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Epilepsy Research 44 (2001) 109–117

Epilepsy Research

www.elsevier.com/locate/epilepsyres

Gamma-vinyl GABA reduces paired pulse inhibition in the rat dentate gyrus in vivo and in vitro

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Received 6 April 2000; received in revised form 11 January 2001; accepted 15 January 2001

Abstract

Gamma vinyl GABA (GVG), an irreversible GABA transaminase inhibitor, has anticonvulsant effects. GVG increases GABA levels in the brain by blocking its degradation, and is presumed to enhance GABAergic inhibition, however, in some cases it exacerbates seizures. We investigated the effects of GVG in vivo and in vitro on paired pulse inhibition (PPI) recorded in the rat dentate gyrus (DG) evoked by perforant path stimulation. At 2.5 h and 24 h after administration of GVG (1 g/kg, i.p.), there was a loss of PPI at both 15- and 25-ms interpulse intervals (IPI). Activation of presynaptic $GABA_B$ autoreceptors could explain this in vivo effect. We therefore further investigated the effects of co-application of GVG with the $GABA_B$ antagonists 2-OH saclofen (saclofen) or CGP 35348 (CGP) on PPI in hippocampal slices by in vitro study. Bath application of GVG (400 and 500 μM) not only resulted in a loss of perforant path evoked PPI at a 15-ms IPI, but produced facilitation of the second population spike relative to the first. Co-application of saclofen (250 μM) with GVG (500 μM) prevented facilitation of the second response of a paired-pulse. The facilitation of the second stimulation response produced by GVG (400 μM) was converted to inhibition by bath application of CGP 35348 (400 μM). These results suggest that activation of presynaptic $GABA_B$ receptors by increased extracellular GABA may be one of the contributing factors to the apparent paradoxical effect of GVG on PPI in the DG.

Keywords: Vigabatrin; GABA; Hippocampus; Inhibition; Dentate gyrus; GVG

1. Introduction

Reduction of GABAergic inhibition can contribute to the generation and propagation of epileptic seizures in a variety of experimental models, while enhancement of GABAergic activ-

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0920-1211/01/$ - see front matter
PII: S0920-1211(01)00200-5

ity has anticonvulsant effects (Olsen and Avoli, 1997; Petroff and Rothman, 1998; Loscher, 1998). Gamma-vinyl GABA (Vigabatrin, GVG), an antiepileptic drug, elevates extracellular GABA concentration in the brain by blocking irreversibly the degrading enzyme GABA transaminase (GABA-T) (Perucca, 1993; de Bittencourt et al., 1994; Ben-Menachem, 1995; Halonen et al., 1990). At twenty-four hours after administration of GVG, GABA levels increase 10-fold in rat brain (Halonen et al., 1990), and fourfold in human epileptic subjects after a single 50 mg/kg dose (Petroff et al., 1996; Petroff and Rothman, 1998). GVG results in a 30% inhibition of GABA-T at 4 h, and 65% inhibition at 48 h (Petroff and Rothman, 1998).

GVG has been shown to be an effective anticonvulsant against seizures produced by kindling, kainic acid, maximal electroshock, and bicuculline (Kalichman et al., 1982; Stevens et al., 1988; Halonen et al., 1995; Iodorala and Gale, 1982), but it has complex dose dependent effects against PTZ seizures. GVG is an anti-convulsant at the dose of 1000 mg/kg against PTZ seizures, however, at a dose of 2000 mg/kg, the anticonvulsant effect was not observed (Sayin et al., 1993, 1995). Bilateral micro-injections of GVG (3–30 μg) into the anterior thalamus were anticonvulsant against PTZ seizures, at higher doses, GVG (100 μg) was less effective (Miller et al., 1987). GVG has been reported to increase seizure frequency and duration in the lethargic mouse model of absence seizures (Hosford and Wang, 1997).

Although GVG reduces seizure frequency by approximately 50–60% and is effective against complex partial seizures (Reynolds et al., 1988; Browne et al., 1987), it may precipitate status epilepticus (de Krom et al., 1995), psychosis (Jawad et al., 1994), or exacerbate primary generalized myoclonic and tonic-clonic seizures (Lortie et al., 1993; Perucca et al., 1998; Luna et al., 1989; McKee et al., 1993).

The explanation for the dose dependant effects of GVG and why GVG exacerbates seizures under some circumstances is uncertain (de Krom et al., 1995; Lortie et al., 1993; Perucca et al., 1998; Luna et al., 1989; McKee et al., 1993). Because the activation of $GABA_B$ autoreceptors on presynaptic terminals of inhibitory interneurons reduces GABA release, a possible explanation for the loss of anticonvulsant effects at higher GVG doses is that increased extracellular GABA after GVG administration could reduce GABA release by activating presynaptic $GABA_B$ autoreceptors (Mott and Lewis, 1994).

To investigate the possibility that the dose dependant effects of GVG may be caused by alterations in the balance of excitation and inhibition, we used the method of paired pulse stimulations, which at 15–40-ms interpulse intervals is sensitive to the strength of Cl^- dependant inhibition, which is mediated by $GABA_A$ receptors (Oliver and Miller, 1985; Xiong and Stringer, 1997). In this study, we investigated the effects of GVG on paired pulse inhibition (PPI) in the rat dentate gyrus in vivo and in vitro, and also assessed whether the effects of GVG on PPI were dependent on presynaptic $GABA_B$ receptor activation.

2. Methods and materials

All procedures involving animals were approved by the University of Wisconsin Research Animal Care Committee, and the Oxford University Animal Care Committee.

2.1. In vivo experiments

The effect of GVG (1000 mg/kg) was assessed 2.5 h or 24 h after injection intraperitoneally (i.p.).

Male Sprague–Dawley rats (250–350 g) were anaesthetized with an i.p. injection of urethane 1.2 mg/kg (Sigma, MO/USA) and placed in a stereotaxic frame. Appropriate holes were drilled in the skull and a bipolar stainless steel stimulating electrode (SN100, Rhodes, USA) was lowered into the region of the angular bundle 8.5 mm posterior to the bregma, 4.4 mm lateral to the midline, 3.5 mm vertical from the dura with location chosen according to the stereotaxic atlas of Paxinos and Watson (1982). A glass microelectrode of 5–10 MΩ, filled with 2 M NaCl, was used to record extracellular field responses from the dentate gyrus at the following coordinates relative to the bregma, 3.5 mm posterior, 1.75 mm lateral, 3.5 mm vertical.

The skull was used as a ground. Recordings were made using an Axoclamp 2B amplifier or CED amplifier. Extracellular field potentials were amplified and displayed on an oscilloscope (Tektronix-2212) and digitized (DIGIDATA 1200/Axon Inst.) using PCLAMP 6.02. The electrode was positioned to obtain a maximal population spike response at the lowest stimulus strengths. Constant current monopolar square waves with a duration of 0.1 ms pulses or different voltage pulses with a duration of 0.1 ms (4 V, 8 V, 12 V, 16 V, 20 V) were used to stimulate perforant pathway fibers. After obtaining a consistent evoked response and stable population spike recordings, the lowest stimulus intensity that produced the maximum population spike was determined and used for single or paired pulse recordings. For evaluating the acute effects of GVG, paired pulse responses of evoked field population spikes from four rats were recorded every 30 min, beginning 30 min before and 2.5 h after the administration of GVG (1 g/kg, i.p.). To assess the long term effects of GVG on PPI after 24 h, seven rats were injected with 1 g/kg GVG, and six rats were injected with an equal volume of saline; 24 h after the injection extracellular field potentials were recorded from the dentate gyrus as described above.

The amplitude of the population spike was measured by averaging the height from the peak

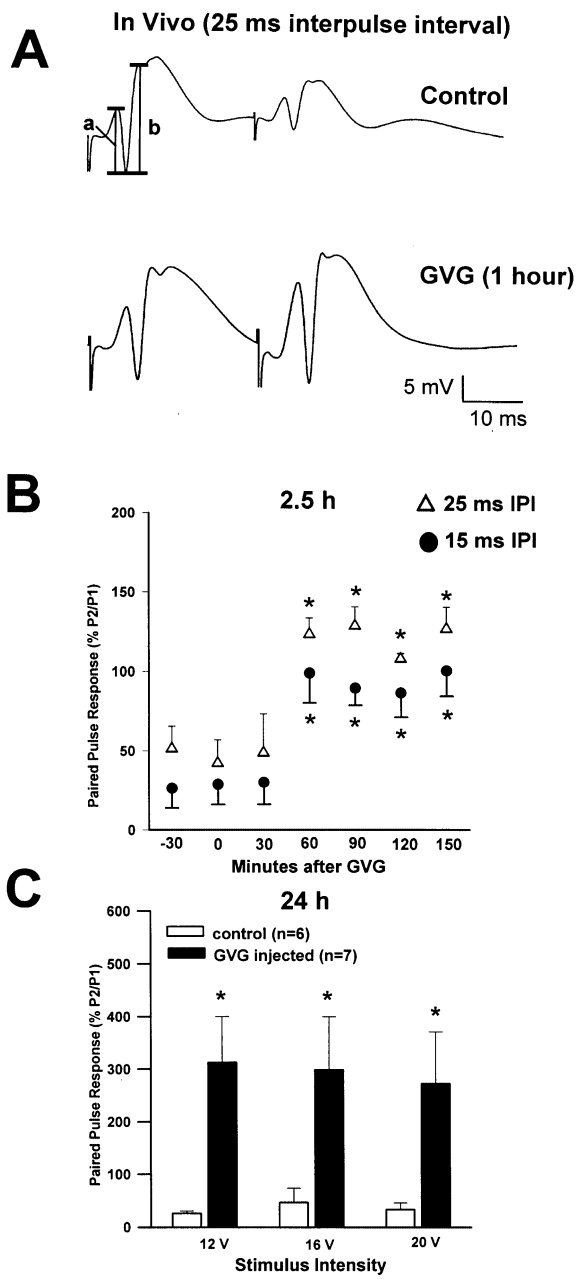

Fig. 1. (*Continued*)

Fig. 1. Effect of GVG on paired pulse inhibition in vivo. (A) Extracellular field potentials evoked in the dentate gyrus in vivo by pairs of perforant path stimuli. GVG had a significant effect on paired pulse inhibition (PPI) at 1 h after the injection. A response at an interpulse interval of 25 ms resulted in a facilitation of the second population spike 1 h after 1 g/kg of GVG was given intraperitoneally. The calculation of population spike amplitude is also depicted. Population spike amplitudes were calculated by averaging the height from the peak of the population EPSPs to maximum downward deflection of the population spike (in the figure, population spike amplitude is $(a+b)/2$). PPI is expressed as the percent ratio of the amplitude of the second population spike (test) to the first (conditioning) (% P2/P1). When the percent of P2/P1 is smaller than 100% there is inhibition; when it is greater than 100%, there is facilitation. Note that the smaller the PPI ratio value, the greater the inhibition. (B) PPI measured 30 min before a 1 g/kg intraperitoneal injection, and every 30 min thereafter for 2.5 h. There was a significant loss of PPI at 15- and 25-ms interpulse intervals beginning 1 h after injection ($^*P < 0.05$, $n = 4$ rats, paired t-test). (C) Mean PPI at the 15-ms interpulse interval in the DG at 24 h after the injection of GVG. Control depicted by open bars ($n = 6$), GVG injected data depicted by closed bars ($n = 7$). The second response was facilitated significantly at three different stimulus intensities following GVG treatment. ($^*P < 0.05$, Dunn's test).

of the population EPSPs to the base of the population spike, as shown in Fig. 1A. The amplitude of the second evoked population spike was expressed as the percentage of the first response.

2.2. In vitro experiments

2.2.1. Slice preparation and maintenance

Male Sprague–Dawley rats (150–250 g) were anesthetized with Nembutal (50 mg/kg), decapitated and the brain was removed rapidly and immersed in iced artificial cerebrospinal fluid (ACSF). The hippocampus was dissected and transverse slices 400–500 μm thick, were prepared using a McIllwain tissue chopper. The slices were maintained in an interface chamber superfused with oxygenated, 95% O_2 and 5% CO_2 ACSF, pH 7.4, at 32–34°C. The ACSF composition was (in mM): NaCl 124, KCl 5, NaH_2PO_4 1.25, $CaCl_2$ 2, $MgCl_2$ 2, $NaHCO_3$ 26, glucose 10. The slices were maintained at least 90–120 min in ACSF prior to recordings.

2.2.2. Recordings

A stainless steel bipolar electrode was placed in the molecular layer of the dentate gyrus to activate perforant path fibers which were stimulated by a constant current pulse (duration of 0.05 ms) ranging from 400 to 700 μamp in intensity. The stimulus intensity was adjusted to the lowest intensity that produced the maximum evoked population spike; this intensity was determined after delivering a series of different stimuli. The intensity of the conditioning (first) and test (second) pulse stimuli of each pair were identical. Extracellular evoked population spikes were recorded at a fixed position from the granule cell layer of the dentate gyrus using glass microelectrodes of 5–10 MΩ resistance filled with 2 M NaCl. Interpulse intervals of 15, 30, 40, 100 and 350 ms were evaluated. Recordings were made using an Axoclamp 2B amplifier. Extracellular field potentials were amplified and displayed on an oscilloscope (Tektronix-2212) and digitized (DIGIDATA 1200/Axon Inst.) Population spikes were measured as described above (Fig. 1A).

2.2.3. Experiments

The effects of GVG (400–500 μM) alone or in co-application with $GABA_B$ antagonists saclofen (250 μM) and CGP 35348 (400 μM) on PPI were evaluated. The concentrations of GVG had an optimal effect on PPI as reported before (Jackson et al., 1994).

2.2.4. Statistics

Data were averaged and expressed as means and standard error of the mean (S.E.M.). Data obtained at different interpulse intervals before and after drug applications or wash-out were compared using a one-way ANOVA followed by Dunnett's method for multiple comparison, or paired t-test when a single comparison was made. Dunn's method was applied if Kruskal–Wallis was used for multiple comparison for the data that were not normally distributed.

2.2.5. Drugs

Vigabatrin (GVG) was a gift of Merrel Dow Institute (Strasbourg, France), CGP 35348 was kindly donated by Ciba-Geigy (Basel, Switzerland). 2-hydroxy-saclofen was purchased from Sigma (St. Louis, MO, USA).

3. Results

3.1. Effects of GVG on paired pulse inhibition in the dentate gyrus in vivo

One hour after injection, GVG (1 g/kg) induced a loss of PPI and facilitation measured at the 15- or 25-ms interpulse interval (Fig. 1A, B) in vivo, but no significant differences were observed at other interpulse intervals (data not shown). The control ratio of the second population spike to the first at 15-ms interpulse interval was $26 \pm 12.4\%$ and the ratio increased to $99 \pm 19\%$ 1 h after GVG application ($n = 4$ rats, $F_{6,21} = 6$, $P = 0.0009$, for paired comparison $P < 0.05$). For 25-ms interpulse intervals the control ratio was $50 \pm 14\%$ and was increased to $127 \pm 24\%$ 1 h after GVG application (Fig. 1B; $F_{6,21} = 7.8$, $P = 0.0002$ and paired comparison $P < 0.05$, $n = 4$).

When rats were pretreated with vehicle, the amplitude of the second response at a 15-ms interpulse interval was $26 \pm 4\%$ of the first in normal rats, but at 24 h after GVG injection the ratio of the second population spike to the first increased to $272 \pm 98\%$ (at 20 V stimulus intensity; $H = 24.4$, $P = 0.0002$, Kruskal–Wallis). The paired pulse facilitation was observed in GVG injected rats at three different stimulus intensities (12, 16, 20 V) including at 20 V, which was the supra maximal stimulus intensity that induced the maximal population spike in the input–output curve (Fig. 1C).

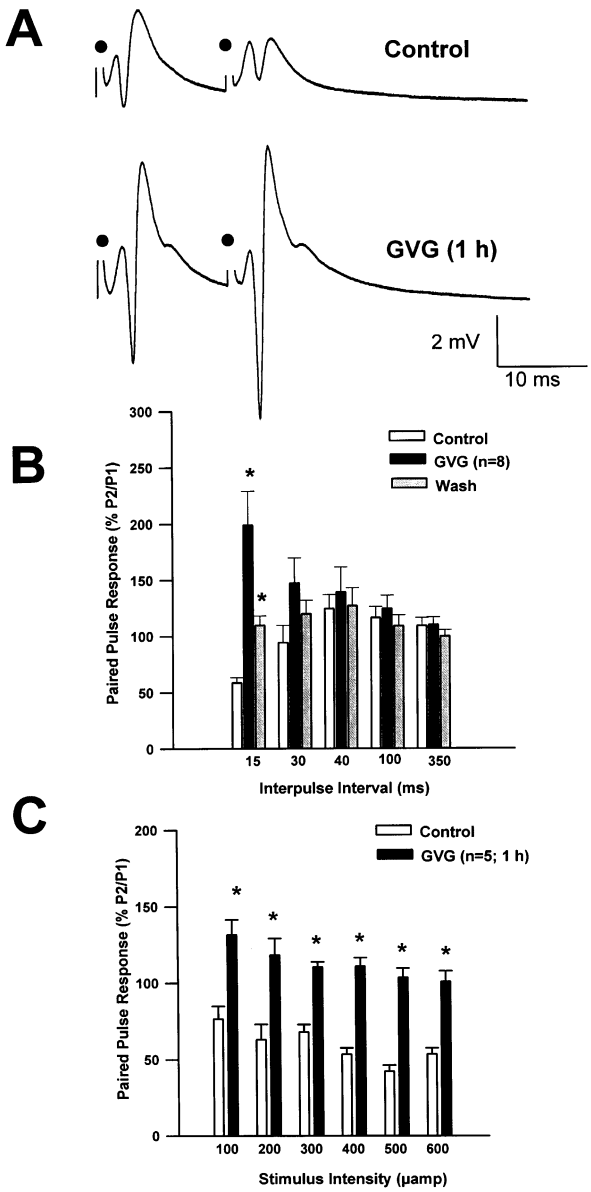

Fig. 2. (*Continued*)

3.2. The effect of GVG on PPI in the dentate gyrus in vitro

Application of GVG (500 μM) for 1 h induced a facilitation of the second population spike altering the control ratio of $59 \pm 5\%$ to $198.3 \pm 29\%$; this facilitation was partially reversed by return to control ACSF, however, PPI did not recover to baseline values ($109 \pm 21.8\%$; $n = 8$, $H = 18.4$, $P = 0.0001$, Kruskal–Wallis; Fig. 2A, B). GVG (400 μM) also produced a less robust loss of inhibition at 15-ms interpulse interval, and this effect was significant at different stimulus intensities (Fig. 2C; $n = 5$; $P < 0.05$). Antagonism of the $GABA_A$ receptor using bicuculline methiodide (BMI; 2, 5, 10 μM) also produced a loss of PPI at 15-ms interpulse interval, suggesting that PPI measured at 15 ms was mediated by $GABA_A$ receptors (Fig. 3A, B).

3.3. The effect of GVG on single population spike in vitro

At a 400 μM concentration GVG induced a significant increase in the amplitude of the first

Fig. 2. Effect of GVG on paired pulse inhibition in vitro. (A) Extracellular field potentials evoked in the dentate gyrus by perforant path stimulation at 15-ms interpulse interval. Potentials evoked at 1 h after the application GVG in vitro demonstrated loss of PPI. Dots represent the time of the stimulation. The stimulation artifact has been truncated. Note that an enhancement in amplitude of the first population spike occurred following GVG (see text). (B) The plot demonstrating the loss of PPI at 15-ms interpulse interval 1 h after the application of GVG (500 μM) in vitro. There was no change at other interpulse intervals. The loss of inhibition did not completely reverse following washout with ACSF for 1 h. $n = 8$ slices; $^*P < 0.05$, Kruskal–Wallis followed by post hoc Dunn's test. (C) The effect of GVG on PPI at 15-ms interpulse interval at different stimulus intensities is depicted. GVG (400 μM) induced a loss of PPI at all stimulus intensities 1 h after in vitro application. $n = 5$, $^*P < 0.01$, paired t-test).

population spike, this effect was significant at supra maximal intensities ($n = 5$; at 600 μamp stimulation, control = 2.76 ± 0.4 mV, 1 h after GVG = 4.5 ± 0.6 mV; $P = 0.045$). At 500 μM GVG, the first population spike was also significantly increased at the supramaximal intensities ($n = 8$, control = 2.90 ± 0.4 mV, 1 h after GVG = 4.45 ± 0.48 mV, also see Fig. 2A).

3.4. Effect of $GABA_B$ antagonists on the effect of GVG in dentate gyrus in vitro

When GVG (500 μM) was co-applied with the $GABA_B$ antagonist saclofen (250 μM), no significant change in PPI was observed (control: 64.2 ± 6%; GVG + saclofen:75.8 ± 6.5%; wash:73 ± 9.4%; $n = 5$, $F_{2,16} = 0.7$, $P = 0.52$; data not shown).

GVG (400 μM) resulted in a loss of PPI and a facilitation that was reversed by the co-application of selective $GABA_B$ antagonist CGP 35348 (400 μM) for 90 min ($n = 6$, Fig. 4). CGP 35348 alone did not significantly alter the PPI measured at 15-ms interpulse interval ($n = 5$; control = 66.8 ± 6.2%, CGP = 45.0 ± 8.9%, Wash = 65 ± 2.7%; $F_{2,12} = 3.54$, $P = 0.06$).

4. Discussion

Paired pulse responses at 15- and 25-ms interpulse intervals are sensitive to $GABA_A$ receptor inhibition. In previous paired pulse studies of the perforant path evoked response at a wide range of interpulse intervals, a chloride-dependent phase of inhibition occurs at 10–40-ms interpulse intervals, a facilitation at 40–100-ms interpulse intervals, and a late chloride-independent phase at interpulse intervals between 250 and 8000 ms (Oliver and Miller, 1985). The changes in PPI at 15–30-ms interpulse intervals reflect the recurrent or feed-forward stimulation of interneurons and the resultant activation of a fast chloride-mediated $GABA_A$ inhibition (See Fig. 3). Bicuculline, a $GABA_A$ antagonist, blocks PPI at 15-ms interpulse interval, in a dose dependent manner, eventually inducing multiple population spikes (Fig. 3; Rich-Bennet et al., 1993).

This study demonstrated that GVG produced a loss of PPI, as well as a facilitation, at 15- or 25-ms interpulse intervals in dentate gyrus in vivo and in vitro. Our finding suggests that this loss of PPI was produced by mechanisms affecting postsynaptic $GABA_A$ function. This result may occur either by a direct effect of GVG on postsynaptic

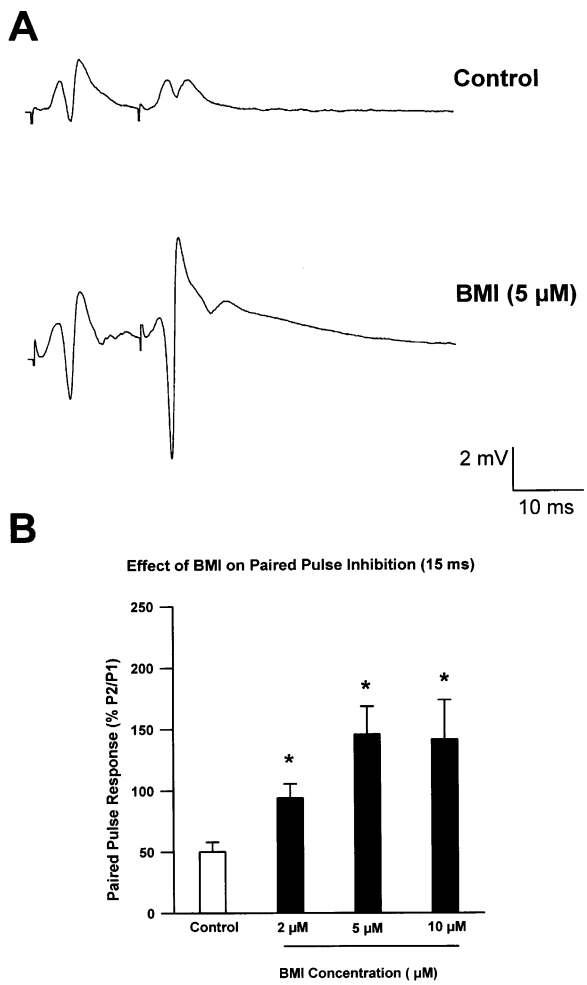

Fig. 3. The effect of $GABA_A$ receptor antagonist on paired pulse inhibition at 15-ms interpulse interval in dentate gyrus. (A) Representative traces of population spikes at 15-ms interpulse interval from dentate gyrus of rat hippocampus before and after the application of 5 μM BMI. Note that the paired pulse inhibition is lost after BMI application. (B) The plot shows the dose–response effect of BMI on paired pulse inhibition at 15 ms. In all concentrations, BMI induced a loss of inhibition or a facilitation ($n = 4$ slices; $P < 0.05$).

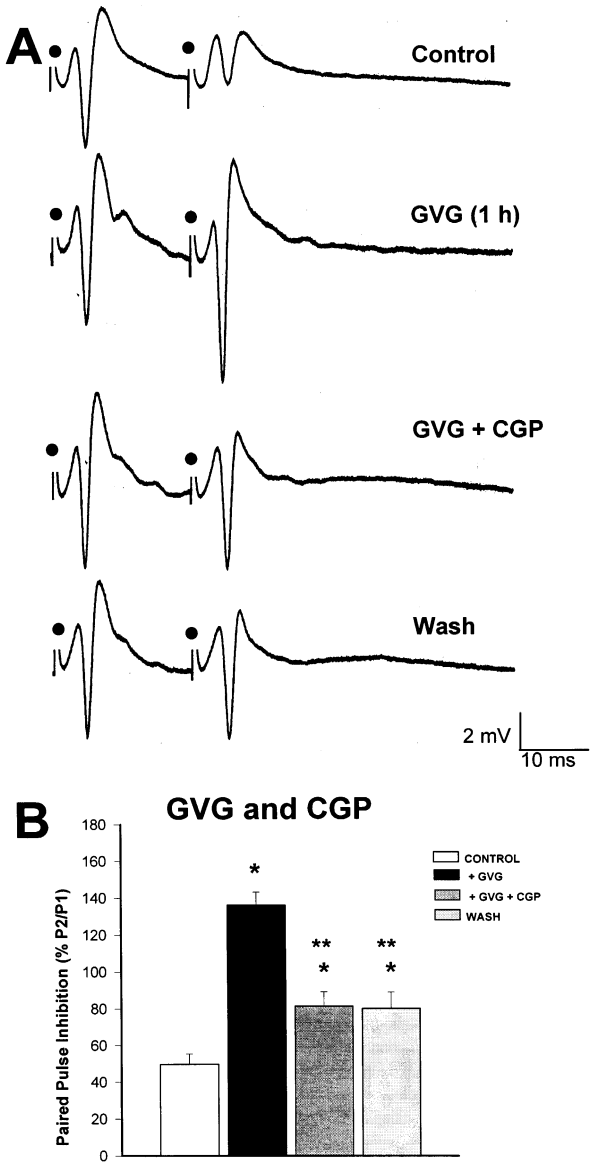

Fig. 4. (*Continued*)

$GABA_A$ receptors, a presynaptic effect that alters the regulation of the release of GABA or by other electrophysiological effects of GVG, not yet defined. GVG does not have a direct antagonistic effect on $GABA_A$ receptors as shown by binding studies (Jackson et al., 1994). Although GABA transaminase inhibition produced by GVG may be expected to increase inhibition postsynaptically by elevating GABA concentrations in the brain, GVG paradoxically produced a loss of PPI and a resultant paired pulse facilitation in the dentate gyrus of rat hippocampus in vivo and in vitro. A similar finding was reported using in vitro methods in the CA1 region of rat hippocampus (Jackson et al., 1994). The facilitation was prevented or reversed by the co-application or subsequent application of the $GABA_B$ antagonists saclofen or CGP 35348, in vitro, suggesting a possible presynaptic $GABA_B$ autoreceptor mechanism to explain our findings.

Another effect of GVG was increasing the amplitude of the single population spike in vitro, but not in vivo, at both concentrations, possibly by either decreasing feed-forward inhibition or changing the balance of excitation/inhibition by means of a mechanism which needs to be further investigated.

GVG exerts its GABA elevating effects through at least two mechanisms. Primarily it blocks irreversibly the enzyme GABA-transaminase that catabolizes GABA in the neurons and glial cells (Ben-Menachem, 1995; Petroff and Rothman, 1998). GVG has also been shown to block uptake of GABA (Loscher, 1980). Elevated levels of

Fig. 4. The effect of $GABA_B$ antagonists on GVG induced reduction of paired pulse inhibition. (A) Extracellular field potentials evoked in the dentate gyrus by perforant path stimulation demonstrate the effect of CGP 35348 (400 μM), a $GABA_B$ antagonist, on the loss of inhibition induced by GVG (400 μM). CGP 35348 reversed the GVG induced loss of inhibition. PPI was not restored fully after washout. (B) Mean paired pulse responses at 15-ms interpulse interval at 1 h after application of GVG (400 μM), at 1 h after application of GVG with CGP 35348 (400 μM) and following wash. GVG alone changed the paired pulse response from inhibition ($<$ 100%) to a facilitation ($>$ 100%). CGP 35348 partially reversed the loss of inhibition induced by the application of GVG. The ratio of %P2/P1 increased from $49.8 \pm 5.7\%$ in controls to $136.2 \pm 7\%$ after the application of GVG, and application of CGP decreased this value to $81.5 \pm 7.7\%$. Wash out did not result in further change and the ratio was still significantly different from the control value ($80 \pm 2.4\%$) ($n = 6$; $F_{3,20} = 23.7$, $P < 0.0001$; $^*P < 0.05$; $n = 6$ slices, one-way ANOVA, followed by Student–Newman–Keuls test). Following CGP 35348 and GVG co-application, the GVG effect on the paired pulse response was reduced significantly ($^{**}P < 0.05$, significant difference from GVG alone). CGP 35348 or washout did not restore PPI.

GABA produced by GVG are expected to have effects at both $GABA_A$ and $GABA_B$ receptors. The $GABA_B$ agonist baclofen reduces PPI at short interpulse intervals in the dentate gyrus of rat hippocampus (Mott et al., 1987; Burgard and Sarvey, 1991). Elevated extracellular GABA levels might reduce the efficacy of inhibitory synaptic transmission by a presynaptic effect on $GABA_B$ autoreceptors. Indeed, Jolkkonen et al. showed that GVG caused a reduction in K^+ stimulated GABA release in vivo as measured in the hippocampus via a microdialysis probe (Jolkkonen et al., 1992). The release of GABA from interneurons has been shown to be decreased by presynaptic $GABA_B$ autoreceptors (Davies et al., 1990; Mott et al., 1993; Davies and Collingridge, 1993; Brucato et al., 1995). Supported by these reports our results suggest that the facilitation in dentate gyrus produced by GVG may be explained by the activation of presynaptic $GABA_B$ autoreceptors that result from increased extracellular GABA concentrations.

The observation of reduced inhibition in the dentate gyrus in this study may explain some of the adverse effects of GVG, and could contribute to paradoxical proconvulsant effects in generalized seizures. Recently, gabapentin, which increases brain GABA concentrations (Loscher et al., 1991), was reported to induce loss of inhibition in the rat dentate gyrus in vivo at short interpulse intervals (Xiong and Stringer, 1997). Further studies may demonstrate possible antiepileptic actions of co-administration of $GABA_B$ antagonists with the drugs that elevate the GABA levels in the brain.

Acknowledgements

The studies were also supported by Oxford University Research Funds, NIH grants NINDS NS25020, NS 28580, and VA research.

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