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Local-spinal Therapy of Spasticity

With 140 Figures and 48 Tables

Springer-Verlag Berlin Heidelberg New York
London Paris Tokyo

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ISBN 3-540-18295-0 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-18295-0 Springer-Verlag New York Berlin Heidelberg

Library of Congress Cataloguing-in-Publication Data:

Local-spinal therapy of spasticity / H. Müller, J. Zierski, R. D. Penn (editors).
p. cm.
Based on papers presented at an international meeting held in Giessen, FRG in Apr. 1986 as well as some additional contributions.
ISBN 0-387-18295-0
1. Spasticity–Chemotherapy–Congresses. 2. Spinal anesthesia–Congresses. I. Müller, H. (Hermann) II. Zierski, J. (Jan), 1940– III. Penn, Richard D.
[DNLM: 1. Muscle Spasticity–drug therapy–congresses. WE 550 L811 1986]
RC935.S64L63 1988
616.8'3–dc19
DNLM/DLC
for Library of Congress 87-37653
CIP

Printed in Germany

Typesetting, printing and binding: Graphischer Betrieb, Konrad Triltsch, Würzburg
2329/3321-543210

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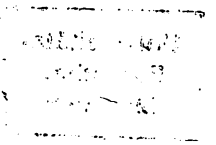

The Neuropharmacology of Baclofen

W. Zieglgänsberger , J. R. Howe, B. Sutor

Introduction

Gamma-aminobutyric acid (GABA) is one of the major inhibitory neurotransmitters in the mammalian central nervous system [see: 36, 69, 92, 98]. GABAergic neurons have been identified throughout the central nervous system with histochemical techniques [see: 75]. GABA is, however, of no therapeutical value because the amino acid does not pass the blood-brain barrier in sufficient amounts to affect neuronal excitability [9, 64].

The GABA analogue baclofen (β-[4-chlorophenyl]-gamma-aminobutyric acid; Lioresal®) was designed to act as a GABA mimetic that because of its lipophilicity would distribute into the central nervous system after systemic application. Baclofen effectively reduces exaggerated stretch reflexes and muscle tone after oral and intravenous administration and is widely used in the treatment of spasticity caused by traumatic spinal lesions, degenerative, neoplastic or infectious diseases of the spinal cord, and multiple sclerosis. It is less effective in ameliorating the spasticity after stroke or cerebral palsy [see: 109] (see also various authors, this volume).

Baclofen reduces muscle tone in patients with spinal transections and reduces muscle rigidity and tonic stretch reflexes in decerebrated animals [see: 13]. It is therefore suggested that the therapeutically relevant effect of baclofen results from a direct action at the spinal level. In addition to its antispastic activity, however, baclofen can cause muscle weakness, ataxia, drowsiness, insomnia, nausea, hypertension, a decrease in growth hormone release and an increase in prolactin secretion. Also, antinociceptive actions of baclofen have been reported [107; 110] (see also Yaksh, this volume). Particularly in elderly patients, the sudden withdrawal of baclofen after chronic use is occasionally associated with the appearance of psychotic symptoms, including dysphoric episodes and even hallucinations [see: 12]. These latter effects clearly indicate that baclofen acts also on receptors remote from the spinal cord.

This chapter examines the neuronal processes affected by baclofen, with an emphasis on electrophysiological findings. The enormous literature precludes an exhaustive documentation of all aspects.

The $GABA_B$ Receptor

The inhibitory actions of GABA are mediated in most neurons studied until now through an increase in chloride conductance of the postsynaptic membrane [see: 39, 69, 101]. These actions are mimicked by muscimol and THIP (4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3[2H]-one) and can be antagonized by bicuculline and picrotoxin [26; see: 36]. These two antagonists seem to block the actions of GABA via different mechanisms. Whereas bicuculline competes for the GABA binding site [74], picrotoxin seems to interact with the chloride-channel in a more direct manner [see: 36]. Because GABA also evokes bicuculline-insensitive responses which are

mimicked by baclofen (e.g. on transmitter release) [15, 67], two classes of GABA receptors, $GABA_A$ and $GABA_B$, have been proposed. The bicuculline-reversible actions of GABA and the GABA mimetic muscimol are mediated through $GABA_A$ receptors, whereas baclofen is considered as a prototypical bicuculline-insensitive agonist at $GABA_B$ receptors [15, 54]. This novel $GABA_B$ receptor mediates ionic processes which are clearly distinct from those sensitive to bicuculline (see below). $GABA_A$ receptor-mediated inhibition is potentiated by barbiturates and by the benzodiazepines [see: 48, 49] and is blocked by some convulsants like penicillin or pentetrazol [see: 36, 68]. Unfortunately, a selective $GABA_B$ receptor antagonist is not yet available.

Data from binding studies also support the existence of different types of GABA receptors. Various studies have corroborated the initial finding that baclofen does not displace ^{3}(H)-GABA from its binding sites on neuronal membranes [111]. Furthermore, the binding of GABA is enhanced by benzodiazepines [see: 48], whereas the binding of baclofen is unaffected by these compounds [108].

Autoradiographic studies with ^{3}(H)-baclofen have shown that, with a few exceptions, the distribution of $GABA_A$ and $GABA_B$ binding sites overlap in most regions of the brain [46]. There are indications, however, that the neuronal distribution of these bindng sites are not identical. For example, $GABA_A$ binding and high affinity $GABA_B$ binding were unchanged by interruption of forebrain noradrenergic projections, whereas low affinity $GABA_B$ binding was reduced [62]. This suggests that these low affinity $GABA_B$ receptor binding sites are located presynaptically on noradrenergic terminals. Baclofen reduces the evoked release of noradrenaline [15, 16, 40] and several other neurotransmitters (see below).

Stereoselectivity of $GABA_B$ Actions

Therapeutically used baclofen (LIORESAL®) is a racemic mixture of the two isomers. In a number of behavioral studies and electrophysiological investigations *in vivo*, it has been shown that the (–)isomer of baclofen is more potent than the (+)isomer [4, 52, 53, 80, 81, 107] (see also Yaksh, this volume). Several *in vitro* electrophysiologic studies have shown that the (–)isomer is at least 100-fold more potent than the (+)isomer [5–7, 20, 47, 56, 59, 78]. Similar stereoselectivity was demonstrated in experiments where baclofen reduced the *in vitro* release of exogeneously loaded ^{3}(H)-neurotransmitters [15, 61] and in studies of baclofen binding to bicuculline-insensitive receptors on synaptic membranes [54].

It was reported by various authors that the (+)isomer can antagonize the actions of the (–)isomer [94, 104, 105] (see also Yaksh, this volume). In recent electrophysiological experiments in which intracellular recording techniques were employed however, no such antagonism could be demonstrated [4, 58]. Thus (+)-baclofen does not appear to be an antagonist at all $GABA_B$ receptors.

Mode of Action of Baclofen

Numerous electrophysiological studies have shown that baclofen has profound inhibitory effects on synaptic transmission in the spinal cord and many other regions of the mammalian central nervous system. Until recently, the majority of the results suggested that baclofen acted presynaptically to selectively reduce excitatory synaptic transmission, a conclusion consistent with reports that baclofen directly reduces the release of excitatory neurotransmitters. It is now clear, however, that baclofen can also reduce inhibitory synaptic transmission and that baclofen directly increases the postsynaptic potassium conductance of many central neurons. In addition, there are several reports that baclofen depresses the firing of central neurons induced by excitatory substances. The following sections review the evidence for each these actions

of baclofen and their relevance to baclofen's effects on central nervous function.

Actions of Baclofen and Synaptic Transmission

In the first study employing intracellular recording techniques, Pierau and Zimmermann [85] reported that baclofen depressed excitatory postsynaptic potentials (EPSPs) evoked in cat motoneurons at doses that did not affect inhibitory processes. Since neither the membrane potential (E_m), input resistance (R_N), nor the direct excitability (action potentials evoked by intracellular current injection) of these cells were affected by baclofen, these authors concluded that baclofen exerts its action through presynaptically located receptors. The occasionally observed slight hyperpolarizations were interpreted as a disfacilitatory effect caused by inhibition of excitatory interneurons.

In several subsequent *in vivo* and *in vitro* electrophysiological studies employing extracellular recording techniques in various structures, further evidence was provided that baclofen preferentially reduces excitatory synaptic transmission by a presynaptic mechanism [5–7, 29, 30, 42, 43, 52, 53, 63, 70, 82–84, 86, 88]. Thus baclofen was shown to produce profound reductions of responses to orthodromic stimulation of excitatory afferent pathways without significantly affecting responses to antidromic responses or presnyaptic fiber volleys [5, 6, 29, 42, 70, 82]. Synaptically evoked responses were shown to be reduced at doses or concentrations of baclofen that had little or no effect on chemically evoked excitation or spontaneous firing [30, 42, 52, 53, 82].

The selectivity of baclofen's depressions of synaptically evoked responses in some structures was also interpreted as being inconsistent with a postsynaptic depressant action of baclofen. Electrophysiological experiments in slice preparations of the hippocampus suggest that baclofen selectively inhibits transmission at putative glutamatergic synapses (Lanthorn and Cotman 1981). In this study, only the CA3-projections to pyramidal cells in the CA1 region (Schaffer collaterals) and mossy fiber synaptic transmission were inhibited [cf. 60]. The excitatory synaptic transmission from the lateral perforant path was insensitive to baclofen. A selective action of baclofen on synaptic tranmission mediated by excitatory amino acids is also suggested by the findings of Ault and Evans [3]. These authors described that baclofen reduced dorsal root potentials recorded from the neonatal isolated spinal cord, potentials which are also reduced by excitatory amino acid antagonists [38], whereas the excitatory responses of cervical ganglion neurons to preganglionic stimulation is not affected even by much higher concentrations. Both excitatory afferent inputs from descending pathways employing still unknown transmitters and cholinergic inputs to motoneurons are not affected by baclofen [11, 63].

In addition to these various extracellular studies, there are now several reports from investigations in which intracellular recordings were obtained that baclofen depresses EPSPs in mammalian central neurons [14, 42, 47, 55, 56, 60, 65, 73, 85, 102]. Although in some of these studies baclofen also hyperpolarized the cells (see below), it was shown that the depressions of EPSPs were not a direct consequence of these hyperpolarizations [14, 60]. In neocortical neurons, baclofen's reductions of EPSP amplitudes were independent of membrane potential over the range of values ± 30 mV from resting E_m [56]. In our studies, baclofen applications that produced 70 to 100% depressions of EPSPs typically produced only 20 to 30% decreases in R_N; baclofen's depressions of EPSPs typically outlasted its effects on E_m and R_N for several minutes. Thus in neocortical neurons, baclofen's reductions of EPSP amplitudes do not appear to be solely the consequence of its action to increase postsynaptic conductance. Another possible interpretation of such findings, however, is that baclofen preferentially increases dendritic conductance, and that only a portion of this conductance increase is detected from intracellular recordings at the neuronal soma. Such an interpretation has been made of results obtained in the hippocampus [47].

The most detailed analyses of baclofen's effects on excitatory synaptic transmission have been performed on nonmammalian preparations. Shapovalov and Shiriaev [97] studied the effect of baclofen on monosynaptic EPSPs in the frog motoneuron. These EPSPs are composed of both a chemically mediated and an electrically mediated component. Baclofen produced marked reductions of the chemically mediated component, but had no effect on the electrically mediated component of these EPSPs. From statistical analyses of single-fiber EPSPs, Shapovalov and Shiriaev concluded that baclofen acted presynaptically to reduce the release of the transmitter which generates chemically mediated EPSPs at these synapses. At the crayfish neuromuscular junction, Barry [8] found that baclofen depressed excitatory transmission without affecting the input resistance of the muscle. She was further able to show that baclofen reduced the frequency of spontaneous excitatory junction potentials without affecting their size, results which clearly indicate a presynaptic site of action. At present, the complexity of mammalian preparations has prohibited these sort of detailed analyses.

Fox et al. [42] noted that, in addition to baclofen's consistent reductions of EPSPs, baclofen also reduced the amplitude of IPSPs recorded in some cells. That baclofen reduces stimulation-evoked GABAergic inhibition in the olfactory cortex and the hippocampus was suggested from extracellular recordings of field potentials [6, 24]. Intracellular studies *in vitro* have shown that baclofen reduces the amplitude of short-latency $GABA_A$ receptor-mediated IPSPs evoked in various hippocampal neurons [14, 60, 73], neurons in the olfactory cortex [96], and neurons in the frontal neocortex [55, 56, 102]. These depressions of IPSP amplitudes are not due to the concomitant action of baclofen to hyperpolarize these neurons. Blaxter and Carlen [14] reported that baclofen's depressions of short-latency GABAergic IPSPs in hippocampal neurons persisted when the membrane potential was returned to its resting value by direct current injection. Short-latency IPSPs in rat neocortical neurons are also $GABA_A$ receptor-mediated [100, 101], and baclofen's depressions of these IPSPs were independent of membrane potential between values of -50 and -110 mV [56]. Importantly, baclofen's reductions of short-latency GABAergic IPSPs in olfactory cortical and neocortical neurons were shown to be accompanied by reductions in the conductance increases measured during these IPSPs [56, 96]. Because baclofen does not reduce responses to exogenously applied GABA or muscimol in these same neurons (see below), a postsynaptic blockade of the IPSP conductance can be excluded and these results argue strongly that baclofen reduces $GABA_A$ receptor-mediated IPSPs by a presynaptic action.

In addition to depressing chloride-dependent $GABA_A$ receptor-mediated IPSPs, baclofen has also been reported to decrease the amplitude of potassium-dependent long-latency IPSPs (slow IPSPs) in hippocampal neurons [14, 60]. Similar potassium-dependent long-latency IPSPs (times to peak of 150 to 250 ms) are also evoked in neocortical neurons [57], and baclofen consistently and markedly reduces the amplitude of these IPSPs [56, 57]. As for reductions of $GABA_A$ receptor-mediated IPSPs in these neurons, baclofen's reductions of long-latency IPSPs are independent of membrane potential and are accompanied by a reduction of the conductance increases associated with these IPSPs [56, 57].

Despite baclofen's action to reduce IPSPs, in most neurons studied baclofen's action to depress EPSPs appears to predominate and baclofen causes an increase in the stimulation intensity required to produce a synaptically evoked action potential [42, 47, 57, 85]. These baclofen-induced increases in action potential stimulation thresholds are consistent with the many extracellular studies cited above in which it was found that baclofen decreased synaptic excitability. There are reports, however, that baclofen can either increase or decrease action potential stimulation thresholds, depending on the cell population investigated and the concentration of baclofen applied [60, 73]. Although baclofen increased the stimulation threshold of synaptically evoked action potentials in

virtually every neocortical neuron tested, baclofen often caused an increase in the number of action potentials produced by suprathreshold stimulation intensities due to baclofen's blockade of IPSPs [56]. Thus there are circumstances in which baclofen can in fact produce increases rather than decreases in synaptic excitability. The action of baclofen is clearly distinguishable from $GABA_A$ receptor antagonists such as bicuculline, however, which commonly produces significant reductions in action potential stimulation thresholds and promotes the generation of epileptiform bursts of action potentials in mammalian central neurons. In contrast, baclofen has been shown to block bicuculline-induced epileptiform activity in *in vitro* preparations of the hippocampus [6, 7, 20; but see: 73] and the frontal neocortex [56]. These results also indicate that baclofen's reductions of excitatory synaptic transmission are resistant to blockade by bicuculline and indeed baclofen's reductions of EPSP amplitudes are not antagonized by this $GABA_A$ receptor antagonist [56].

The advent of *in vitro* slice preparations of the mammalian CNS has made it possible to evaluate the action of known concentrations of drugs on neurons in these preparations under steady state conditions. The EC_{50} for baclofen's depressions of excitatory synaptic transmission is approximately 1 μM and significant depressions are observed at concentrations between 10 and 100 nM [5–7, 24, 47, 56, 70, 82]. These latter concentrations are approximately equal to those obtained in the cerebrospinal fluid after systemic administration of therapeutic doses in man [66, 103]. In our study of neocortical neurons, there was no apparent difference in the concentration dependence of baclofen's reductions of EPSPs and its reductions of either type of IPSP [56].

In summary, the majority of the studies on the action of baclofen on synaptic transmission seem to favor the conclusion that baclofen reduces synaptic transmission by a presynaptic action. It should be noted, however, that none of these studies provide direct evidence for such a mechanism, with the exceptions of the studies on the frog motoneuron and the crayfish neuromuscular junction. In most studies, it was concluded that the action was presynaptic either because no evidence of a postsynaptic action was found or the postsynaptic changes that were observed were considered to be insufficient to account for the effects on postsynaptic potentials. As we already mentioned, there is, however, direct evidence for effects of baclofen on neurotransmitter release and also recent evidence that baclofen has a direct effect on postsynaptic membrane conductance. In addition, there are several electrophysiological studies which have directly addressed the effects of baclofen on presynaptic afferent terminals or experimental models thereof. These results are presented in the following sections.

Presynaptic Actions of Baclofen

The most direct evidence for a presynaptic action of baclofen is its demonstrated inhibition of neurotransmitter release. Baclofen has been shown to decrease the evoked release of several putative neurotransmitters, including monoamines [15, 40, 94] and excitatory amino acids [24, 61, 82, 89, 90]. Baclofen's action to reduce the release of excitatory amino acids is consistent with baclofen's selective inhibition of synaptic transmission that is thought to be mediated by these excitatory amino acids.

Although baclofen depresses $GABA_A$ receptor-mediated IPSPs by an action which is not postsynaptic [56, 96] and dendritically located $GABA_B$ receptors have been demonstrated on central GABAergic neurons [19, 106], baclofen does not reduce the directly evoked release of GABA from brain slices [24, 61, 89]. Collins et al. [24] demonstrated, however, that baclofen significantly reduces GABA release that is evoked by electrical stimulation of excitatory afferents. They proposed that baclofen reduces stimulation-evoked GABA release and GABAergic inhibition via its direct action to reduce the release of excitatory amino acid neurotransmitters and consequently, the excitatory drive of GABA releasing interneurons [cf. 56, 96].

Several careful electrophysiological studies have addressed the mechanism of baclofen's putative presynaptic inhibition of syn-

aptic transmission. Unfortunately these studies have not provided any consistent and positive evidence in this regard. The first suggestion that baclofen may activate presynaptic inhibitory mechanisms in the spinal cord by enhancing primary afferent depolarization as described for benzodiazepines [see: 49, 95] was abandoned after more experimental data were obtained. It was shown that baclofen depresses rather than enhances the excitability of primary afferents [22, 29, 42] and presynaptic inhibition was unchanged or reduced by baclofen [1, 71, 72].

Davidoff and Sears proposed that baclofen's depressions of afferent excitability were secondary to its action of hyperpolarizing presynaptic terminals and suggested that this action might account for baclofen's depressions of synaptic transmission [29]. The magnitude of baclofen's reductions of terminal excitability were considered to be insufficient, however, to account for its depressions of synaptically evoked responses [42]. The action potential invasion of the terminal region of afferent fibers does not seem to be impaired by baclofen, because its depressions of spinal monosynaptic reflex responses can be temporarily overcome by post-tetanic potentiation [22]. Shapovalov and Shiriaev also concluded that baclofen did not impair presynaptic terminal invasion [97].

The terminal region of primary afferent fibers carry $GABA_B$ binding sites [91] and $GABA_A$ and $GABA_B$ receptors coexist on the perikarya of small caliber primary afferent fibers [33]. However, due to their small size, primary afferent terminals have resisted analysis with intracellular recording techniques. An often used substitute for the analysis of ionic mechanisms that are supposed to occur in the terminal region are recordings from dorsal root ganglion cells *in vivo* and *in vitro*. In dorsal root ganglion neurons in culture, baclofen reduces the duration of the calcium component of action potentials [35]. Similar results were obtained in neurons of the myenteric plexus [23]. These results provide suggestive evidence that baclofen reduces neurotransmitter release by blocking inward calcium currents in presynaptic terminals [see also: 97].

Baclofen had no effect, however, on inward calcium currents recorded from cultured hippocampal neurons under voltage-clamp conditions [45], nor on the duration of the calcium component of action potentials recorded from rat neocortical neurons [56]. Barry [8] concluded that baclofen's presynaptic inhibition of synaptic transmission at the crayfish neuromuscular junction was unlikely to be the result of an effect on presynaptic calcium influx. In an *in vitro* preparation of the hippocampus, baclofen reduced the extracellular calcium concentration measured with ion-sensitive microelectrodes ([50] decreases in extracellular calcium concentration reflect the movement of calcium ions into pre- and postsynaptic elements as a consequence of neuronal activity). In these experiments, however, consistent reductions in the presynaptic component of stimulation-evoked calcium entry were only observed when baclofen was applied at a concentration of 50 μM. This is approximately 50-fold greater than the EC_{50} for baclofen's depressions of synaptic transmission (see above). Thus the findings that baclofen reduces somatic calcium currents in dorsal root ganglion or myenteric plexus neurons do not necessarily extrapolate to CNS neurons, and at present there is little evidence to support the claim that baclofen inhibits transmitter release and, thereby, synaptic transmission by reducing presynaptic calcium influx.

Postsynaptic Actions of Baclofen

Baclofen has a dose- and concentration-dependent hyperpolarizing action on some mammalian central neurons [65, 73, 79] which is associated with an increase of postsynaptic conductance [20, 44, 47, 56, 59, 76, 78, 87, 99]. This action is unaffected by blockade of synaptic transmission and is therefore indeed a direct postsynaptic action and not a disfacilitation secondary to removal of tonic excitatory input [20, 76, 78, 87, 99]. This action of baclofen results in decreases in the direct excitability of central neurons [56, 60]. The baclofen concentrations at which these effects become apparent are approximately equal

to the concentrations at which baclofen produces effects on synaptic transmission ($EC_{50} < 2$ μM) [56, 59, 78, 99].

The mean reversal potential of baclofen-induced changes in E_m and the dependence of this reversal potential on the extracellular potassium concentration indicate that these changes are secondary to an increase in the conductance of the postsynaptic membrane to potassium ions [56, 59, 78, 99]. In contrast to $GABA_A$ receptor-mediated responses, the amplitude and reversal potential of baclofen-induced changes in E_m are unaffected by reductions of the extracellular chloride concentration [59, 78] or by intracellular injections of chloride ions [14, 76, 78].

It was suggested on the basis of current clamp recordings from hippocampal neurons that baclofen-induced conductance changes were voltage-dependent [59, 78]. This was verified directly in voltage clamp experiments on cultured hippocampal neurons in which baclofen was shown to activate a potassium conductance which is voltage-dependent and inward rectifying [45]. Baclofen-induced currents were also recorded under voltage clamp conditions from rat neocortical neurons [56]. The conductance activated by baclofen is sensitive to blockade by the potassium channel blockers 4-aminopyridine and barium ions; however, the present results indicate that it is different from any of the previously identified potassium conductances [45, 59, 78, 99; but see: 14].

Baclofen-induced increases in postsynaptic potassium conductance are insensitive to blockade by concentrations of $GABA_A$ receptor antagonists that completely antagonize GABA-mediated increases in chloride conductance [20, 44, 45, 56, 59, 76, 78, 87; but see: 60]. Pentobarbitone, which increases the effect of GABA on chloride-conductance, does not alter the action of baclofen [78]. GABA can, however, mimic the action of baclofen to increase postsynaptic potassium conductance when $GABA_A$ receptors are blocked with appropriate antagonists [44, 45, 78]. These results are consistent with the conclusion that the postsynaptic effects of baclofen are mediated by $GABA_B$ receptors.

The extent to which baclofen's action to increase postsynaptic potassium conductance contributes to its depressions of synaptic transmission in various structures or to the *in vivo* effects of baclofen is debatable. As noted, there are many studies in which baclofen produced profound effects on synaptic transmission and yet no evidence for a postsynaptic action was found. That an increase in postsynaptic potassium conductance is inhibitory is obvious, however, and in some neurons the hyperpolarizations observed are as great as 20 mV. It is unfortunate that in many of these studies the effects on synaptic responses were not investigated. Gähwiler and Brown [45] proposed that if baclofen increased the potassium conductance of presynaptic terminals, this action might indirectly lead to a decrease in presynaptic calcium influx by decreasing the duration of the action potential. In neocortical neurons, however, baclofen's depressions of postsynaptic potentials and its action to increase somatic potassium conductance could be temporally dissociated.

Effect of Baclofen on Exogeneously Applied Neurotransmitters

Saito et al. [93] reported that, in low concentrations, baclofen selectively reduced the depolarizing actions of substance P in spinal motoneurons and suggested that it was a substance P antagonist. This suggestion was not supported by subsequent electrophysiological studies however [31, 37, 41, 42, 51, 84], and baclofen does not interfer with the binding of ^3H substance P [see: 17].

It was shown in several extracellularly conducted studies that baclofen can inhibit responses to exogenously applied excitatory neurotransmitters [27, 32, 41, 80, 83, 93]. In further such investigations, however, it was demonstrated that inhibitions of responses to these chemical excitants required doses or concentrations of baclofen significantly greater than those at which baclofen inhibited synaptically evoked responses [30, 42, 52, 82]. In our intracellular study of neocortical neurons, we found that applications of baclofen that produced virtually complete depressions of stimu-

lation-evoked EPSPs did not significantly reduce depolarizations produced by L-glutamate, L-aspartate, or N-methyl-D-aspartate [56]. The observed occasional and modest reductions of depolarizations produced by these excitatory amino acids were similar in magnitude and duration to baclofen-induced decreases in direct excitability, thus suggesting that they were the result of baclofen's action to increase the postsynaptic potassium conductance of rat neocortical neurons. That baclofen does not postsynaptically block conductance increases produced by these substances is directly supported by our findings that baclofen had no effect on L-glutamate-evoked inward currents recorded in neocortical neurons under voltage clamp conditions.

Baclofen applications that reduce the conductance increases associated with stimulation-evoked GABAergic IPSPs have no effect on conductance increases produced by the direct application of GABA or the $GABA_A$ agonist muscimol [56, 96]. Even at high concentrations, baclofen had no effect on currents evoked in neocortical neurons by iontophoretically applied GABA [56].

$GABA_B$ Receptor Mediated Synaptic Processes

It was proposed by Newberry and Nicoll [77, 78] that slow (long-latency) IPSPs evoked in hippocampal CA1 neurons and hyperpolarizations produced by baclofen may each be secondary to activation of $GABA_B$ receptors. According to this assumption, baclofen and the endogenous transmitter responsible for the long-latency IPSPs should act on the same population of postsynaptic receptors to increase the same postsynaptic potassium conductance. Due to the lack of established antagonists of either baclofen-induced hyperpolarizations or long-latency IPSPs, this possibility cannot be tested directly at present. Interestingly, however, baclofen reduces slow IPSPs in hippocampal neurons [14, 60] and similar IPSPs evoked in neocortical neurons [56, 57]. The mechanism of this effect of baclofen is unresolved.

Conclusions

The presently available data indicates that baclofen has both presynaptic and postsynaptic effects in the mammalian CNS. Baclofen's action to increase postsynaptic potassium conductance directly depresses neuronal excitability, however, several lines of evidence indicate that this effect is not alone responsible for baclofen's marked depression of postsynaptic potentials. Although most of the recordings probably have been obtained by somatic impalements, the data suggest that the primary mechanism by which baclofen depresses synaptic transmission is a presynaptic reduction of transmitter release. This conclusion is supported directly by the established effect of baclofen to reduce the evoked release of several putative neurotransmitters.

At present, the mechanism by which baclofen reduces presynaptic transmitter release is unclear. Presynaptic inhibition secondary to depolarization of afferent terminals can be excluded, however, and the data indicate that baclofen does not reduce synaptic transmission by hyperpolarizing presynaptic fibers sufficiently to impair action potential invasion of the terminal region. There is some evidence which suggests that baclofen may reduce transmitter release by reducing inward calcium currents in presynaptic terminals. There is no direct evidence for such a mechanism, however, and at least some calcium currents do not appear to be affected by baclofen.

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