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My close encounter with $GABA_B$ receptors

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Abstract

In this review, I summarize the sequence of events involved in characterizing the functional role of $GABA_B$ receptors in the CNS and their involvement in synaptic transmission. The story was launched with the realization that baclofen was a selective agonist of $GABA_B$ receptors. This lead to the discovery in the CNS that $GABA_B$ receptor activation could result in a presynaptic inhibition of transmitter release as well as a postsynaptic increase in potassium conductance. Based on this information, it was found that GABA also activated a potassium conductance. A role for $GABA_B$ receptors in synaptic transmission was suggested by the fact that activation of GABAergic interneurons could generate a slow IPSP mediated by an increase in potassium conductance. To link this slow IPSP to $GABA_B$ receptors required a selective $GABA_B$ antagonist. Phaclofen was the first antagonist developed and was found to antagonize the action of baclofen and the $GABA_A$ independent action of GABA. Most importantly, it blocked the slow IPSP. The properties of $GABA_A$ and $GABA_B$ IPSPs are remarkably different. $GABA_A$ IPSPs powerfully inhibit neurons and rapidly curtail excitatory inputs. This greatly enhances the precision of excitatory synaptic transmission. $GABA_B$ IPSPs are recruited with repetitive and synchronous activity and are postulated to modulate the rhythmic network activity of cortical tissue.

Keywords: $GABA_B$ receptors; Synaptic transmission; Baclofen

1. Introduction

In this article, I review my rather tortuous journey exploring the physiological role of $GABA_B$ receptors in the CNS. It was the elegant series of experiments by Norman Bowery [1] that first established that GABA could act at entirely distinct sites from that responsible for activating chloride conductance. These studies relied heavily on the finding that baclofen, an analogue of GABA, caused presynaptic inhibition of transmitter release in the superior cervical ganglion. Importantly, GABA mimicked this inhibitory action, and the classic GABA receptor antagonists, picrotoxin and bicuculline, had no effect on this action. This lead Bowery to proposed the existence of two subtypes of GABA receptor, a $GABA_A$ receptor that increased chloride permeability and was blocked by picrotoxin and bicuculline, and a $GABA_B$ receptor for which baclofen was a selective agonist [2,3]. This receptor caused a presynaptic decrease in transmitter release by an unknown mechanism. Studies by Dunlap and co-worker [4,5] on cultured sensory neurons showed that both baclofen and GABA could inhibit calcium currents and this action was resistant to picrotoxin. These neurons also expressed $GABA_A$ receptors coupled to a chloride conductance increase. Thus, a single neuron appeared to express both $GABA_A$ and $GABA_B$ receptors that initiated entirely distinct actions.

2. $GABA_B$ receptors open potassium channels

$GABA_B$ receptor binding was found to be present at high amounts throughout the brain [1] and ionotophoretic application of baclofen depressed neuronal activity [6]. In addition, numerous studies indicated that baclofen depressed transmitter release in the CNS [7]. Thus, we decided to look for an action of baclofen in hippocampal pyramidal cells. The plan was to look at the effect of baclofen on synaptic transmission and calcium spikes, the two previously described actions of baclofen. However, much to our surprise baclofen had a potent and highly

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reproducible hyperpolarizing action on pyramidal cells (Fig. 1) [8,9]. This action was clearly not due to an increase in chloride conductance because in neurons loaded with chloride the baclofen response was still hyperpolarizing, despite the fact that GABA responses were depolarizing. Further studies indicated that the response was due to an increase in potassium conductance [9,10]. Finally, the response was resistant to the $GABA_A$ receptor antagonist bicuculline. These results had a profound affect on me. Up to this point, it was assumed that all of the actions of GABA in the CNS were mediated by an increase in chloride conductance and this assumption was used in interpreting complex responses generated by the ionotophoretic application of GABA to the dendrites of hippocampal pyramidal cells [11]. Thus, with the knowledge that baclofen, a $GABA_B$ selective agonist, could activate a potassium conductance we went back to see if GABA, itself, could cause an increase in potassium conductance. Indeed, in the presence of high concentrations of $GABA_A$ antagonists we were able to detect a hyperpolarization induced by GABA that was due to an increase in potassium conductance [9]. Interestingly, re-examining figures in our earlier publication [11] shows the presence of bicuculline resistant responses to GABA ionotophoresis that had a reversal potential far more negative than that for chloride.

3. $GABA_B$ receptors couple to a GIRK2 containing potassium channel

What is the nature of the potassium conductance activated by $GABA_B$ receptors? The conductance has a delayed onset of 20 ms and lasts for many hundreds of ms. These findings are very similar to the properties of the cardiac muscarinic potassium current, suggesting that the receptor might be indirectly coupled to the potassium channel, as is the case for the cardiac current. Hippocampal pyramidal cells also respond to serotonin acting on 5-HT1A receptors generating a potassium conductance identical to that generated by $GABA_B$ receptor activation [12]. Furthermore, fully activating the conductance with one agonist entirely occludes the action of the other, suggesting that the two receptors act on the same limited pool of potassium channels (Fig. 2) [13]. Evidence that G-proteins

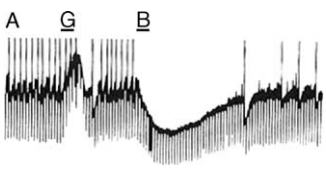

Fig. 1. Baclofen hyperpolarizes hippocampal pyramidal cells by a chloride independent mechanism. Loading a pyramidal cell with chloride with a KCl-filled electrode causes the response to ionotophoretic GABA (G; 10 nA) to be depolarizing, while the response to baclofen (B; 70 nA) remains hyperpolarizing. The resting potential was −54 mV. Reprinted with permission from [9].

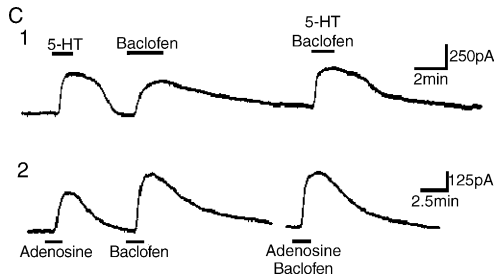

Fig. 2. 5-HT, baclofen, and adenosine hyperpolarize pyramidal cells through a common conductance mechanism. (1) Continuous voltage clamp record of the outward currents evoked by 5-HT (30 μM) and baclofen (30 μM) applied in the bath alone or together. Reprinted with permission from [13]. (2) Voltage clamp records of the outward currents evoked by adenosine (100 μM) and baclofen (30 μM) applied in the bath alone or together. Reprinted with permission from [48].

provided the link between the receptor and potassium channels was found by applying GDPβS, which blocks G-protein function, and by applying GTPγS, which locks G-proteins into an activated state [13]. GDPβS blocked the action of baclofen and serotonin and GTPγS generated a potassium conductance that occluded the action of the two

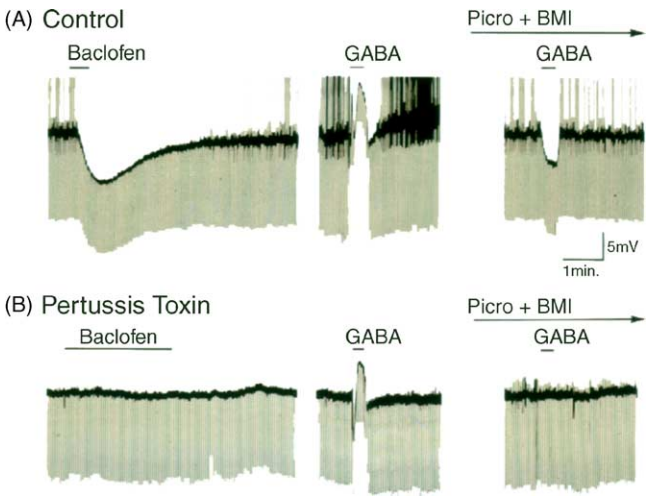

Fig. 3. Comparison of the postsynaptic actions of baclofen and GABA in control and pertussis toxin-treated rats. (A) Intracellular recordings from a pyramidal neuron in a control rat. Baclofen (100 nA) applied by microionotophoresis in the dendritic field of the neuron induces a large, reversible hyperpolarization. GABA (100 nA) applied by microionotophoresis on the dendrites induces a complex response including a depolarization and a hyperpolarization mediated, respectively, by $GABA_A$ and $GABA_B$ receptor activation. Ten minutes after addition of bicuculline methiodide (BMI, 100 μM) and picrotoxin (Picro, 50 μM) to the superfusion medium, GABA evokes a pure hyperpolarizing response. Downward deflections in the records are hyperpolarizing responses to constant current pulses applied at 0.3 Hz, which were used to monitor the input resistance of the cell. Resting membrane potential is −57 mV. (B) This cell was recorded from a slice from a rat with pertussis toxin (PTX). Baclofen (30 μM) was applied in the bath during the time indicated by the bar, but the postsynaptic response is absent. GABA (60 nA) applied by microionotophoresis in the dendritic field induces a $GABA_A$ depolarizing response. In the presence of bicuculline and picrotoxin, GABA does not evoke the hyperpolarizing response present in normal rats. Resting membrane potential is −55 mV. Calibrations in (A) also apply to (B). Reprinted with permission from [14].

agonists. Finally, the actions of baclofen and serotonin were blocked by pertussis toxin, which selectively inactivates G-proteins of the $G_{i/o}$ type (Fig. 3) [13,14]. These findings strongly suggested that $GABA_B$ receptors, as well as 5-HT1A receptors, activate a G-protein of either the G_i or G_o type, which in turn activates potassium channels. These potassium channels are referred to as G-protein-coupled potassium channels or GIRKs. Four subunits have been cloned and the channels are tetramers consisting of GIRK1 and one of the other three subunits. The most prevalent GIRK channel in the CNS consists of GIRK1 and GIRK2 heteromers. The GIRK2 subunit has been knocked out in mice leading to a severe loss of GIRK1 protein. These mice permitted us to determine if these channels are responsible for the actions of GABA and serotonin [15]. The GIRK2 knockout mouse was an extremely valuable tool because claims had been presented that GABA and the slow IPSP transmitter activated a different potassium conductance from baclofen [16–18], challenging our proposal that these two agonists acted on the same receptor [9,19] and that baclofen and serotonin activated potassium channels with different single channel conductances [20], challenging our proposal that these two receptors shared the same conductance mechanism [13]. We found that the postsynaptic action of GABA, baclofen and serotonin, as well as the slow IPSP, in hippocampal pyramidal cells was absent in the GIRK2 knockout (Fig. 4) [15]. In addition, we found that the presynaptic inhibitory action of baclofen was unaltered in these mice, indicating that GIRK2 containing channels are not involved in the presynaptic action. A similar loss of postsynaptic currents has been reported for the *weaver* mouse, which has a pore mutation in the GIRK2 subunit [21].

4. $GABA_B$ receptors mediated the slow IPSP in hippocampal pyramidal cells

Since hippocampal pyramidal cells possess postsynaptic $GABA_B$ receptors, we next carried out experiments to determine if this receptor is involved in synaptic transmission. Stimulation of afferents to CA1 hippocampal pyramidal cells results in a stereotyped series of potentials. These include: (1) an excitatory post-synaptic potential (EPSP), which if large enough, generates a single action potential; (2) a subsequent hyperpolarizing postsynaptic

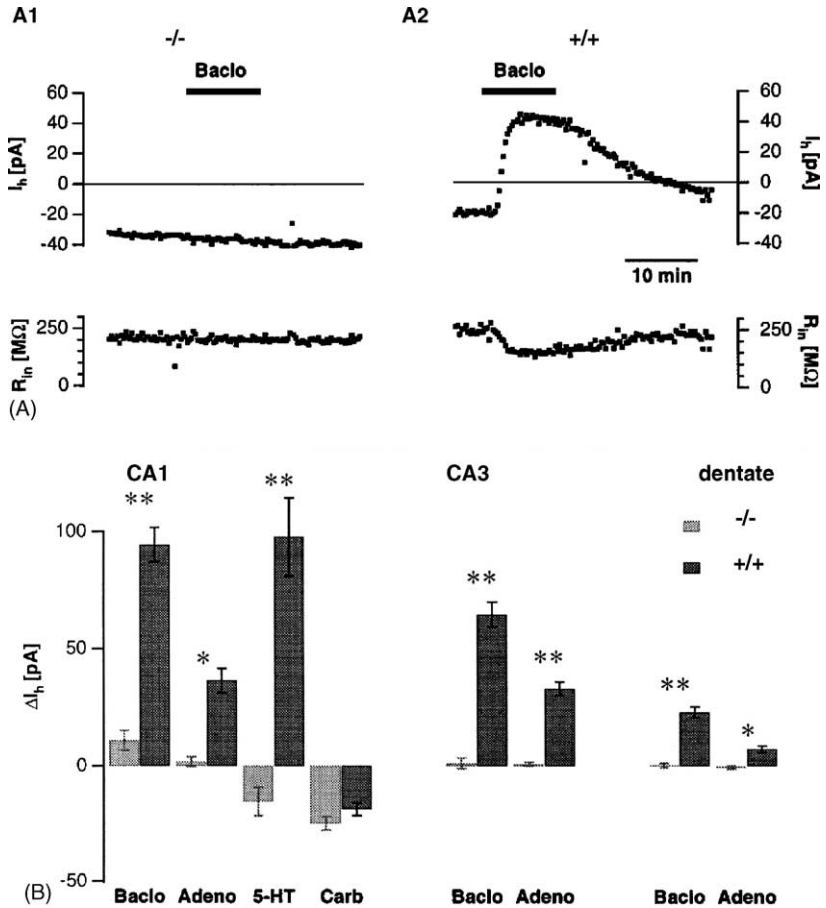

Fig. 4. Reduction of G-protein-coupled receptor-mediated outward currents in the $GIRK2^{-/-}$ mouse. (A1) Holding current (upper trace) and input resistance (lower trace) of a representative CA1 pyramidal cell voltage clamp ($V_h = -70$ mV) in a $GIRK2^{-/-}$ mouse. Neither parameter changed when baclofen (40 μM) was applied to the bath. (A2) In a $GIRK2^{+/+}$ cell, bath application of baclofen led to an outward current (upper trace, $V_h = -79$ mV), which was associated with a decrease of the input resistance (lower trace), suggesting the opening of a K^+ conductance. Reprinted with permission from [15].

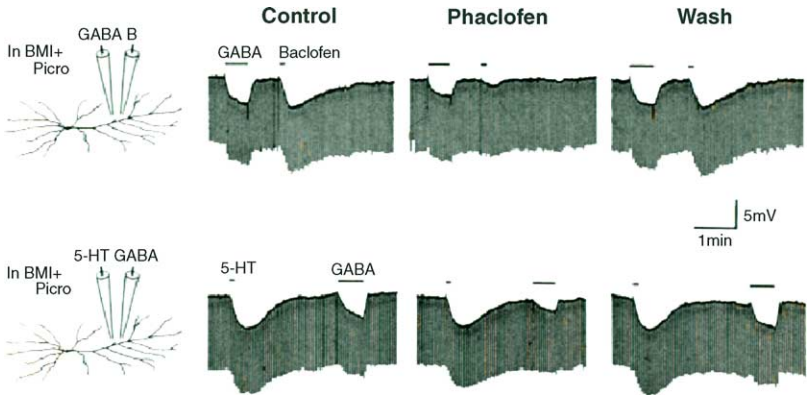

Fig. 5. Phaclofen antagonizes the action of baclofen and the bicuculline resistant GABA response, but not the action of 5-HT. Schematic location of ionotophoretic electrodes is shown on the left. To the right, GABA ionotophoresed in stratum radiatum in the presence of bicuculline (BMI) (40 μM) and picrotoxin (Picro) (20 μM) evokes hyperpolarizing responses (control traces). Phaclofen (0.5 mM) applied for 15 min in the bath antagonizes both the baclofen and bicuculline resistant GABA responses, but not the 5-HT response. Reprinted with permission from [19].

potential (IPSP), which peaks at a latency of about 50 ms; and (3) a late hyperpolarizing potential, which peaks at about 150 ms [22,23]. The IPSP is blocked by the GABA antagonists picrotoxin and bicuculline, but the late hyperpolarizing potential was actually increased in size and duration. A similar potential was reported in the dentate gyrus [24]. It was proposed that this potential might reflect a calcium activated potassium conductance [22]. However, further investigation of the late hyperpolarizing potential indicated that is was a bicuculline resistant slow IPSP mediated by an unknown transmitter released from feed forward interneurons [23]. A rigorous comparison of the bicuculline resistant action of GABA to that of the slow IPSP strongly implicated $GABA_B$ receptors as the mechanism for the slow IPSP [9].

However, mimicry is not sufficient for assigning a transmitter to a particular synaptic response, because numerous receptors can generate the same conductance mechanism. Thus, a selective $GABA_B$ antagonist was necessary to directly link $GABA_B$ receptors to the slow IPSP. Phaclofen, developed by Kerr et al. [25], was the first $GABA_B$ antagonist. We found that, while it was quite weak, it did antagonize the action of baclofen and more importantly the bicuculline resistant action of GABA (Fig. 5) [19]. In addition, concentrations of phaclofen that blocked the action of baclofen had no effect on the action of serotonin, which activates the same potassium conductance. Thus, phaclofen was found to be an effective antagonist of $GABA_B$ receptors on hippocampal pyramidal cells. With this knowledge, we could then answer the question of whether the slow IPSP is, in fact, mediated by $GABA_B$ receptors. Indeed, phaclofen effectively blocked the slow IPSP (Fig. 6) [19]. However, phaclofen is a weak antagonist and our results suggesting that $GABA_B$ receptors mediate the slow IPSP were challenged [17]. Fortunately, a far more potent antagonist CGP 35348 was developed which allowed us to repeat these experiments and fully confirm the hypothesis that the slow IPSP is mediated by GABA released from interneurons and acting on $GABA_B$ receptors [26,27]. Furthermore, we used an independent pharmacological approach to establish that GABA is, indeed, the transmitter mediating the slow IPSP. We examined effect of the specific GABA uptake blocker SKF 89976A on the slow IPSC. SKF 89976A enhanced

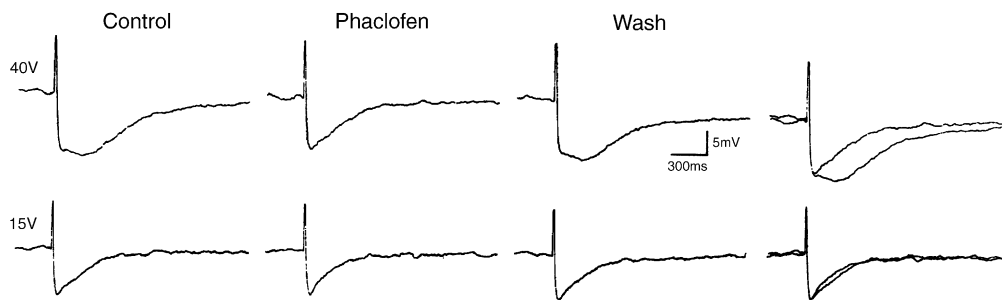

Fig. 6. Phaclofen selectively blocks the slow IPSP. Synaptically evoked potentials induced by orthodromic stimulation in stratum radiatum are recorded from a CA1 pyramidal cell. In the top trace, the stimulation intensity (40 V) evokes a biphasic hyperpolarizing response which includes both the fast and slow IPSP. At lower intensity (15 V), only the fast IPSP is elicited (bottom trace). In the presence of phaclofen (0.2 mM), applied for 5 min, the slow IPSP is abolished (top trace). In contrast, the fast IPSP is unchanged (bottom trace). Top and bottom traces are from the same cell. Resting membrane potential, −56 mV. The records on the right are superimposed tracings of the control response and the response in phaclofen. Reprinted with permission from [19].

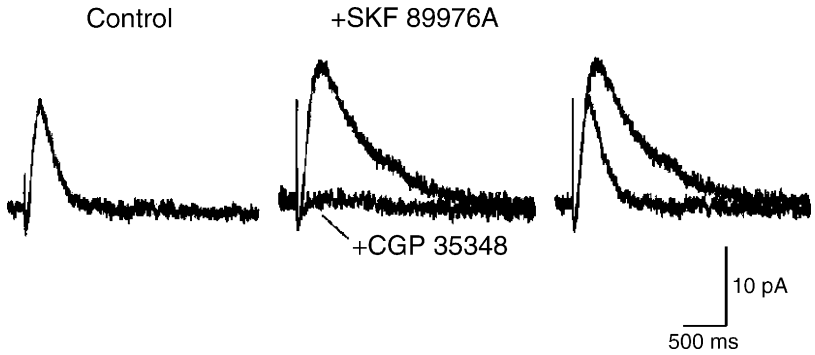

Fig. 7. Enhancement of the slow IPSC by the GABA uptake blocker SKF 89976A. Whole-cell recording techniques were used to record the slow IPSC in a CA1 pyramidal cell. The excitatory synaptic inputs were blocked by CNQX (20 μM) and APV (50 μM) and $GABA_A$ receptors were blocked with picrotoxin (100 μM). The membrane potential was held at −60 mV and SKF 89976A (20 μM) was applied for 5 min. Each record is the average of eight traces. Reprinted with permission from [27].

and prolonged the slow IPSC, independently supporting that GABA is the transmitter that mediates the slow IPSC (Fig. 7) [28].

How are postsynaptic $GABA_B$ receptors activated by synaptically released GABA? An early finding is that only strong stimulation evoked a slow IPSC, suggesting that concomitant release of GABA by several interneurons may be necessary [19,29]. In agreement with this notion, recordings from interneuron/pyramidal cell pairs showed that only $GABA_A$ receptor currents could be evoked, even with repetitive stimulation [30]. However, in the presence of GABA uptake blockers a slow IPSC could be evoked. Since the $GABA_B$ receptors have a higher affinity than the $GABA_A$ receptors, this finding indicates that the $GABA_B$ receptors are located extrasynaptically. These findings suggest that to activate $GABA_B$ receptors synaptically, a cooperativity among release sites is necessary. This, in turn, implies that under physiological conditions $GABA_B$ receptors would only be recruited during synchronous activity in inhibitory interneurons, as occurs, for instance, during the theta rhythm. In support of this hypothesis, it has been found that $GABA_B$ receptors are engaged during rhythmic activity in the hippocampus and sculpt this activity [30]. However, there may be some specialization regarding interneuron subtype in terms of activation of $GABA_B$ receptors. In the thalamus activation of single perigeniculate, inhibitory neurons generate pure $GABA_A$ IPSPs at low frequency stimulation, but also recruit a $GABA_B$ IPSP with prolonged stimulation [31]. In the neocortex neurogliaform cells, unlike basket cells, and bitufted cells, in this structure routinely evoked $GABA_B$ IPSPs, as well as $GABA_A$ IPSPs, to single presynaptic action potentials [32].

5. $GABA_B$ receptors decrease transmitter release

Inhibition of transmitter release was the first CNS action described for baclofen [7]. This was prior to the findings of Bowery establishing the existence of $GABA_B$ receptors. In the hippocampus, presynaptic $GABA_B$ receptors are present on both inhibitory and excitatory synaptic terminals. The mechanism involved in the inhibition of release is not entirely established. In the hippocampus, the inhibition remains intact in the GIRK2 knockout mouse, indicating that a mechanism distinct from the postsynaptic action in involved [15]. The most likely mechanism is a reduction in calcium channel function as first described by Dunlap and co-worker [4,5] and convincingly shown to account for the reduction in transmitter release at the calyx of Held [33]. However, there is also evidence that $GABA_B$ receptors can act downstream of calcium entry [34,35]. Paired pulse stimulation of inhibitory synapses at intervals of a few100 ms results in a depression of the second response. This paired pulse depression is partially reversed by $GABA_B$ receptor antagonists, indicating that synaptically released GABA can feed back onto presynaptic $GABA_B$ autoreceptors and inhibit GABA release [36]. Interestingly, the involvement of $GABA_B$ receptors in paired pulse depression depends on the strength of stimulation [37]. Only when a substantial number of inhibitory synapses are activated are the presynaptic $GABA_B$ receptors recruited. This requirement, which is very similar to that for activation of postsynaptic $GABA_B$ receptors, indicates that pooling of GABA is necessary to reach high enough levels of GABA to activate the presynaptic $GABA_B$ receptors.

Unlike the spinal cord, excitatory synapses in other areas of the brain do not receive GABAergic axo-axonic synapses. How, then, do presynaptic $GABA_B$ receptors on excitatory synaptic terminals see synaptically released GABA? We have examined this question by determining if activation of GABAergic synapses can cause a presynaptic $GABA_B$-mediated inhibition of excitatory synaptic transmission [28]. Repetitive, but not single, stimulation of inhibitory synapses resulted in a slow presynaptic inhibition of excitatory synaptic transmission that was blocked by $GABA_B$ receptor antagonists (Fig. 8). Application of a GABA uptake blocker greatly enhanced this heterosynaptic inhibition. These findings indicate that with repetitive activation of inhibitory synapses GABA can escape from

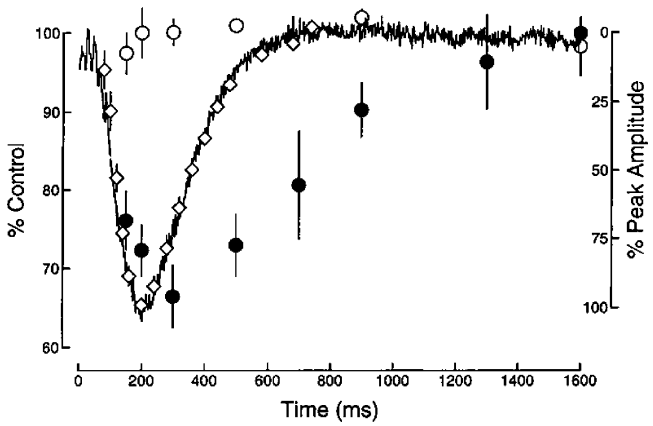

Fig. 8. The time course of heterosynaptic depression is similar to the time course of the slow IPSC. The time course of heterosynaptic depression was studied by varying the interval between the conditioning tetanus (five pulses, 50 Hz) and test stimulus. The amount of depression is plotted as the amplitude of the test pulse when preceded by the conditioning tetanus relative to the amplitude of the test pulse alone (closed circles, $n = 9$ cells). In four of the cells, CGP 35348 was added to the superfusing solution. The $GABA_B$ antagonist completely blocked the depression at the 6 intervals tested (open circles). A monosynaptic slow $GABA_B$ IPSC was evoked with a brief tetanus (five pulses, 50 Hz) in a cell recorded with K^+ in place of Cs^+ in the patch electrode and with 20 μM CNQX added to the superfusing solution. The trace is shown inverted for comparison with the time course of heterosynaptic depression. The peak amplitude of the slow IPSC was 60 pA. Superimposed on the individual trace is the average time course of the slow IPSC derived from four cells (diamonds) plotted relative to their peak amplitude. The slow IPSCs were normalized with respect to their peak amplitude before averaging. Reprinted with permission from [28].

the synapses and act at a distance from where it is released (Fig. 8).

6. Multiple $GABA_B$ receptor subtypes

Based on differences in the sensitivity of pre- and postsynaptic $GABA_B$ receptors in the hippocampus to phaclofen and pertussis toxin, it was suggested that the receptors at these two sites might be different [14]. However, further studies indicated that the more potent $GABA_B$ antagonist CGP 35348 did effectively block presynaptic effects [26] and, although a number of studies confirmed the lack of effect of pertussis toxin on the presynaptic action, e.g. [38], others did find a blockade, e.g. [39]. Nevertheless, considerable evidence has accumulated over the years using a variety of preparations and techniques to support the notion that multiple subtypes of $GABA_B$ receptors do exist, e.g. [40–44]. However, the cloning of the $GABA_B$ receptor has not yet provided a clear molecular basis for this proposed subunit heterogeneity [45,46].

7. Conclusions

The initial discovery of $GABA_B$ receptors was made in the peripheral nervous system, as has often been the case in the discovery of neurotransmitters and their receptors. This can be explained primarily to the simplicity of peripheral systems and also helps explain why progress in the CNS has been so slow. The critical steps in identifying the physiological role for $GABA_B$ receptors were remarkably similar to those made for numerous other neurotransmitter systems in the CNS. These steps involved the use of selective receptor agonists and antagonists and highlight the essential role that pharmacology has played in characterizing synaptic function in a tissue as complex as the CNS. In understanding the role of $GABA_B$-mediated synaptic transmission, it is informative to compare it to $GABA_A$-mediated transmission, since in most, if not all, cases they both depend on GABA release from the same presynaptic sites. The properties of these two receptor systems are extraordinarily different and the differences can be explain in large part by two properties: (1) the coupling of receptor activation to conductance increase; and (2) the location of the receptors in relation to the release site. $GABA_A$ receptors are typically of relatively low affinity and located at the synapse, although extrasynaptic receptors with high affinity exist. The $GABA_A$ receptor forms the chloride channels that open immediately upon GABA binding to the receptor. As a result, $GABA_A$ mediate IPSPs are very fast and mediate point-to-point transmission in a faithful manner. Thus, the $GABA_A$ IPSP will rapidly curtail the excitatory synaptic inputs, which is essential for precise timing of action potentials [47]. In contrast to $GABA_A$ receptors, $GABA_B$ receptors are indirectly coupled to potassium channels via G-proteins. This accounts for the delay in the onset of the IPSP as well as its slow time course. Because of the slow time course, the $GABA_B$ IPSP shows pronounced summation upon repetitive stimulation, in striking contrast to the fast $GABA_A$ IPSP. However, an equally important feature in defining the properties of $GABA_B$ synaptic signaling is the localization of the receptors. $GABA_B$ receptors have a higher affinity for GABA than $GABA_A$ receptors, but the evidence indicates that both pre- and postsynaptic $GABA_B$ receptors are located some distance from the site of release. This means that to recruit $GABA_B$ receptors, the concentration of GABA must be high so that it can escape from the synaptic cleft. This condition can occur in two ways. First, repetitive activation of the synapse can lead to the spill over of GABA onto $GABA_B$ receptors. However, for a single synapse this process is variable and at some synapses GABA is unable to reach these receptors, even with rather intense repetitive stimulation. The more important mechanism is the simultaneous activation of a number of release sites. This results in pooling of GABA and effectively raises the concentration of GABA in the extrasynaptic space. As a result, both the pre- and postsynaptic $GABA_B$ receptors will be recruited specifically during synchronous rhythmic activity [30], which will sculpt the pattern of activity.

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