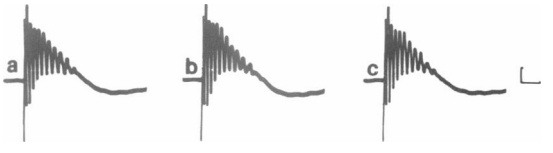

Figure 5 Lack of effect of (−)-baclofen on afterdischarge evoked by stimulation of the perforant path in the presence of 100 μM bicuculline. Responses shown were recorded before (a), during (b) and after (c) superfusion of the slice with medium containing 5 μM (−)-baclofen. Calibrations: vertical line, 0.5 mV; horizontal line, 20 ms.

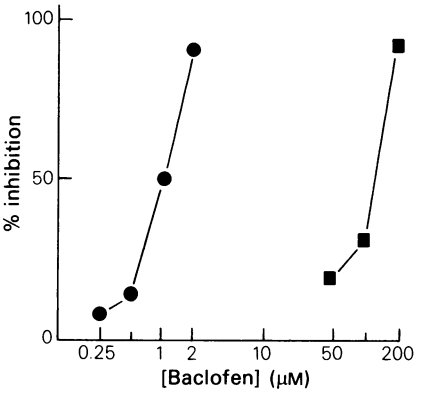

Figure 6 Dose-response curves for the (−) and (+)-isomers of baclofen. The isomers were tested on the response to stimulation of Schaffer collateral-commissural fibres in the presence of 100 μM bicuculline. Results of a representative experiment are shown. Points indicate the maximum depresson of this response during superfusion with 5 ml of drug-containing medium. (●) (−)-baclofen; (■) (+)-baclofen.

Recurrent inhibition

A number of anticonvulsants that attenuate hippocampal afterdischarge are thought to act, at least in part, by potentiating GABAergic inhibition (Olsen

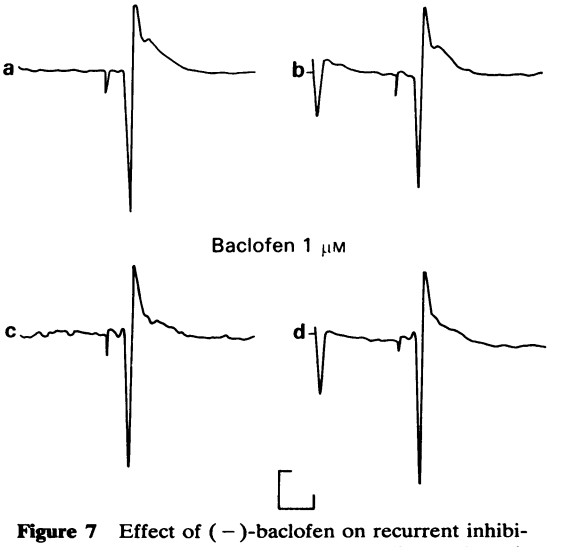

Figure 7 Effect of (−)-baclofen on recurrent inhibition in area CA1. In control Elliott's medium, submaximal Schaffer collateral-commissural population spikes (a) were depressed by an antidromic conditioning volley (b). In the presence of 1 μM (−)-baclofen, such recurrent inhibition was abolished and sometimes potentiation was observed (c,d). Calibrations: vertical line, 0.5 mV; horizontal line, 10 ms.

& Leeb-Lundberg, 1981). To determine whether baclofen inhibits hippocampal afterdischarge by a similar mechanism, we studied its effect on recurrent inhibition in area CA1, which is known to be mediated by GABAergic interneurones (Storm-Mathisen, 1977). In three slices tested, a preceding antidromic volley depressed the amplitude of the Schaffer collateral-commissural population spike by 17, 19 and 32%. Superfusion of the slices with 1 μM (−)-baclofen not only failed to potentiate recurrent inhibition, but actually abolished it (Figure 7). A preceding antidromic volley failed to affect the orthodromic population spike in one slice and increased its amplitude by 9% and 41% in the other two slices.

Discussion

Our results demonstrate that baclofen reversibly suppresses afterdischarge that can be evoked in hippocampal areas CA1 and CA3 by electrical stimulation in the presence of Bic. Its potency for this anticonvulsant-like action approximately equals its potency for diminishing the amplitude of single population spikes evoked by stimulating axons of CA3 pyramidal cells (Ault & Nadler, 1982b) and slightly exceeds its potency for depressing the extracellular e.p.s.p. elicited by stimulating the same fibres at lower intensity (Ault & Nadler, 1982a). All these actions exhibit a similar degree of stereospecificity, and they can also be replicated by superfusion of the slices with GABA in the presence of Bic (Ault & Nadler, 1982a,b and unpublished observations). These results support the view that baclofen acts at a single type of Bic-insensitive GABA receptor.

Numerous investigators have studied the repetitive discharge of CA1 and CA3 hippocampal pyramidal cells during stimulation in the presence of GABA antagonists, such as Bic or penicillin (Alger & Nicoll, 1980; Schwartzkroin & Prince, 1980; Gjerstad *et al.*, 1981; Traub & Wong, 1981; 1982). Their results suggest a number of ways in which baclofen might act to inhibit afterdischarge. Four factors that must be considered in interpreting data from the present study are: the ability of the stimulus to activate the neuronal population, intrinsic cellular bursting activity, synchronization of repetitive firing by excitatory synaptic circuits and depression of firing by intrinsic inhibitory synaptic circuits.

One might expect that baclofen would suppress afterdischarge evoked by stimulating the Schaffer collateral-commissural fibres, at least in part, through its inhibition of excitatory transmission at these synapses. However, baclofen inhibited the afterdischarge evoked by antidromic stimulation of CA1 pyramidal cells with about equal potency, although it did not affect the antidromic population spike. Assuming that no significant orthodromic component contaminated the antidromic volley, these findings suggest that baclofen does not suppress afterdischarge and inhibit the firing of single population spikes by exactly the same mechanism. The drug may therefore interfere specifically with the initiation or synchronization of afterdischarge. At the single cell level, stimulation of Schaffer collateral-commissural fibres with GABAergic inhibition suppressed initiates burst discharge by opening Ca^{2+} channels in the plasma membrane (Alger & Nicoll, 1980). Antidromic activation of CA1 pyramidal cells also increases Ca^{2+} influx, and this current can initiate bursting if it is of sufficient magnitude (Wong & Prince, 1981). Baclofen might conceivably block these postsynaptic Ca^{2+} currents, as it does in chick sensory neurones (Dunlap, 1981). In the present study, afterdischarge clearly did not depend on connections between the CA1 and CA3 areas and neither anatomical nor electrophysiological studies have disclosed evidence of recurrent excitation wholly intrinsic to area CA1 (Knowles & Schwartzkroin, 1981). Accordingly, afterdischarge in area CA1 *in vitro* appears to be generated mainly by synchronization of intrinsically-generated bursts, possibly involving electrotonic coupling among pyramidal cells (Taylor & Dudek, 1982), and not by recurrent excitation. Thus baclofen appears not to inhibit afterdischarge in this region by blocking transmission at a recurrent excitatory synapse. We are now investigating these possible mechanisms of action with intracellular recording techniques.

The response of CA3 pyramidal cells to mossy fibre stimulation in the presence of Bic resembles their response to the same stimulus in Cl^--free medium (Yamamoto, 1972). Baclofen suppresses afterdischarge evoked by mossy fibre stimulation without affecting the initial activation of pyramidal cells. The drug might therefore act, in part, by depressing Ca^{2+} influx. In contrast to area CA1, however, repetitive firing of the CA3 pyramidal cell population depends significantly on recurrent excitatory circuitry (Hablitz & Johnston, 1981; Traub & Wong, 1982). Baclofen potently inhibits transmission at these CA3–CA3 associational synapses (Ault & Nadler, 1982a). Such an action would tend to shorten the duration of afterdischarge, as was indeed observed.

Perforant path stimulation in the presence of Bic evoked repetitive discharge only when the initial population spike was already of 1–2 mV amplitude. Our results resembled those reported by Yamamoto & Kawai (1968), who blocked GABAergic inhibition with Cl^--free medium. Baclofen failed to inhibit any aspect of this response, even at a concentration

which usually totally suppressed afterdischarge in areas CA1 and CA3. Although at higher concentrations it reduces the amplitude of single population spikes evoked by perforant path stimulation (Ault & Nadler, 1982b) and partially inhibits transmission at medial perforant path synapses (Lanthorn & Cotman, 1981), these actions did not influence responses to perforant path stimulation recorded in the present study. Our use of relatively low drug concentrations and maximal test responses probably counteracted the rather weak inhibitory action of baclofen on perforant path transmission. Since a complete recurrent excitatory circuit appears not to exist within the fascia dentata of a single transverse slice (Nadler, Tauck, Evenson & Davis, 1982), afterdischarge in this region may consist of intrinsically generated bursts synchronized by electrotonic coupling among the granule cells (MacVicar & Dudek, 1983). The genesis of granule cell bursting has been little investigated. If baclofen suppresses afterdischarge in areas CA1 and CA3 by blocking the initiation of intrinsic bursting in pyramidal cells, then its failure to do so in the fascia dentata suggests a difference between pyramidal and granule cells in the mechanism of burst generation.

Unlike many anticonvulsants, baclofen does not suppress hippocampal afterdischarge by potentiating GABAergic inhibition. In fact, it actually reduced the intensity of recurrent inhibition in area CA1. A similar disinhibitory action of baclofen has been demonstrated in the spinal cord (Kudo, Kurachi & Fukuda, 1981). In area CA1 such disinhibition is probably explained by blockade of excitatory transmission at synapses made by pyramidal cell axons on inhibitory interneurones, since baclofen has this action at synapses made by other hippocampal pyramidal cells.

Although baclofen is now employed only for its antispastic action, its anticonvulsant-like effects on the hippocampus may nonetheless be clinically relevant. The drug attenuated even maximal afterdischarge of hippocampal pyramidal cells at concentrations within the range of cerebrospinal fluid levels attained in patients treated for spasticity (Knutsson, Lindblom & Mårtensson, 1974). This finding, along with previous reports of anticonvulsant efficacy in animals (Benedito & Leite, 1981; Meldrum, 1981), suggests that baclofen could be therapeutically valuable in seizure disorders that involve the hippocampus, such as temporal lobe epilepsy. On the other hand, proconvulsant effects of baclofen might also be found in situations where its disinhibitory effect predominates.

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