Interplay Between Activation of GIRK Current and Deactivation of $I_h$ Modifies Temporal Integration of Excitatory Input in CA1 Pyramidal Cells

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Submitted 21 November 2002; accepted in final form 22 November 2002

Takigawa, Tomoko and Christian Alzheimer. Interplay between activation of GIRK current and deactivation of $I_h$ modifies temporal integration of excitatory input in CA1 pyramidal cells. J Neurophysiol 89: 2238–2244, 2003. First published November 27, 2002; 10.1152/jn.00957.2002. Trains of brief iontophoretic glutamate pulses were delivered onto the apical dendrites of CA1 pyramidal cells at variable frequencies (3–100 Hz) to examine how the activation of a G protein–activated, inwardly rectifying K ($I_{GIRK}$) conductance alters the postsynaptic processing of repetitive excitatory input. Application of the GIRK channel agonist baclofen (20 μM) reduced the amplitude of individual glutamate-evoked postsynaptic potentials (GPSPs) and attenuated summation of GPSPs so that higher stimulus intensities were required to fire the cell. Notably, GIRK channel activation not only decreased GPSPs, but also suppressed the subsequent afterhyperpolarization (AHP), which arises from a transient deactivation of the hyperpolarization-activated cation current ($I_h$). Voltage-clamp recordings ruled out a direct modulatory action of baclofen on $I_h$. GIRK channel activation alone accounts for AHP suppression, firstly because, with smaller GPSP amplitudes, fewer $I_h$ channels are deactivated, resulting in a diminished AHP, and secondly because, owing to its progressive increase in the hyperpolarizing direction, the GIRK conductance shunts a large portion of the remaining AHP. We provide experimental evidence that the suppression of the $I_h$-dependent AHP by GIRK channel activation bears particular significance on the processing of repetitive excitatory inputs at frequencies at which the deactivation kinetics of $I_h$ exert a prominent depressing effect. In functional terms, activation of GIRK current not only produces a time-independent mitigation of incoming excitatory input, which results directly from the opening of an instantaneous K$^+$ conductance, but might also cause a time-dependent redistribution of synaptic weight within a stimulus train, which we link to an interplay with the deactivation of $I_h$.

INTRODUCTION

At excitatory synapses of the CNS, the transfer of presynaptic action potentials to the postsynaptic neuron can be profoundly influenced by both presynaptic and postsynaptic mechanisms. For example, repetitive firing of presynaptic fibers has been shown to evoke a sequence of either gradually increasing or decreasing excitatory postsynaptic potentials (EPSPs) in the target cell, which is usually referred to as facilitation or depression. Although axons from a single presynaptic neuron might produce facilitating and depressing postsynaptic responses in different cells (Markram et al. 1998; Reyes et al. 1998), demonstrating the target cell specificity of these phenomena, synaptic facilitation and depression have been largely attributed to the presynaptic site, reflecting an increase or decrease, respectively, in the probability of transmitter release (Thomson 2000). In addition to such presynaptically mediated actions, the passive and, more so, the active electrical properties endow the postsynaptic neuron with enormous computational power to control and modify the integration of EPSPs in its somatodendritic compartments. With the advent of patch-clamp recordings from dendrites of various types of CNS neurons, it became evident over the past several years that dendrites were not only capable of generating Na$^+$ and Ca$^{2+}$ spikes, but that they also possessed the complete repertoire of voltage-dependent ion currents that are activated in the subthreshold range and thus bear particular significance on the integration of phasic and tonic input (Schwindt and Crill 1997; reviewed in Magee 2000; Reyes 2001). Underscoring the functional significance of these currents for the processing of synaptic signals, most of them are present at higher densities in the dendrites than in the soma when investigated in pyramidal neurons of the neocortex and hippocampus. This holds for the transient K$^+$ (A-type) current (Hoffman et al. 1997), for the low voltage–activated (T-type) Ca$^{2+}$ current (Christie et al. 1996), and for the hyperpolarization-activated inward rectifier current ($I_h$) (Magee 1998). We have recently demonstrated that a similar somatodendritic gradient of channel density also exists for G protein–activated, inwardly rectifying K$^+$ (GIRK) channels (Takigawa and Alzheimer 1999). These channels are recruited by a large spectrum of neurotransmitters and modulators, including serotonin, noradrenalin, GABA (acting via GABA$_B$ receptors), acetylcholine, adenosine, somatostatin, and opioid peptides (Dascal 1997; Yamada et al. 1998). Here we used the GABA$_B$ agonist baclofen to investigate the effects of GIRK current activation on the temporal processing of EPSPs that were elicited by trains with variable interstimulus intervals. Since GIRK channel agonists also exert presynaptic effects on transmitter release, which are apparently not related to GIRK channel activation (Lüscher et al. 1997), we used very short iontophoretic glutamate pulses delivered to the apical dendrite of CA1 hippocampal pyramidal cells to isolate the postsynaptic GIRK current-mediated effect. We report here that GIRK channel activation has two different effects on the EPSP-like voltage deviations: one results from a shunting inhibition of EPSPs due to the opening of GIRK channels; the
other results from an indirect modulatory effect of the GIRK conductance on an afterhyperpolarization (AHP)-like undershoot of the membrane potential that is mediated by \( I_h \) (Pape 1996; Storm 1989). Whereas the former equally affects all EPSPs in a train, the latter redistributes the synaptic weight between the incoming excitatory inputs.

METHODS

Using standard procedures, transverse hippocampal slices, 300 μm thick, were prepared from the brain of Wistar rats (2–3 wk old), which were deeply anesthetized with a ketamine–xylazine solution (1 ml/kg K-113, RBI/Sigma, Deisenhofen, Germany) prior to decapitation. All experiments were carried out according to the guidelines and with the approval of the Animal Care Committee at the University of Munich. After dissection, slices were incubated in warmed (35°C) artificial cerebrospinal fluid (ACSF) for 25 min and then maintained at room temperature (21–24°C) in the same solution. ACSF was constantly gassed with 95% O\(_2\)-5% CO\(_2\) and had the following composition (in mM): 125 NaCl, 3 KCl, 2 CaCl\(_2\), 2 MgCl\(_2\), 1.25 NaH\(_2\)PO\(_4\), 25 NaHCO\(_3\), and 10 d-glucose (pH 7.4). For electrophysiological measurements, individual slices were transferred to the recording chamber that was mounted on the stage of an upright microscope (Olympus BX50WI). Dodt infrared gradient contrast in conjunction with a contrast-enhanced CCD camera (Hamamatsu) served to identify somata and dendritic processes of pyramidal cells in the hippocampal CA1 region. During experiments, slices were kept submerged in ACSF that was constantly exchanged by means of a gravity-driven superfusion system (flow rate 2–3 ml/min).

EPSP-like waveforms were evoked using short iontophoretic pulses of Na–glutamate (250 mM), which was locally applied onto the apical dendrite of CA1 pyramidal neurons (100–150 μm from the soma) by means of a new iontophoretic device with fast capacity compensation (MVC-02C, npi, Tamm, Germany). In most experiments, iontophoretic pulses 0.5- to 1-ms long were delivered as trains of four stimuli at 3–100 Hz. Illustrated membrane potential responses to glutamate are averages of four consecutive sweeps. To functionally isolate the recorded neuron from synaptic input arising in neighboring neurons coactivated by glutamate pulses, experiments were conducted in the presence of TTX (1 μM) unless otherwise stated. The N-methyl-d-aspartate (NMDA) component of EPSPs was suppressed with (−)-2-amino-5-phosphonopentanoic acid (−APV) (20 μM) to eliminate nonlinearities due to NMDA receptor activation. Spontaneous inhibitory postsynaptic potentials (IPSPs) were abolished with bicuculline (10 μM). Using the same pharmacological cocktail, EPSP-like waveforms were also evoked by trains of triangular current pulses that were delivered through the recording pipette. Electrophysiological signals obtained in the whole-cell configuration of the patch-clamp technique were recorded, amplified, and analyzed with the use of an Axopatch 200B amplifier (Axon Instruments) in conjunction with a Digidata 1200 interface and pClamp 6 software (Axon Instruments). All recordings were made at room temperature. Recording pipettes were filled with (in mM) 130 KMeSO\(_4\), 10 KCl, 2 MgCl\(_2\), 10 EGTA, 10 HEPES, 2 Na\(_2\)-ATP, and 2 Na\(_2\)-GTP (pH 7.25–7.30) and had a resistance of about 5 MΩ. In the whole cell configuration, series resistance was about 12 MΩ, which was, in voltage-clamp experiments, compensated by 75–85%. Voltage readings were corrected for experimentally determined liquid junction potentials (10 mV). TTX was purchased from Alomone Labs (Jerusalem, Israel), all other substances were from Sigma (Deisenhofen, Germany).

Data are presented as means ± SE. Statistical analysis (t-test, significance set at \( P < 0.05 \)) was performed with the use of Origin (4.1) software.

RESULTS

Effects of GIRK conductance on summation of excitatory inputs

After pharmacological suppression of GABA\(_A\) and NMDA receptors, very brief iontophoretic pulses of glutamate delivered onto the apical dendrite of CA1 pyramidal cells elicited pure AMPA receptor–mediated EPSP-like voltage deviations, which we refer to as glutamate-evoked postsynaptic potentials (GPSPs). To examine the effect of GIRK channel activation on the summation of GPSPs, we applied four identical pulses of glutamate at a membrane potential of −80 mV and varied the interstimulus interval between 300 and 10 ms (\( n = 4 \)). As illustrated in Fig. 1, the progressively shorter intervals between the glutamate pulses led to an increasing summation of GPSPs, which eventually reached the threshold for the firing of an action potential (Fig. 1A–D, left). When we repeated this stimulation protocol in the presence of the GIRK channel activator baclofen (20 μM), we observed a substantial attenuation of individual GPSPs (Fig. 1, A and B, middle), which consequently failed to sum up to the firing threshold (Fig. 1, C and D, middle). This inhibitory effect of baclofen was fully reversible in control solution (data not shown), as demonstrated previously (Takigawa and Alzheimer 2002). That this effect of baclofen was indeed mediated by the activation of GIRK channels was demonstrated by the reversal of the drug-induced inhibition of GPSPs by Ba\(^{2+}\), which was applied at a concentration (200 μM) that suppresses selectively inwardly rectifying K\(^+\) channels. As during the application of baclofen, DC injection through the recording pipette served to hold the membrane potential at −80 mV, thereby maintaining equal driving forces for GPSPs. Without DC injection, the neurons had a resting membrane potential (RMP) of −70.7 ± 2.0 mV under control conditions and −77.3 ± 2.6 mV in baclofen (\( n = 15 \)). It is noteworthy that Ba\(^{2+}\) not only reversed the attenuation of GPSPs by baclofen, but actually made GPSPs larger than under control conditions (Fig. 1A–C, right), so that the suprathreshold stimulation now elicited a doublet of action potentials (Fig. 1D, right). Based on previous work from our laboratory (Takigawa and Alzheimer 2002), we attribute this apparently overshooting response to Ba\(^{2+}\) to the fact that the cation not only inhibits GIRK channels, but also constitutive inward rectifier K\(^+\) channels, which exert a tonic control over GPSPs.

Effects of GIRK conductance on AHP

Although it appears that the predominant effect of baclofen is a reduction of the size of GPSPs so that a stronger input is required to fire the neuron, closer examination revealed a second effect, namely the suppression of the AHP-like undershoot that typically followed sub- and suprathreshold GPSPs (Fig. 1, C and D, arrows). The suppression of AHP was also observed, when the membrane potential was depolarized by DC injection to its control value during baclofen application (Fig. 1D, inset of middle panel), ruling out that this effect was a peculiarity of more negative membrane potentials. To elucidate the ionic mechanism underlying the inhibition of AHPs by baclofen, we performed experiments in the presence of TTX (1 μM), which excludes any interference by slow IPSPs. As illustrated in Fig. 2A, baclofen continued to abrogate AHPs in

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AHP reduction did not differ significantly between the 2 groups. Data were lumped together, since the relative AHP reduction did not differ significantly between the 2 groups. B: the I_h inhibitor ZD7288 (20 μM) consistently enhanced GPSP amplitude and completely abrogated AHPs (n = 4, neurons were held at −110 mV). Effect of ZD7288 was complete within <20 min of drug washin. **P < 0.01.
Although we used iontophoretic application of brief glutamate pulses in the presence of TTX to isolate the effects of baclofen on the somatodendritic processing of EPSPs, the interpretation of our results might be possibly confounded by effects of baclofen and glutamate on presynaptic glutamate release and/or on the desensitization properties of postsynaptic glutamate receptors. To demonstrate that the reduction of AHPs in baclofen resulted indeed from an interplay between baclofen, namely reduction of depolarizing inputs and decline of subsequent undershoot, were fully reproduced under these recording conditions (n = 6). To determine to what extent the baclofen-induced reduction of GPSP amplitude is responsible for the decrease in AHP, we enhanced, in the continued presence of baclofen, the strength of the iontophoretic glutamate pulse until we obtained GPSP waveforms that closely matched those of control. As illustrated in Fig. 3B, this protocol restored only partially the size of the control AHP, indicating that, in baclofen, the decreased amplitude of the preceding depolarization is not the sole cause of the AHP suppression. This experiment still leaves open the question of whether baclofen directly affects \( I_h \) or whether the activation of the GIRK conductance is sufficient to account for a concomitant reduction of AHPs. We used two experimental paradigms to address this issue. In the first set of experiments, we examined whether the baclofen-induced suppression of AHPs is sensitive to the GIRK channel blocker \( \text{Ba}^{2+} \), which does not inhibit \( I_h \) in the micromolar range. If added to a baclofen-containing bath solution, \( \text{Ba}^{2+} \) (200 \( \mu \)M) indeed produced a complete reversal of the decrease in AHP amplitude (Fig. 3, C and D), suggesting that baclofen does not exert an independent effect on \( I_h \). Vice versa, preincubation with \( \text{Ba}^{2+} \) abrogated any effect of baclofen on GPSP amplitude and subsequent AHP (Fig. 3E).

It might be still argued, however, that, owing to the stronger depolarization attained by GPSPs in \( \text{Ba}^{2+} \), more \( I_h \) is deactivated, thereby giving rise to a larger AHP. To dispel any concerns regarding the ionic mechanism of AHP suppression, we performed, as the second set of experiments, voltage-clamp recordings and examined the action of baclofen on the I-V relationship of CA1 pyramidal cells in the presence of \( \text{Ba}^{2+} \) (200 \( \mu \)M, \( n = 4 \)). Figure 4A depicts the current responses to a hyperpolarizing voltage step from \(-80 \) to \(-150 \) mV. \( \text{Ba}^{2+} \) reduced the apparently instantaneous inward rectification that is attributed to constitutive inward rectifier \( K^+ \) current, but did not affect the gradually developing inward current that results from the slow activation of \( I_h \). If examined during inhibition of GIRK channels, i.e., in the presence of \( \text{Ba}^{2+} \), baclofen did not alter the hyperpolarizing current response (Fig. 4A) nor the neuronal I-V relationship (Fig. 4B), indicating that the suppression of AHPs in current-clamp experiments is secondary to the activation of the GIRK conductance.

**Effects of GIRK conductance on depressing response to repetitive excitatory input**

What is the functional significance of the decrease of AHPs that accompanies the opening of GIRK channels? We speculated that this effect should be particularly important for repetitive excitatory inputs whose interstimulus intervals allow for substantial deactivation of \( I_h \) during the train. To mimic this situation, we applied a 14-Hz train of four identical glutamate pulses. Owing to the gradual deactivation of \( I_h \) and the resulting buildup of the AHP, this protocol gave rise to a sequence of progressively declining GPSPs (Fig. 5A, black trace). In the presence of baclofen, the amplitude of GPSPs was reduced as expected for a \( K^+ \) channel activator (Fig. 5A, red trace). It is noteworthy, however, that a second, time-dependent effect occurred: the extent of inhibition of GPSPs within a train became substantially smaller from stimulus to stimulus. This

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**FIG. 3.** Suppression of AHP by baclofen requires GIRK channel activation. **A:** brief triangular current pulses through whole cell pipette served to mimic trains of EPSPs (membrane potential \(-90 \) mV). Baclofen (20 \( \mu \)M) reduced amplitude of depolarizations and strongly attenuated subsequent AHPs. **Inset:** Like-colored columns indicate baclofen-induced decline of AHP after normalization to control. **B-E:** effects of baclofen on GPSPs. Dashed line indicates \(-100 \) mV **B:** suppression of AHP by baclofen (20 \( \mu \)M) only partially recovered when stimulus intensity was enhanced to produce GPSP of control amplitude. **Inset:** like-colored columns indicate relative change in AHP amplitude in baclofen before (red) and during restoration of control GPSP amplitude (blue, \( n = 5 \)). **C** and **D:** suppression of AHPs by baclofen at low- (**C**) and high-frequency stimulation (**D**) is reversed by \( \text{Ba}^{2+} \) (200 \( \mu \)M). **Inset** in **C** summarizes relative change of AHP following first GPSP at low frequency stimulation (\( n = 4 \)). **E:** if baclofen was added to a \( \text{Ba}^{2+} \) (200 \( \mu \)M)-containing bath solution, it failed to affect GPSP or AHP. (**C** = 2, stimulation at 33 Hz). * \( P < 0.05 \), ** \( P < 0.01 \).
effect of baclofen was also observed if we used brief triangular somatic current injections in lieu of iontophoretic glutamate pulses to mimic trains of depolarizing inputs. Again, baclofen not only reduced each depolarizing voltage deviation, but also equalized the response (Fig. 5B, n = 4). To quantify the intriguing action of baclofen, we compared the ratio between peak amplitudes of the first or the second GPSP and the last (fourth) GPSP (Fig. 5C) and calculated the relative reduction by baclofen for each GPSP in a train (Fig. 5D). These data indicate that, for later GPSPs, the inhibitory potency of baclofen becomes significantly smaller compared with the first GPSP. In other words, baclofen transformed a strongly depressing response into a mildly depressing one.

The pivotal role of the $I_h$-associated AHP for the depressing response was corroborated in the experiments depicted in Figs. 6 and 7. First, we used different stimulus intensities to evoke GPSPs of various size. As shown in Fig. 6, a stepwise increase of the iontophoretic current from 200 to 300 nA not only increased the amplitude of the GPSPs but also introduced a time-dependent effect, so that a response that displayed no time-dependent change in amplitude at 200 nA was transformed into a depressing response at higher stimulus intensities. The gradual enhancement of AHPs with each increase in stimulus strength argues strongly in favor of $I_h$ deactivation being the underlying ionic mechanism of this depressing response. In fact, inhibition of $I_h$ with ZD7288 (20 μM) completely abrogated the progressive depression of GPSPs in this stimulus paradigm (Fig. 7A, n = 3). Under this condition, baclofen was no longer capable of altering the relative weight of GPSPs within a stimulus train but exerted an equally inhibitory action on all GPSPs (Fig. 7B, n = 4).

**DISCUSSION**

Using brief iontophoretic glutamate pulses (in lieu of afferent stimulation), we found that activation of GIRK channels exerts two different effects on the postsynaptic processing of repetitive excitatory input. First, the opening of GIRK channels produces an increase in membrane conductance, which shunts the excitatory synaptic current in part, thereby reducing the time-dependent change in amplitude at 200 nA was transformed into a depressing response at higher stimulus intensities. The gradual enhancement of AHPs with each increase in stimulus strength argues strongly in favor of $I_h$ deactivation being the underlying ionic mechanism of this depressing response. In fact, inhibition of $I_h$ with ZD7288 (20 μM) completely abrogated the progressive depression of GPSPs in this stimulus paradigm (Fig. 7A, n = 3). Under this condition, baclofen was no longer capable of altering the relative weight of GPSPs within a stimulus train but exerted an equally inhibitory action on all GPSPs (Fig. 7B, n = 4).
The AHP (Maccaferri et al. 1993; Pape 1996; Spain et al. 1987).  

brane potential back to its original value, thereby terminating  
when glutamate pulses were delivered at frequencies of 10  
prevents summation of EPSPs (cf. Magee 1999; Williams and  
summation. Here we show that slow deactivation of  
strated that the kinetics of  
progressive declining responses. We relate the second effect to  
acting of GIRK current provides an effective mechanism to  
linear proper-

size of the EPSPs arriving at the soma (Seeger and Alzheimer  
As a consequence, summation of EPSPs is reduced, and  
stronger or more frequent input signals are required to initiate  
an action potential in the neuron. Second, activation of GIRK  
current alters the time-dependent transfer characteristics of the  
neuron. In the presence of the GIRK channel agonist baclofen,  
a strongly depressing response pattern was substantially attenu-
ated so that later stimuli in the train no longer evoked pro-
gressively declining responses. We relate the second effect to  
an intricate interplay between the activation of GIRK current  
and the deactivation of $I_h$. This notion was corroborated by  
experiments in which we reproduced the effects of baclofen  
using trains of brief current pulses instead of glutamate pulses  
to simulate trains of EPSPs.

Under control conditions, incoming excitatory signals deac-
tivate a standing $I_h$ by virtue of their depolarizing action on the  
membrane potential, producing an effectively outward current  
during the input. On repolarization, the membrane potential  
trajectory displays a transient undershoot in the hyperpolariz-
ing direction, before the slow activation of $I_h$ brings the mem-
brane potential back to its original value, thereby terminat-
ing the AHP (Maccaferri et al. 1993; Pape 1996; Spain et al. 1987).  
Because the activation and deactivation kinetics of $I_h$ are much  
slower than those of GIRK current, which are almost instant-
aneous, activation of the latter will not per se introduce a  
time-dependent component in the process of synaptic input  
trains.

In elegant studies of pyramidal cells of rat hippocampus and  
eocortex, Magee (1999) and Williams and Stuart (2000) demon-
strated that the kinetics of $I_h$ in particular of dendritic $I_h$ are  
an essential intrinsic mechanism that allows for normalization,  
i.e., site independence of EPSP time course and temporal  
summation. Here we show that slow deactivation of $I_h$ not only  
prevents summation of EPSPs (cf. Magee 1999; Williams and  
Stuart 2000) but might also account for a depressing response  
when glutamate pulses were delivered at frequencies of 10–14  
Hz. This depressing response and the subsequent AHP were  
largely attenuated by baclofen. Owing to the shunting inhibi-
tion of the baclofen-induced GIRK conductance, the first GPSP  
in a train produced less membrane depolarization, which, in  
turn, reduced the amount of deactivation of $I_h$. With less $I_h$  
deactivating during the train, less effective outward current  
becomes available to dampen the subsequent GPSPs. In addi-
tion, the progressive increase in membrane conductance in the  
hyperpolarizing direction resulting from the nonlinear prop-
ers of the GIRK current provides an effective mechanism to  
further mitigate the AHP.

The following observations link the apparently time-depen-
dent effect of GIRK current activation on temporal processing  
to its (indirect) effect on the $I_h$-associated AHP.  

1) The de-
pressing response and the subsequent AHP were abrogated in  
the presence of the $I_h$ inhibitor ZD7288.  

2) After suppression  
of $I_h$, baclofen failed to exert a time-dependent effect on  
repetitive excitatory input.  

3) Inhibition of GIRK channels by Ba$^{2+}$ reversed the baclofen-induced decrease of AHPs.  

4) In voltage clamp experiments, baclofen failed to influence $I_h$  
during suppression of GIRK channels, consistent with previous  
findings from substantia nigra neurons (Watts et al. 1996; but  
see Jiang et al. 1993).

Depending on RMP and input frequency, time-dependent  
($I_h$ and time-independent hyperpolarizing inward rectifica-
tion (GIRK current) might have profound influence on the temporal  
weighing of repetitive excitatory input. Notably, both types of  
inward rectifiers are targets of a broad variety of neurotrans-
mitters and -modulators, which use changes in intracellular  
cAMP and a membrane-delimited G protein–dependent path-
way to control the gating of $I_h$ and GIRK current, respectively  
(Andrade et al. 1986; Pedarzani and Storm 1995). From this, a  
scenario emerges by which the processing of incoming signals  
occur in a highly dynamic fashion so that the upregulation of a  
single conductance, as demonstrated here for GIRK current,  
is sufficient to substantially alter the computational properties  
of the neuron. The present experiments do not allow us to infer  
at which location along the somatodendritic axis the GIRK  
channel activation has the strongest effect. It is well estab-
lished, however, that the density of both GIRK channels and H  
channels is severalfold higher in the apical dendrite than in the  
soma (see INTRODUCTION). It is hence easily conceivable that  
both channels are expressed in close proximity to each other,  
allowing for an intimate biophysical interaction. It is not  
known yet whether the two channel types are colocalized on  
dendrites or dendritic processes such as spines, where their  
interplay would have the most immediate impact on incoming

![FIG. 6. Increase of stimulus intensity induces depressing response. A train of four iontophoretic glutamate pulses (14 Hz) was delivered at stimulus intensities of 200, 250, and 300 nA. Note the gradual transformation of a regular into a depressing response, which coincides with the gradual increase in AHP amplitude (arrow). Dashed line indicates $-90$ mV. Inset: data from $n = 4$ experiments. Like-colored columns indicate ratio between first and fourth GPSPs for the 3 recording conditions. **P < 0.01.](http://jn.physiology.org/)

![FIG. 7. Inhibition of $I_h$ abrogates depressing response and time-dependent action of baclofen. A: application of ZD7288 (20 μM) enhanced GPSP amplitudes and abrogated the depressing response to this 10-Hz stimulation. Note the concomitant inhibition of the AHP. B: during inhibition of $I_h$, baclofen (20 μM) produced an equal reduction of all 4 GPSPs. Dashed line indicates $-110$ mV. Recordings in A and B are from the same neuron.](http://jn.physiology.org/)
excitatory input. Although the subcellular (co)localization of GIRK and H channels on dendrites remains to be determined, we would predict that the dendrites are the site where signal processing is most sensitive to the interaction between GIRK current and $I_{\text{h}}$.

We thank L. Kargl for technical assistance.

This work was supported by the Deutsche Forschungs Gemeinschaft (SFB 391 A9) and a Heisenberg-Fellowship to C. Alzheimer.

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