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Effects of baclofen on synaptically-induced cell firing in the rat hippocampal slice

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1 The effects of baclofen on the synaptically-induced firing of pyramidal and granule cell populations were tested in the rat hippocampal slice. Population spikes were evoked by stimulating excitatory pathways in the presence and absence of bath-applied drug.

2 (±)-Baclofen (20 μM) completely blocked the firing of CA1 or CA3 hippocampal pyramidal cells subsequent to stimulation of projections that originate in area CA3. In contrast, the firing of dentate granule cells evoked by stimulation of the perforant path fibres was depressed by only 46% and baclofen did not affect the monosynaptic firing of CA3 pyramidal cells evoked by mossy fibre stimulation. These results are consistent with the effects of baclofen on the corresponding extracellularly-recorded excitatory postsynaptic potentials (e.p.s.ps).

3 The Schaffer collateral-commissural population spike in area CA1 was depressed by (−)-baclofen (EC_{50} = 2.8 μM), GABA (EC_{50} = 2.2 mM) and 3-aminopropanesulphonic acid (3-APS) (EC_{50} = 0.34 mM). (−)-Baclofen was 180 times as potent as (+)-baclofen.

4 Bicuculline methiodide (100 μM) did not reverse the depressant action of (−)-baclofen. GABA-induced depressions were antagonized to only a small degree, whilst the effect of 3-APS was readily reversed. Raising the concentration of bicuculline from 100 μM to 500 μM did not further reverse the action of GABA.

5 The effects of (−)-baclofen and 3-APS on the relationship between extracellular e.p.s.p. and population spike were tested by stimulation of the Schaffer collateral-commissural fibres in area CA1. (−)-Baclofen shifted the 'input/output' curve to the right at a concentration of 1 μM, but less or not at all at 3 μM. In contrast, increasing the concentration of 3-APS shifted this curve farther to the right.

6 These results are consistent with the hypothesis that baclofen and GABA can depress neuronal firing by interacting with a bicuculline-insensitive receptor. In the CA1 area, activation of these receptors mainly depresses transmitter release from terminals of projections from area CA3, but also reduces pyramidal cell excitability.

Introduction

Baclofen [β-(*p*-chlorophenyl)-GABA, Lioresal] is a γ-aminobutyric acid (GABA) analogue capable of penetrating the blood-brain barrier. It is used clinically as a centrally-acting muscle relaxant, whose effect is thought to be exerted at the level of the spinal cord (Bein, 1972). Accordingly, baclofen has been shown to depress excitatory neurotransmission in the spinal cord *in vivo* (Pierau & Zimmerman, 1973; Fox, Krnjević, Morris, Puil & Werman, 1978; Ono, Fukuda & Kudo, 1979; Curtis, Lodge, Bornstein & Peet, 1981; Davies, 1981) and *in vitro* (Davidoff & Sears, 1974; Saito, Konishi & Otsuka, 1975; Ault & Evans, 1981). This action appears to be due mainly to a decrease in the release of transmitter from synaptic terminals. Glutamate and aspartate are the putative transmitters of the relevant excitatory pathways in the spinal cord (Watkins & Evans, 1981), and baclofen has been shown to depress the release of excitatory amino acids from various CNS preparations (Potashner, 1979; Johnston, Hailstone & Freeman, 1980; Collins, Anson & Kelly, 1982).

We have shown that, in the rat hippocampal slice, baclofen preferentially depresses transmission at synapses made by axons of CA3 pyramidal cells (Ault & Nadler, 1982a). The transmitter employed by these fibres is also likely to be glutamate and/or aspartate (Cotman & Nadler, 1981). That study used the extracellular or population excitatory postsynap-

tic potential (e.p.s.p.) as a measure of synaptic transmission and the results suggested that baclofen acted presynaptically to reduce transmitter release. In the present study, we tested the effect of baclofen on the population spike, an extracellular measure of the number of cells brought to threshold by a stimulus (Andersen, Bliss & Skrede, 1971), to determine whether, in addition, baclofen acts postsynaptically to alter pyramidal cell excitability. Moreover, it has been proposed that baclofen inhibits synaptic transmission by interacting with a subpopulation of GABA receptors that is insensitive to bicuculline (Bic) (Bowery, Hill, Hudson, Doble, Middlemiss, Shaw & Turnbull, 1980; Hill & Bowery, 1981; Bowery, Hill & Hudson, 1983). We have therefore compared some of the depressant actions of baclofen with those produced by GABA and 3-aminopropanesulphonic acid (3-APS), an agonist that acts mainly at Bic-sensitive GABA receptors (Bowery *et al.*, 1980; Hill & Bowery, 1981), and we have determined their sensitivity to Bic. A preliminary account of some of this work has been presented (Ault & Nadler, 1982b).

Methods

Slice preparation

Adult female Sprague-Dawley rats were killed by cervical dislocation and the brains were removed. Hippocampi were rapidly dissected and cut into transverse slices of 500 μm thickness. Individual slices were suspended upon small nylon nets in superfusion chambers of the type described by White, Nadler & Cotman (1978) and superfused with Elliott's (1969) artificial cerebrospinal fluid (composition (mM): NaCl 122, $NaHCO_3$ 25, KCl 3.1, $CaCl_2$ 1.3, $MgSO_4$ 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. A peristaltic pump recirculated 3 ml of this medium through each chamber 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 equilibration of drugs between the medium and the extracellular fluid within the slice. Media were superfused at a rate of 1.2–1.5 ml min^{-1} from pressurized flasks and were mainly removed by gravity from the bottom of the chamber. To keep the fluid level constant, excess medium was aspirated from the fluid surface by use of a glass pipette. When Bic was used, it was present continuously in the medium. To generate dose-response curves, it was found most convenient to prepare each desired concentration of agonist in 5 ml of Elliott's medium, which was then introduced into one of the superfusion lines by use of a three-way valve. A six-way valve was used to switch between control and test media. We found 5 ml of solution sufficient to produce a maximal effect.

Electrophysiological responses were recorded before and during the period for which an agonist was superfused. The slice was then washed with control medium to regain its initial responsiveness before further drug application. The degree of inhibition was calculated as the maximal depression of the response expressed as a percentage of the mean of the three control responses that immediately preceded introduction of the test compound into the chamber.

Stimulation and recording

Cathodal constant current pulses, usually of 40–100 μs duration, were applied through the inner wire of a concentric bipolar electrode (Ault & Nadler, 1982a; 1983). Afferent fibre tracts were stimulated at a rate of 2 per min, except when input/output (extracellular e.p.s.p./population spike) relationships were investigated. In the latter experiments, stimuli were delivered at 0.1 Hz. Glass micropipettes filled with 4 M NaCl (2–10 MΩ impedance) were used to record extracellular field potentials. These signals were filtered above 1 kHz, amplified, displayed on an oscilloscope and usually recorded on film.

The medial perforant path extracellular e.p.s.p. was recorded in the middle third of the dentate molecular layer and the lateral perforant path extracellular e.p.s.p. was recorded in the outer third. Responses to stimulation of the medial perforant path were differentiated from responses to stimulation of the lateral by the characteristic paired-pulse depression observed with an interstimulus interval of 200 ms (McNaughton, 1980). The stimulus strength was maintained just below the threshold for evoking a population spike. Extracellular e.p.s.p. amplitude was measured 2 ms after onset.

Population spikes were recorded from the pyramidal and granule cell body layers. Stimulating and recording electrodes were placed as described previously (Ault & Nadler, 1982a; 1983). The amplitudes of population spikes recorded on film were measured from onset to peak negativity. Control responses were routinely standardized by adjusting the stimulus current to evoke a just-maximal population spike.

To investigate input/output relationships, a single recording electrode was placed in the appropriate cell

body layer. Stimulus current and pulse duration were varied to evoke population spikes from threshold to maximum amplitude. Extracellular e.p.s.p. amplitudes were measured from the initial positive-going wave 1–2 ms after onset. These measurements and those of population spike amplitude were made with the aid of a microcomputer (Teyler, Mayhew, Chrin & Kane, 1982). After generating an input/output curve in control medium, agonist was introduced and the procedure was repeated. The agonist was then washed out and an input/output curve was again generated in control medium.

Materials

(±)-Baclofen and the individual isomers were gifts from Ciba-Geigy Corp. (Ardsley, NY, U.S.A.) and Ciba-Geigy Ltd (Basel, Switzerland), respectively. Bicuculline methiodide was purchased from Pierce Chemicals (Rockford, IL, U.S.A.) and GABA and 3-APS were obtained from Sigma Chemical Co. (St Louis, MO, U.S.A.).

Results

Effects of (±)-baclofen on hippocampal population spikes

At a concentration of 20 μM (which substantially depresses excitatory transmission in the spinal cord (Ault & Evans, 1981)), (±)-baclofen abolished population spikes evoked in the CA1 or CA3 pyramidal cell layer by stimulation of Schaffer collateral-commissural fibres and population spikes evoked in the CA1 pyramidal cell layer by stimulation of associational-commissural fibres in stratum oriens (Figure 1, Table 1). The initial negative wave evoked by stimulating the Schaffer collateral-commissural fibres in area CA3 was composed of both a compound fibre potential and an antidromic population spike generated by firing those CA3 pyramidal cells whose Schaffer collaterals were activated by the stimulus. In agreement with our previous observations (Ault & Nadler, 1982a), these responses were not depressed by baclofen. The depressant effect of 20 μM (±)-baclofen on orthodromic

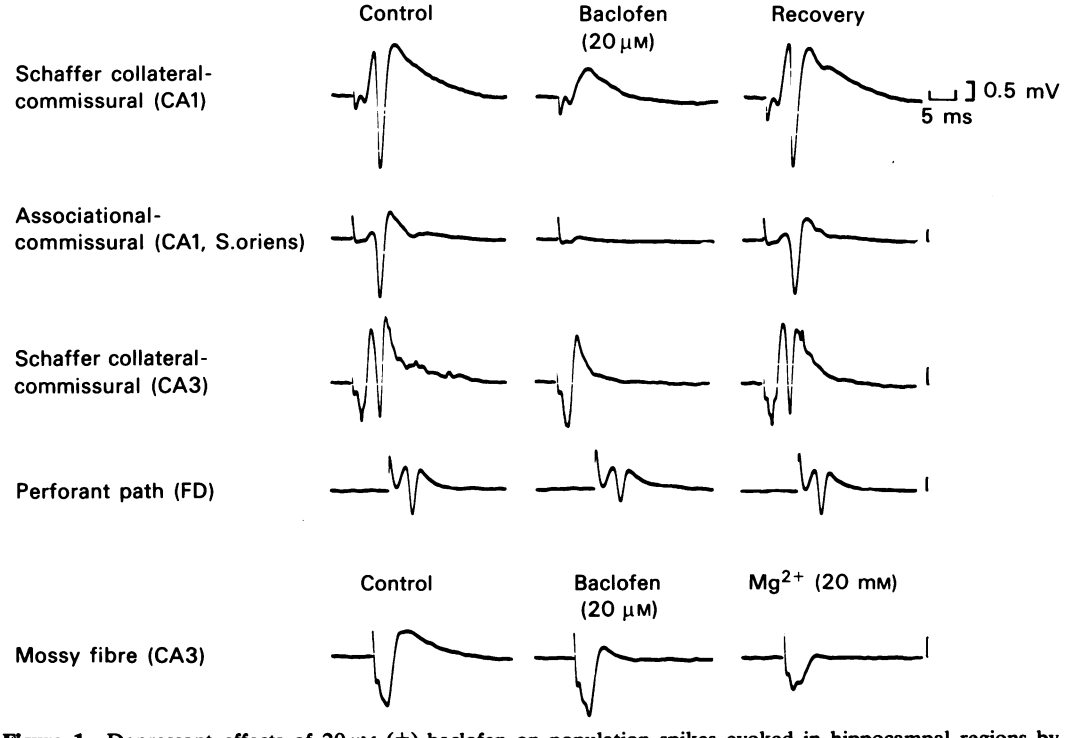

Figure 1 Depressant effects of 20 μM (±)-baclofen on population spikes evoked in hippocampal regions by stimulation of excitatory afferent fibres. FD, fascia dentata. The potentials shown are single a.c.-coupled recordings that illustrate the maximal inhibitory action of a 5 ml pulse of baclofen and reversal of the depression upon washing the slice with drug-free medium. The synaptic component of the response to mossy fibre stimulation was blocked by addition of 20 mM Mg^{2+} to 5 ml of the medium.

Table 1 Effect of 20 μM (±)-baclofen on excitatory transmission in the rat hippocampal slice

Pathway	% Depression: Extracellular e.p.s.p.	% Depression: Population spike
Area CA1		
Schaffer collateral-commissural	80 ± 7 (5)	100 (4)
Associational-commissural	75 ± 12 (3)	100 (4)
Temporo-ammonic	8 ± 6 (3)	*
Area CA3		
Mossy fibre	2 ± 3 (3)	1 ± 1 (3)
Schaffer collateral-commissural	56 ± 10 (3)	100 (4)
Fascia dentata		
Perforant path (lateral)	4 ± 3 (3)	43 ± 10 (3)
Perforant path (medial)	24 ± 4 (3)	
Associational-commissural	6 ± 4 (3)	*

Values indicate the maximal depression of response amplitude produced by superfusion with 20 μM (±)-baclofen and are expressed as means ± s.e.mean for the number of experiments in parentheses. Where s.e.mean is not given, the drug completely abolished the population spike in all experiments. Extracellular e.p.s.p. data, except for those on medial perforant path, are taken from Ault & Nadler (1982a).

* A population spike could not be evoked by stimulation of these pathways, except with stimulus currents great enough to activate adjacent pathways.

population spikes evoked by stimulating axons of CA3 pyramidal cells correlated with its depression of the corresponding extracellular e.p.s.ps, although at this concentration the drug more effectively inhibited generation of the population spike (Table 1).

Since the mossy fibres form synapses close to the cell bodies of CA3 pyramidal cells, both the extracellular e.p.s.p. and population spike evoked by mossy fibre stimulation are represented by negative deflections when they are recorded in the cell body layer. Thus the two responses cannot be readily distinguished. To optimize the contribution of orthodromically-evoked cell firing, the stimulus intensity was adjusted to yield a just maximal composite response. Under these conditions the negative wave was unaffected by 20 μM (±)-baclofen (Figure 1, Table 1). The amplitude of the positive wave that followed this potential was, however, reduced by baclofen. This result suggests that the positive wave is at least partly generated by a recurrent e.p.s.p. and/or inhibitory postsynaptic potential (i.p.s.p.), both of which are sensitive to baclofen (Ault & Nadler, 1983).

The population spike recorded in the granule cell layer of the fascia dentata after stimulation of perforant path fibres was depressed by 20 μM (±)-baclofen, but to a lesser degree than population spikes evoked in other hippocampal regions by stimulating axons of CA3 pyramidal cells (Figure 1, Table 1). In agreement with Lanthorn & Cotman (1981), this concentration of (±)-baclofen somewhat reduced the amplitude of the extracellular e.p.s.p. evoked by stimulating the medial perforant path (Table 1). Thus, as with stimulation of CA3 pyramidal cell axons, depression of the population spike correlated with a lesser reduction in amplitude of the extracellular e.p.s.p.

Stereospecificity

The (−)-and (+)-isomers of baclofen were tested for their ability to reduce the amplitude of the population spike evoked in area CA1 by stimulating Schaffer collateral-commissural fibres (Figure 2). (−)-Baclofen depressed this response with an EC_{50} of

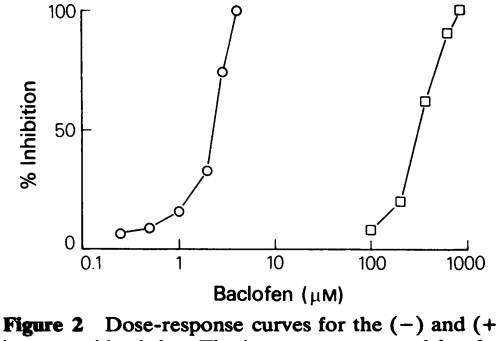

Figure 2 Dose-response curves for the (−) and (+)-isomers of baclofen. The isomers were tested for their ability to reduce the amplitude of the Schaffer collateral-commissural population spike recorded in area CA1. Points indicate the maximal inhibition during superfusion of 5 ml of drug-containing medium. (○), (−)-baclofen; (□), (+)-baclofen. In this and in Figures 3 and 4 results of single experiments are presented, rather than means, because the concentrations of test substances varied among experiments.

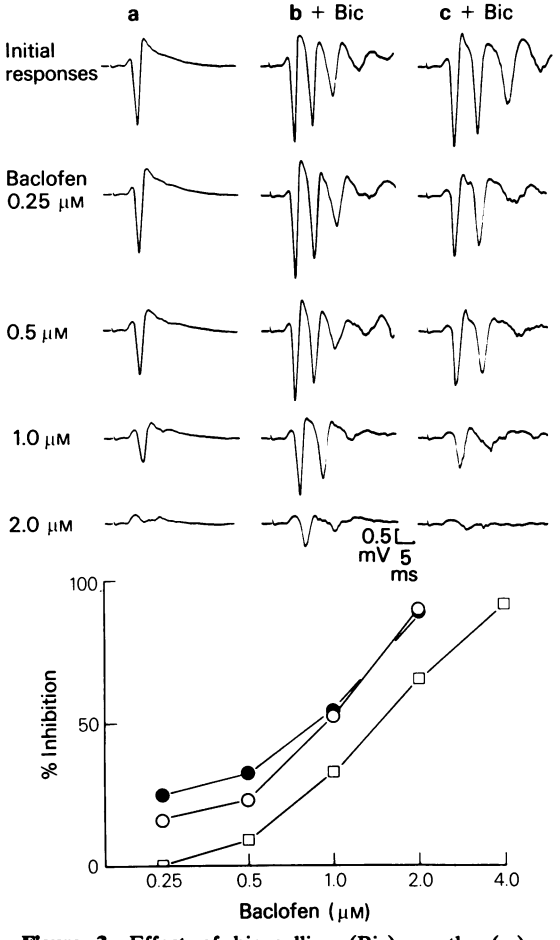

Figure 3 Effect of bicuculline (Bic) on the (−)-baclofen-induced depression of the Schaffer collateral-commissural (CA1) population spike. Initial responses were recorded in the absence of baclofen. (−)-Baclofen was then tested in the absence (a), (○) and presence (b), (□) of 100 μM Bic using the same stimulus intensity. The stimulus was then reduced so that, as in control medium, it evoked a just-maximal population spike. The effect of (−)-baclofen was then re-examined (c), (●).

2.8 ± 0.5 μM ($n = 8$) and was 180 ± 20 times as potent as (+)-baclofen in three experiments where the isomers were directly compared.

Effect of bicuculline

An antagonistic effect of Bic was sought by comparing agonist dose-response curves in control and Bic-containing media. Figure 3 shows a representative example of results from an experiment in which we investigated the ability of Bic to reverse the depressant effect of (−)-baclofen on the Schaffer collateral-commissural population spike in area CA1. Introduction of 100 μM Bic into the superfusion medium increased the amplitude of the initial population spike and produced repetitive discharge, as expected from its blockade of GABAergic inhibition (Dingledine & Gjerstad, 1980; Schwartzkroin & Prince, 1980). Some reversal of the depressant effect of (−)-baclofen was then observed. However, the stimulus that had evoked a just-maximal population spike in control medium was found to be supramaximal in the presence of Bic. In most experiments therefore the stimulus current was reduced until it was again just maximal and the effect of (−)-baclofen was re-examined. (−)-Baclofen was then found to depress the population spike with a potency similar to that determined in control medium (Table 2).

The same regimen was employed to study the Bic-sensitivity of depressions produced by GABA and 3-APS (Figure 4). Again, Bic shifted the dose-response curves to the right. After the stimulus intensity was reduced to evoke a just-maximal population spike once more, both dose-response curves were shifted less far rightward. When concentration ratios were compared, it was clear that Bic hardly reversed the action of GABA, but strongly antagonized the action of 3-APS (Table 2). Furthermore, raising the concentration of Bic from 100 μM to 500 μM did not reverse the action of submaximal concentrations of GABA to any greater degree ($n = 3$).

Input/output curves

Our studies of pathway specificity suggested that baclofen inhibited synaptically-induced neuronal firing, at least in part, by reducing the synaptic drive imparted by the stimulus. However, the drug might also have depressed the excitability of the postsynaptic cells. To determine whether baclofen reduced pyramidal cell excitability, the relationship between the extracellular e.p.s.p. and the population spike was studied after stimulating the Schaffer collateral-commissural projection to area CA1. Initially, concentrations of (−)-baclofen (1 μM) and 3-APS (100 μM) were chosen that similarly reduced the amplitude of a just-maximal population spike (46 ± 10% ($n = 5$) and 58 ± 13% ($n = 5$), respectively). If a test compound reduces population spike amplitude by inhibiting either transmitter release or interaction of the transmitter with the postsynaptic receptor-ionophore complex, it should not alter this type of input/output curve. If it depresses the excitability of the postsynaptic cell, however, a shift of the curve to the right would be expected. According to this analysis, both compounds depressed pyramidal cell excitability to some extent at these concentrations (Figure 5a,b). When the concentrations of (−)-baclofen and 3-APS were tripled, (−)-baclofen pro-

Table 2 Concentration ratios for reduction of Schaffer collateral-commissural (CA1) population spike amplitude in the absence and presence of bicuculline (Bic)

Test compound	EC_{50} (a)	*Concentration ratio* (b)	(c)
(−)-Baclofen	2.8 ±0.5 μM (8)	1.8±0.3 (5)	0.9±0.2 (3)
GABA	2.2 ±0.3 mM (5)	1.9±0.2 (4)	1.6±0.5 (4)
3-APS	0.34±0.13 mM (4)	14±3 (5)	13±4 (3)

In (a) experiments were carried out in the absence of Bic. EC_{50} values were determined from dose-response curves by log probit analysis. Concentration ratios (b) and (c) were calculated by dividing the EC_{50} determined in the presence of 100 μM Bic by the EC_{50} determined in Bic-free medium. (b) Stimulus intensity was the same in the presence and absence of Bic. (c) Stimulus intensity was adjusted after the addition of Bic to the medium, so that it again evoked a just-maximal population spike. Values are means ± s.e.mean for the number of experiments in parentheses.

duced a less obvious rightward shift or none at all (Figure 5c), whereas the effect of 3-APS was accentuated (Figure 5d).

Discussion

These data provide further evidence that, in the hippocampal slice, baclofen preferentially depresses transmission at synapses made by axons of CA3 pyramidal cells. Baclofen also inhibits transmission at the medial perforant path-granule cell synapse, although it appears to be less potent at this site. (−)-Baclofen is two orders of magnitude more potent than the (+)-isomer in reducing the amplitude of the Schaffer collateral-commissural population spike, which is in agreement with the stereospecificity of the drug in reducing the amplitude of the corresponding extracellular e.p.s.p. (Ault & Nadler, 1982a) and in attenuating afterdischarge evoked by stimulating these fibres in the presence of Bic (Ault & Nadler, 1983). Moreover, its EC_{50} value for these actions differs by only about a factor of 3. Thus, at least in area CA1, baclofen probably acts at a single type of receptor.

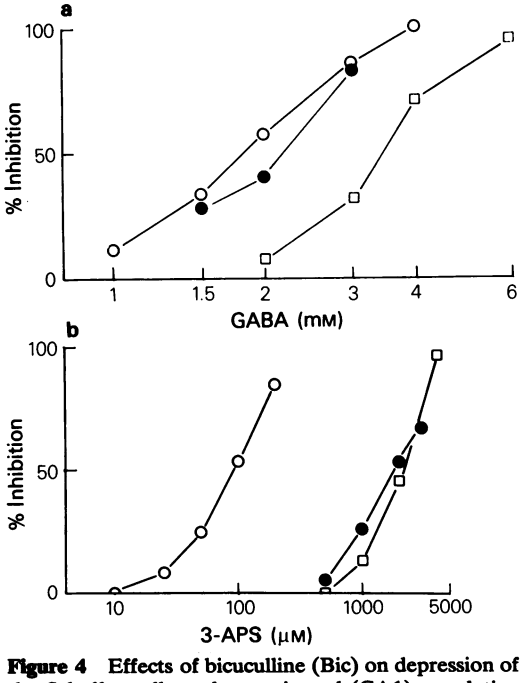

Figure 4 Effects of bicuculline (Bic) on depression of the Schaffer collateral-commissural (CA1) population spike produced by (a) GABA and (b) 3-APS; (○) initial responses in absence of Bic; (□) responses in presence of 100 μM Bic using same stimulus intensity; (●) responses in presence of 100 μM Bic using a reduced stimulus intensity (as for Figure 3).

GABA agonists are believed to act at two types of receptor distinguished by their sensitivity to the antagonist, Bic. In the present study, the (−)-baclofen-induced reduction of Schaffer collateral-commissural population spike amplitude was not reversed by Bic when physiologically equivalent stimuli were employed in control and Bic-containing media. GABA-induced depressions were rather weakly reversed by Bic, whereas Bic strongly reversed the action of 3-APS. These results are consistent with the relative affinities of the three agonists for Bic-sensitive and Bic-insensitive receptors, as determined in membrane binding studies (Hill & Bowery, 1981; Bowery *et al.*, 1983). Also, in the presence of 100 μM Bic, GABA appeared to act only through Bic-insensitive receptors, since raising the Bic concentration to 500 μM did not further reverse the action of GABA. Similar results were obtained when these agonists were tested for their ability to reduce the amplitude of the Schaffer collateral-commissural extracellular e.p.s.p. (Ault & Nadler, 1982a) and preliminary data indicate that GABA, in the presence of 100–500 μM Bic, reproduces baclofen's suppression of epilep-

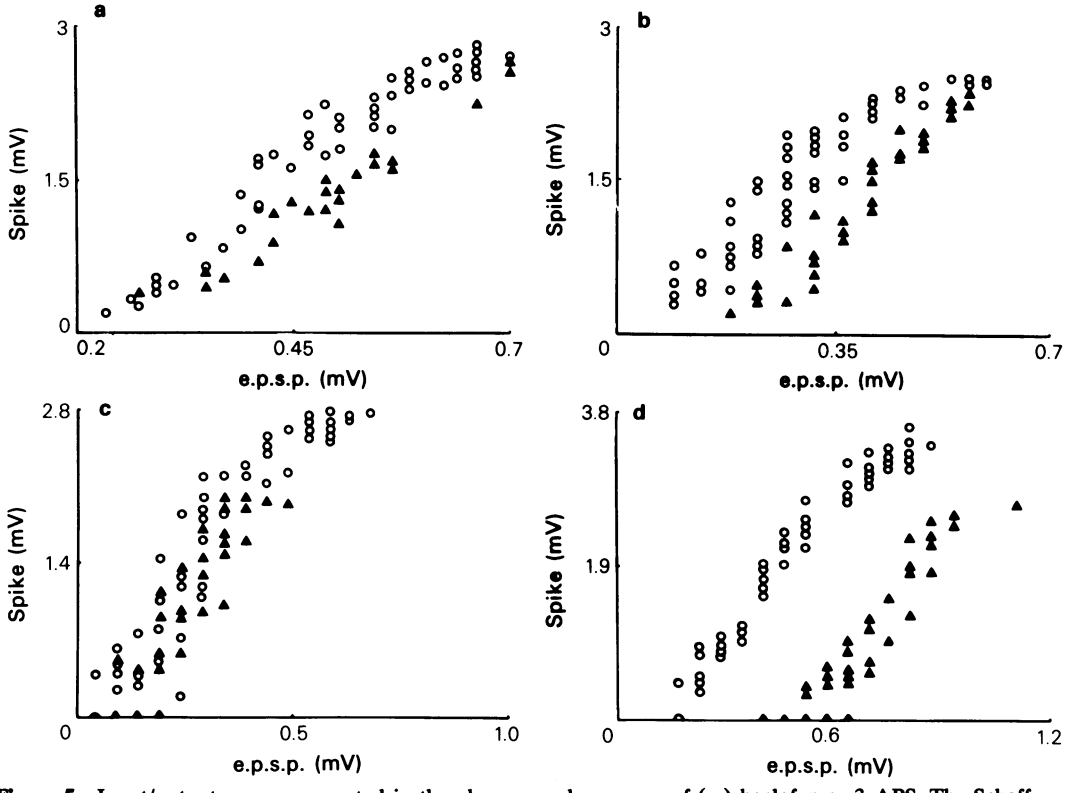

Figure 5 Input/output curves generated in the absence and presence of (−)-baclofen or 3-APS. The Schaffer collateral-commissural extracellular e.p.s.p. and population spike were recorded from the CA1 pyramidal cell body layer and analysed by microcomputer. Test compound was introduced into the superfusion medium, and after 5 min the stimulus intensity was increased to evoke responses with population spikes of similar amplitude to those obtained in control medium. (○), Control medium; (▲), agonist-containing medium. The agonist concentrations were: (a) (−)-baclofen 1 μM ($n = 5$); (b) 3-APS 100 μM ($n = 5$); (c) (−)-baclofen 3 μM ($n = 3$); (d) 3-APS 300 μM ($n = 3$), where n = number of experiments. The axes have slightly different ranges because the plots were derived from arbitrary computer-generated units and a calibration pulse was then used to calculate the true values.

tiform discharge. Taken together, these results support the view that baclofen depresses excitatory synaptic activity by acting at a single Bic-insensitive GABA receptor. To what extent these receptors mediate the physiological actions of GABA remains problematic.

Our data suggest that baclofen-sensitive receptors are localized both pre- and postsynaptically. At present, therapeutically-effective concentrations of baclofen are thought to inhibit synaptic transmission predominantly by suppressing transmitter release. Supporting evidence for this hypothesis includes demonstrations that baclofen does not suppress neuronal responses evoked by applied electrical pulses or exogenous excitants at concentrations that markedly depress synaptic activity (Davidoff & Sears, 1974; Fox *et al.*, 1978; Ault & Evans, 1981; Davies, 1981). In addition, baclofen has been shown to reduce transmitter release from a number of CNS preparations (Potashner, 1979; Bowery *et al.*, 1980; Johnston *et al.*, 1980; Collins *et al.*, 1982). In the hippocampal formation also, baclofen inhibits the release of exogenously loaded glutamate, but does not reduce glutamate-evoked cell firing (Olpe, Baudry, Fagni & Lynch, 1982). Moreover, baclofen inhibits transmission at certain excitatory synapses on pyramidal and granule cells, but not at other excitatory synapses on those same cells. Its specificity therefore is clearly for the presynaptic element and is the same for synaptic potentials and synaptically-induced firing. Finally, (−)-baclofen little affects the relation between the Schaffer collateral-commissural population spike and extracellular e.p.s.p. at a concentration of 3 μM, implying that it acts predominantly either by reducing transmitter release or by blocking the postsynaptic action of the transmitter. Since glutamate and/or aspartate probably mediates transmission at this site, the data of Olpe *et al.* (1982)

argue against the latter possibility. Hippocampal data therefore strongly suggest that baclofen inhibits excitatory transmission largely by depressing transmitter release.

Depression of excitatory transmitter release probably cannot explain two other observations, however. At a concentration of 1 μM, (−)-baclofen shifted the input/output curve for Schaffer collateral-commissural synaptic transmission to the right. This result implies a depression of pyramidal cell excitability. Conceivably, a reduction in spontaneous release of transmitter from afferent fibres could account for this finding. At 30°C, however, there is little spontaneous activity in these slices. More likely, baclofen depresses the excitability of pyramidal cells through a postsynaptic action. This effect of the drug appears most prominent at relatively low concentrations, whereas at higher concentrations inhibition of excitatory transmitter release predominates. In contrast to baclofen, 3-APS shifted the input/output curve to the right in a dose-dependent manner. This is expected of a GABA receptor agonist which principally acts at the Bic-sensitive GABA receptors on pyramidal cell somata and dendrites (Alger & Nicoll, 1982). A postsynaptic action of baclofen has also been proposed to explain the inhibition of CA1 pyramidal cell afterdischarge subsequent to antidromic stimulation in the presence of Bic (Ault & Nadler, 1983). This action probably does not involve depression of excitatory transmitter release, since repetitive firing evoked in this manner has been shown not to depend on synaptic transmission (Jeffreys & Haas, 1982; Taylor & Dudek, 1982). Baclofen attenuated antidromically-elicited afterdischarge with significantly greater potency than that with which it depressed the Schaffer collateral-commissural extracellular e.p.s.p. Previous investigators found that baclofen can non-specifically depress neuronal firing (Davies & Watkins, 1974; Phillis, 1976; Olpe, Koella, Wolf & Haas, 1977; Fox *et al.*, 1978), and a postsynaptic action of the drug may underlie this effect also. However, the doses required were greater than those needed to inhibit synaptic transmission.

The specificity with which baclofen reduces excitatory synaptic responses suggests that its postsynaptic action involves primarily the suppression of cell firing in response to stimulation of specific afferent fibres, rather than a more generalized alteration of membrane properties. Although intracellular recordings are required to determine the mechanism of this effect, one attractive possibility is that baclofen blocks postsynaptic Ca^{2+} currents in hippocampal pyramidal cells, as it does in chick sensory neurones (Dunlap, 1981). Dendritic Ca^{2+} spikes (or fast prepotentials) can be evoked in pyramidal cells by excitatory synaptic input (Schwartzkroin & Slawsky, 1977; Wong & Prince, 1978; Schwartzkroin & Prince, 1980) and are thought to facilitate the generation of action potentials (Andersen & Lømo, 1966; Schwartzkroin, 1977). Increased Ca^{2+} conductance also underlies burst discharge in these cells (Wong & Prince, 1978; Wong, Prince & Basbaum, 1979; Schwartzkroin & Wyler, 1980). Thus inhibition of postsynaptic Ca^{2+} conductance could partially explain the mechanism of action of baclofen. Obviously, interference with Ca^{2+} movements could also account for the depression of transmitter release, but there is no direct evidence at present to support such a mechanism.

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