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γ-Hydroxybutyrate inhibits excitatory postsynaptic potentials in rat hippocampal slices

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Abstract

γ-Hydroxybutyrate (GHB) has been shown to mimic different central actions of ethanol, to suppress alcohol withdrawal syndrome, and to reduce alcohol consumption both in rats and in humans. The aim of the present study was to determine if GHB shared with alcohol the ability to inhibit glutamate action at both NMDA and AMPA/kainate receptors. The NMDA or the AMPA/kainate receptors-mediated postsynaptic potentials were evoked in CA1 pyramidal neurons by stimulation of Schaffer-collateral commissural fibers in the presence of CGP 35348, bicuculline to block the $GABA_B$ and $GABA_A$ receptors, and 10 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX) or 30 μM DL-2-amino-5-phosphonovalerate (d-APV) to block AMPA/kainate or NMDA receptors, respectively. GHB (600 μM) produced a depression of both NMDA and AMPA/kainate receptors-mediated excitatory postsynaptic potentials with recovery on washout. The GHB receptors antagonist, NCS-382, at the concentration of 500 μM had no effect per se on these responses but prevented the depressant effect of GHB (600 μM) on the NMDA and AMPA/kainate-mediated responses. In the paired-pulse experiments, GHB (600 μM) depressed the amplitude of the first and the second evoked AMPA/kainate excitatory postsynaptic potentials, and significantly increased the paired-pulse facilitation (PPF). These results suggest that GHB inhibits excitatory synaptic transmission at Schaffer-collateral commissural–pyramidal neurons synapses by decreasing the probability of release of glutamate.

Keywords: GHB (γ-hydroxybutyrate); $GABA_B$ receptor; NMDA receptor; AMPA/kainate receptor; Excitatory postsynaptic potential; NCS-382; Paired-pulse facilitation; Hippocampal slice

1. Introduction

γ-Hydroxybutyrate (GHB) is a naturally occurring metabolite of γ-aminobutyric acid (GABA) present in micromolar quantities in the central nervous system (Roth and Giarman, 1970; Maitre, 1997). The highest concentration of GHB is found in the synaptosomal fraction (Maitre et al., 1983b; Snead, 1987) and in vitro, GHB is released by neuronal depolarization in a Ca^{2+}-dependent manner (Maitre and Mandel, 1982; Maitre et al., 1983a). A high-affinity, Na^+-dependent uptake system for GHB has also been reported (Benavides et al., 1982a; Hechler et al., 1985; Vayer et al., 1987a). GHB high-affinity binding sites are present only in neurons, with a restricted specific distribution in the hippocampus, cortex and basal ganglia of the rat brain (Benavides et al., 1982b; Hechler et al., 1987; Hechler et al., 1991). Maximal high-affinity binding occurs in the CA1 field of the hippocampus where GHB induces increase of guanosine cyclic 3′,5′-phosphate (cGMP) levels (Vayer et al., 1987b; Vayer and Maitre, 1989; Hechler et al., 1992). This effect is blocked by the GHB receptors antagonist, NCS-382 (Maitre et al., 1990). The central GHB receptors are of G protein-linked receptor type, and it has been suggested that the G proteins implicated in GHB receptor coupling are of the G_i or G_o family (Ratomponirina et al., 1995).

Electrophysiological recordings of hippocampal or thalamocortical neurons in vitro have revealed a hyperpolarization of the membrane potential after local application of GHB (Olpe and Koella, 1979; Kozhechkin, 1980; Xie and Smart, 1992a; Williams et al., 1995). In hippocampal CA1

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pyramidal neurons, a decrease in excitatory and inhibitory postsynaptic potentials was also described. These actions were blocked by $GABA_B$ receptor antagonists, CGP 36742 or CGP 35348, suggesting that GHB can activate pre- and postsynaptic $GABA_B$ receptors (Xie and Smart, 1992b). However, it has been shown that some neurophysiological and neuropharmacological effects of GHB are mediated by specific receptors. Indeed, NCS-382 has been reported to antagonize GHB-induced increase in guanosine cGMP levels in hippocampus and in vivo release of both dopamine and opioid-like substances (Vayer et al., 1987b). In the prefrontal cortex, two opposite effects on neuronal firing rate were observed with high and low doses of GHB where only the increase of firing rate of neurons at low doses was blocked by NCS-382 (Godbout et al., 1995).

GHB has been shown to reduce voluntary alcohol intake in alcohol-preferring rats (Fadda et al., 1988) and alcohol craving in humans (Gallimberti et al., 1992; Addolorato et al., 1998). In addition, GHB has been shown to suppress the severity of alcohol withdrawal symptoms in both ethanol-dependent rats (Fadda et al., 1989) and alcoholics (Gallimberti et al., 1989). The presence of symmetrical generalization between the discriminative stimulus effects of GHB and ethanol in rats (Colombo et al., 1995) could explain the pharmacotherapeutic use of GHB besides supporting the hypothesis that GHB may have ethanol-like action. Limited double-blind and more extended open studies indicate that GHB is highly effective in reducing craving, alcohol intake and relapses in alcoholic patients. GHB is self-administrated by rats, induces conditioned place preference, is voluntarily consumed by alcohol-preferring rats and is potentially abused by humans (Gallimberti et al., 1992; Addolorato et al., 1996). Although these studies reported no withdrawal symptoms when GHB was discontinued, it is worthy to mention that GHB has the potential to cause physical dependence (Galloway et al., 1997; Tunnicliff, 1997). Accumulating evidences suggest that neurophysiological and pathological effects of ethanol are mediated to considerable extent through the glutamatergic system (Tsai et al., 1995).

Ethanol inhibits both *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA/kainate) types of glutamatergic synaptic transmission (Lovinger et al., 1989; Weight et al., 1991; Lovinger, 1993; Nie et al., 1994).

The aim of the present study was to determine whether GHB shares with alcohol the ability to inhibit both NMDA and AMPA/kainate-mediated excitatory postsynaptic potentials in the CA1 pyramidal cells in hippocampal slices.

2. Materials and methods

2.1. Slice preparation

We prepared hippocampal slices as described previously (Berretta et al., 1990). Briefly, male Wistar rats (100–150 g) were anaesthetized with halothane (3% in air) and decapitated, and their brain rapidly removed and placed in ice-cold artificial cerebrospinal fluid (aCSF) gassed with 95% O_2, 5% CO_2. The aCSF composition (in mM) was: NaCl (130); KCl (3.5); NaH_2PO_4 (1.25); $MgSO_4 \cdot 7H_2O$ (1.5); $CaCl_2 \cdot 2H_2O$ (2); $NaHCO_3$ (24); and glucose (10). To pharmacologically isolate the NMDA or the AMPA/kainate synaptic components, we superfused the slices with 10 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX) or 30 μM DL-2-amino-5-phosphonovalerate (d-APV), respectively, together with bicuculline (30 μM) and 0.5 mM CGP 35348 to block $GABA_A$ and $GABA_B$ receptors.

Transverse hippocampal slices 400-μm thick were cut on a brain slicer, incubated in an interface recording chamber for 15 min, and then completely submerged and continuously superfused with warm (33°–34°C) gassed aCSF at a constant flow rate of 2–4 ml/min.

2.2. Intracellular recordings

CA1 pyramidal neurons were recorded in the current-clamp mode with 4 M K-acetate-filled electrodes (80–120 MΩ). Current-clamp studies were performed with an Axoclamp-2B amplifier (Axon Instruments). Selected traces were stored on a PC for data analysis using a software developed using LABVIEW of the National Instruments.

Several criteria were used to accept cells for experiments: stable resting membrane potentials of at least −60 mV and no spontaneous firing of action potentials; no sudden drops in the input resistance, indicating cell damage; and constant amplitude of the spike (>80 mV) obtained by direct activation of the cell. The postsynaptic excitatory and inhibitory potentials were evoked by orthodromic stimulation (80 μs stimulus duration, 0.05 Hz frequency) of Schaffer-collateral commissural fibers with a bipolar tungsten electrode placed in the stratum radiatum. We averaged evoked responses from five sweeps and measured the peak amplitude. The usual testing protocol was: recording of excitatory or inhibitory postsynaptic potentials for 10–15 min during superfusion of aCSF containing 10 μM DNQX or 30 μM d-APV, 30 μM bicuculline and 0.5 mM CGP 35348 (''control''), followed by switching to the same solution with GHB (100–600 μM) and repeating these measures after 5, 10, and 15 min of drug, followed by switching again to control solution for 15–20 min with subsequent measures (''washout'').

For paired-pulse facilitation (PPF) experiments, low-strength paired responses were elicited by twin pulse (60 ms apart) in CA1 pyramidal neurons. The PPF is expressed as a ratio of the second to the first AMPA/kainate-mediated excitatory postsynaptic potential amplitude.

2.3. Data analysis

Data are expressed as mean ± standard error of the mean (±S.E.M.). For statistical analysis, we used a one-

factor ANOVA (one-way analysis of variance) with repeated measures; when appropriate, this was followed by the Newman–Keul's posthoc test. Statistical significance is considered to be $P < 0.05$.

3. Results

We recorded results from 62 hippocampal CA1 pyramidal neurons. The neurons had a mean resting membrane potential of -67.3 ± 0.7 mV (range: -60 to -78 mV, $n = 38$) and input resistance of 40.3 ± 2.8 MΩ ($n = 24$). The mean spike amplitude was 101.4 ± 1.7 mV (range: 90 to 120 mV, $n = 19$). These measures of passive membrane properties are in agreement with those of previously reported studies. Stable recordings could be maintained for up to 3 h, suggesting a relative lack of injury by the electrode penetration.

In general, GHB superfusion at 100–600 μM had little effect on membrane potential of CA1 pyramidal neurons (resting membrane potential mean value of -66.8 ± 0.5 mV). Therefore, analysis of synaptic responses could proceed without the confounding effects of direct potential change. Furthermore, GHB (100–600 μM) caused no significant change in the current–voltage relationships of CA1 neurons.

In CA1 neurons, a sequence of excitatory and inhibitory postsynaptic potentials could be evoked by stimulation of the Schaffer-collateral commissural fibers (Fig. 1A, upper trace). The same intensity stimulation of these fibers was not able to evoke the synaptic response in slices superfused with 10 μM DNQX, 30 μM bicuculline and 0.5 mM CGP 35348 to block AMPA/kainate, $GABA_A$ and $GABA_B$ receptors, respectively. However, a DNQX-resistant excitatory postsynaptic potential was elicited, increasing the intensity of the stimulation (Fig. 1A, lower trace). This response was voltage-sensitive with larger amplitude on depolarization (Fig. 1B), had longer duration than AMPA/kainate-mediated excitatory postsynaptic potentials, and was abolished by 30 μM d-APV, a specific NMDA receptor antagonist (Fig. 2A). The current–voltage relationship of this synaptic potential (Fig. 1B) had characteristics similar to the NMDA receptor-mediated responses previously found in hippocampal neurons.

In 26 cells, we examined the effect of GHB on the NMDA-mediated postsynaptic potential. Superfusion of GHB (100–600 μM) for 15 min produced a concentration-dependent depression of the excitatory postsynaptic potential peak amplitude. The decrease in the amplitude of this NMDA-mediated response usually occurred within 5 to 8 min after GHB had reached the slice chamber, with a peak GHB effect occurring at 8 to 12 min, and full recovery to control levels within 20 min of drug washout at all concentrations. d-APV (30 μM) superfusion blocked the NMDA-mediated excitatory postsynaptic potential in all cells tested.

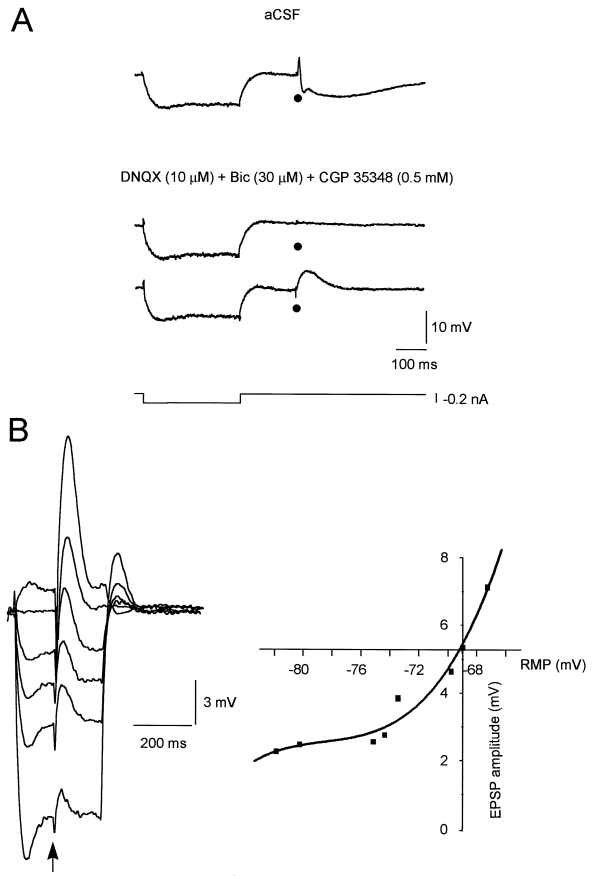

Fig. 1. Characteristics of the postsynaptic potentials elicited in a pyramidal neuron by local stimulation of the Schaffer-collateral commissural fibers. (A) Upper trace: excitatory postsynaptic potential followed by a sequence of fast and slow inhibitory postsynaptic potentials in a CA1 neuron evoked by orthodromic stimulation (black dots) of the Schaffer-collateral commissural fibers (0.3 mA, 80 μs, one every 20 s) in aCSF solution; medium trace: superfusion with DNQX (10 μM), bicuculline (30 μM), and CGP 35348 (0.5 mM) abolishes the synaptic responses evoked in the same cell; lower trace: increasing the strength of the orthodromic stimulation (1.1 mA, 80 μs, one every 20 s) elicits a DNQX-resistant excitatory postsynaptic potential with a time to peak at 45 ms and duration of 150 ms. In every trace, downward deflections of the membrane potential that precedes synaptic response are electrotonic potentials induced by hyperpolarizing current pulse (-0.2 nA, 300 ms). (B) Left side: Schaffer-collateral commissural fibers stimulation-evoked (arrow) excitatory postsynaptic potentials superimposed on a series of voltage steps. Cell recorded in the presence of DNQX (10 μM), bicuculline (30 μM) and CGP 35348 (0.5 mM) to isolate the NMDA-excitatory postsynaptic potential; right side: voltage sensitivity of the NMDA response of the same cell as in (A). RMP = -68 mV.

We examined the dose–response characteristics of the GHB effects on NMDA-mediated postsynaptic potentials in 20 pyramidal neurons. Fig. 2A shows a representative cell where 600 μM GHB markedly depressed this synaptic response.

Statistical analysis showed that GHB significantly reduced the mean amplitude of this synaptic component from 4.6 ± 0.34 to 3.6 ± 0.28 mV [$F(2,9) = 8.168$, $P < 0.05$], from 3.8 ± 1.3 to 2.3 ± 0.98 mV [$F(2,9) = 14.711$, $P < 0.05$] for GHB 100 μM and 300 μM, respectively,

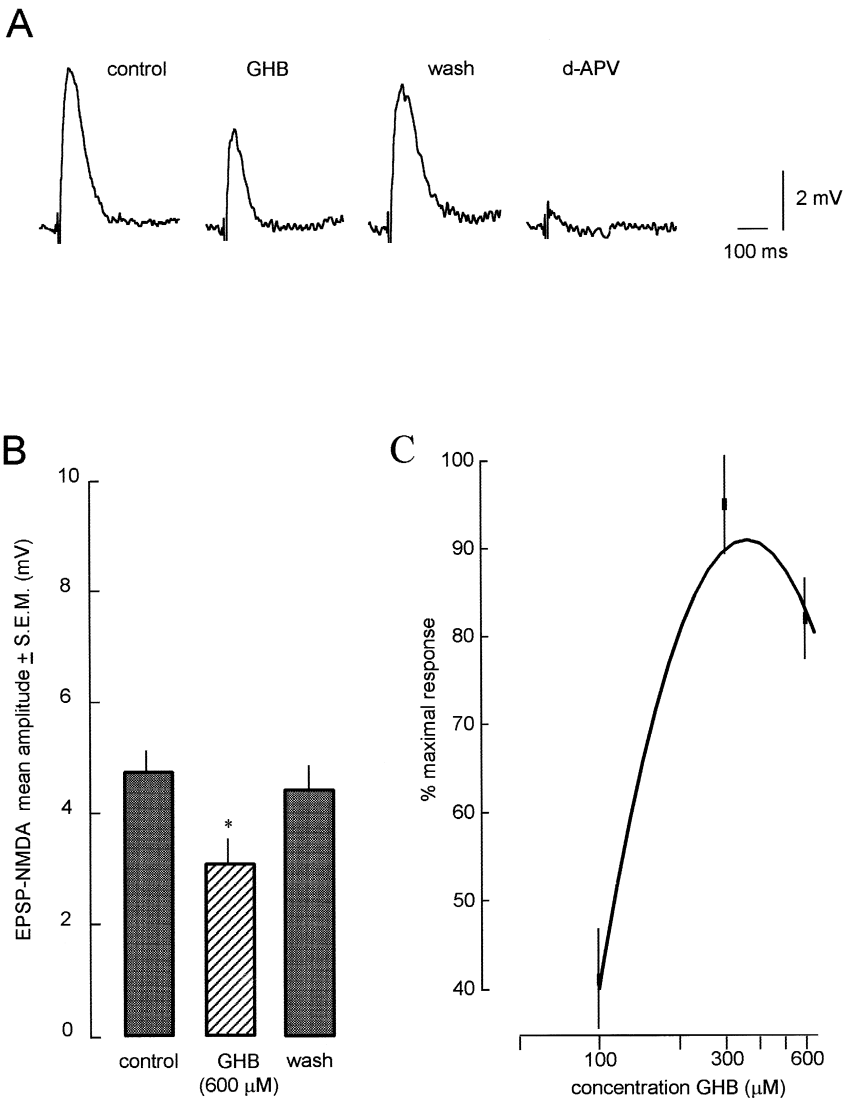

Fig. 2. GHB depresses NMDA-excitatory postsynaptic potentials. (A) isolated NMDA-excitatory postsynaptic potentials in the presence of 10 μM DNQX, 30 μM bicuculline, and 0.5 mM CGP 35348 from a representative pyramidal neuron are depressed reversibly by GHB (600 μM, 10 min). d-APV (30 μM) blocks the NMDA-excitatory postsynaptic potential. RMP = −65 mV. (B) Mean peak amplitude from 12 cells showing that GHB (600 μM) significantly (asterisk) attenuates the mean NMDA-excitatory postsynaptic potentials amplitude in a reversible manner. Error bars = S.E.M. (C) Dose–response curve for GHB inhibition of NMDA-response amplitude as percent of maximal GHB effect. The data are normalized to the maximal effect. For each concentration, $n = 4$ except for 600 μM where $n = 12$; GHB concentration is plotted on a log scale; dose–response curve was fitted by software (Origin, Microcal Software) to a logistic curve. Error bars = S.E.M.

and from to 4.7 ± 0.4 to 3.05 ± 0.49 mV [$F(2,33) = 16.532$, $P < 0.001$] for GHB 600 μM (Fig. 2B).

Averaging across all cells tested, 100, 300, and 600 μM of GHB reduced the NMDA-mediated excitatory postsynaptic potentials by $16.8 \pm 8.2\%$, $39.1 \pm 7.4\%$, and $33.7 \pm 6.9\%$ of control, respectively. Statistical analysis revealed no significant differences between the effects of GHB at the concentration of 300 and 600 μM. We normalized the GHB effect at each concentration to the percent of the effect on response amplitude elicited by 300 μM GHB (Fig. 2C).

To characterize the receptors involved in GHB-induced reduction of NMDA-mediated excitatory postsynaptic potentials, we repeated the experiments in the presence of the GHB antagonist, NCS-382 in six neurons. As shown in Fig. 3, NCS-382 (500 μM) applied alone for 15 min had no significant effects on the amplitude of this postsynaptic potential (from 3.4 ± 0.5 to 3.3 ± 0.4 mV). However, NCS-382 (500 μM) was able to significantly block the action of GHB (600 μM) on the NMDA component of the postsynaptic potential ($33.7 \pm 6.9\%$ depression induced by GHB alone, $2.3 \pm 0.5\%$ depression induced by GHB in the presence of NCS-382 [$n = 6$, $P < 0.005$]) (Fig. 3).

We focused next on possible interactions between GHB and the AMPA/kainate receptor-mediated synaptic events. In 12 neurons, superfusion of GHB (600μM) for 15 min produced a reduction of the mean amplitude of this postsynaptic response, with recovery on washout (Fig. 4A,B).

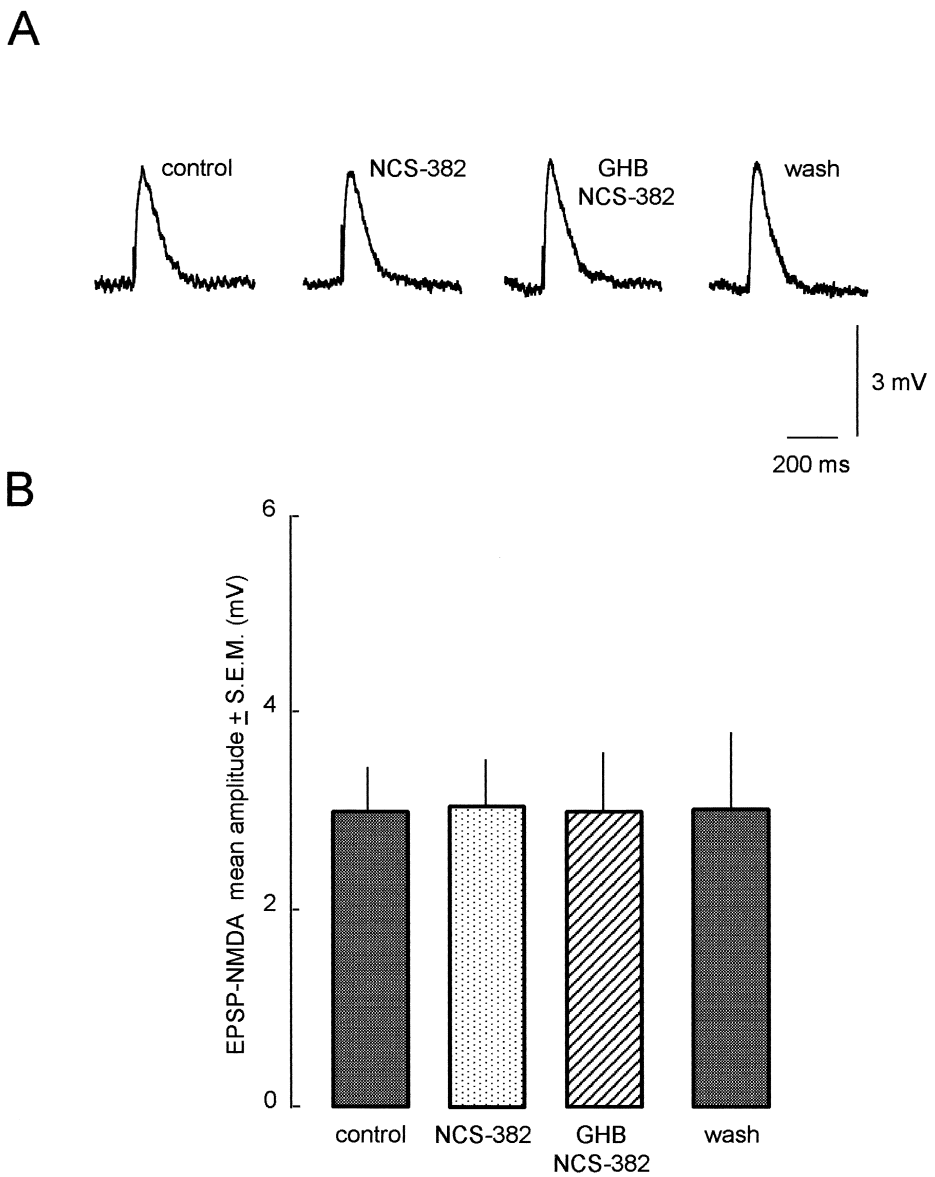

Fig. 3. Treatment with NCS-382 (500 μM) reduces the ability of GHB to inhibit the NMDA-excitatory postsynaptic potentials. (A) NMDA-excitatory postsynaptic potential from a representative cell. Superfusion of NCS-382 (500 μM, 15 min) does not alter the NMDA-excitatory postsynaptic potential. After treatment, GHB (600 μM) is ineffective in depressing the NMDA-mediated response. RMP = −65 mV. (B) Mean data from five cells showing that NCS-382 (500 μM) treatment greatly attenuates the depression of the NMDA-excitatory postsynaptic potential amplitude by GHB (600 μM). Error bars = S.E.M.

The GHB depression of AMPA/kainate receptor-mediated synaptic response was observed with an onset of 8–10 min. Statistical analysis showed that GHB significantly [$F(2,33) = 19.487$, $P < 0.001$] decreased peak amplitude of AMPA/kainate-mediated synaptic responses from 4.5 ± 0.49 to 2.8 ± 0.67 mV, with recovery to 4.2 ± 0.64 mV on washout (Fig. 4B).

In six neurons, we repeated the experiments in the presence of NCS-382. As previously described for NMDA-mediated response, NCS-382 (500 μM) applied alone for 15 min did not modify the amplitude of AMPA/kainate response (from 3.2 ± 0.63 to 3.3 ± 0.64 mV), whereas it was able to significantly block the depressant effect of 600 μM of GHB (37.8 ± 1.2% depression induced by GHB alone, 9.4 ± 0.6% depression induced by GHB in the presence of NCS-382, [$P < 0.005$]) (Fig. 4C).

The previous series of experiments shows that GHB decreases both NMDA and AMPA/kainate components of the excitatory postsynaptic potential, and implies that either the drug affects also postsynaptic glutamatergic receptors or it has additional effects at the presynaptic level, which may impair glutamate release.

To investigate the location of GHB action, we studied the effects of GHB on PPF. This parameter has been shown to be sensitive to pharmacological manipulations at the presynaptic level, but not to blockade of postsynaptic

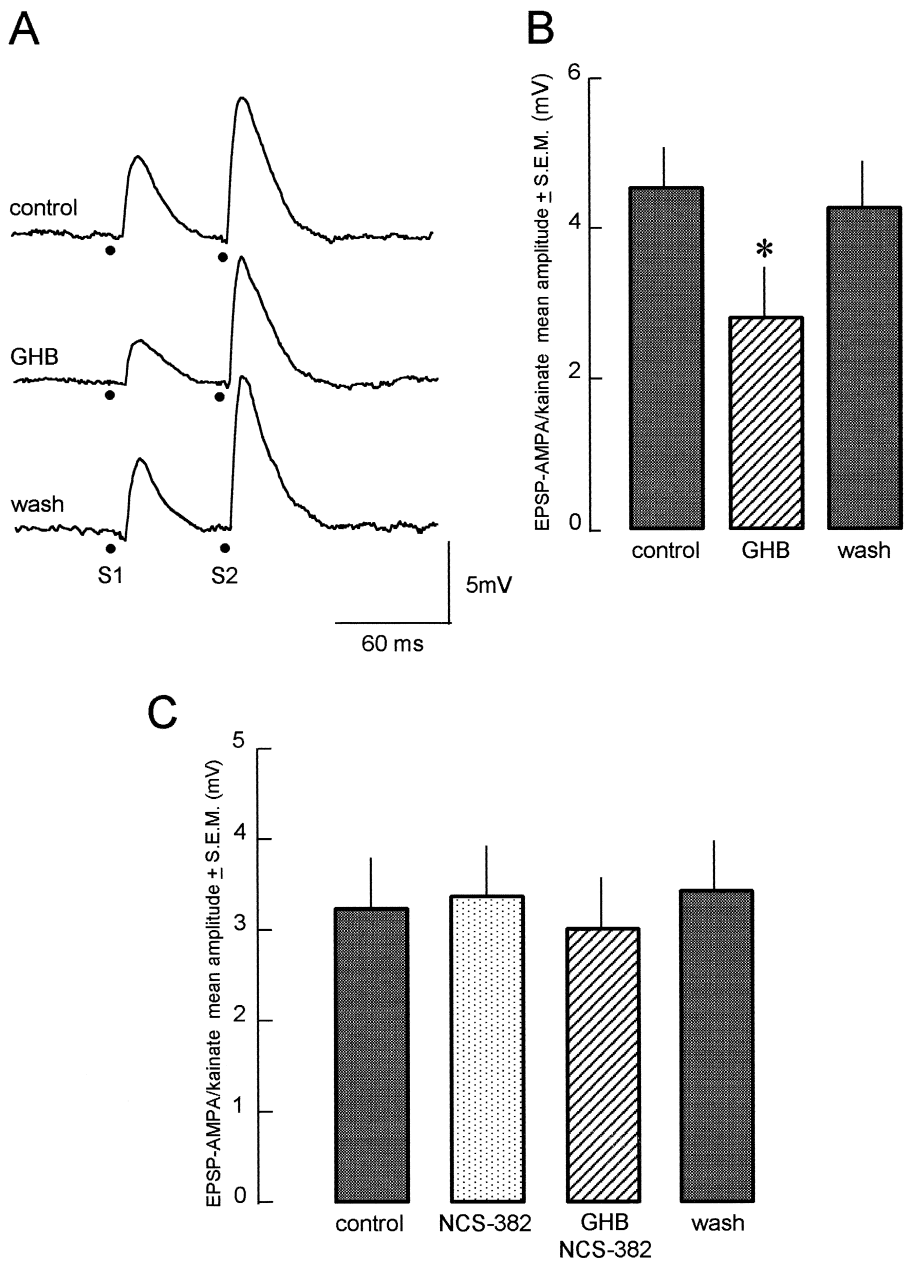

Fig. 4. GHB depresses AMPA/kainate-excitatory postsynaptic potentials. (A) AMPA/kainate-excitatory postsynaptic potential in the presence of 30 μM d-APV, 30 μM bicuculline, and 0.5 mM CGP 35348 from a representative cell. Superfusion of GHB (600μM, 10 min) depressed the excitatory postsynaptic potential. Black dots: onset of first and second stimuli, S1 and S2, respectively. RMP = −68 mV. (B) Mean peak amplitude from 12 cells showing that GHB (600 μM) significantly (asterisk) attenuates the mean AMPA/kainate-excitatory postsynaptic potentials amplitude in a reversible manner. Error bars = S.E.M. (C) Mean data from six cells showing that NCS-382 (500 μM) treatment greatly attenuates the effect of GHB (600 μM) on the AMPA/kainate-excitatory postsynaptic potential amplitude. Error bars = S.E.M.

AMPA/kainate and/or NMDA receptors (Manabe et al., 1993).

In the presence of d-APV (30 μM), bicuculline (30 μM), and CGP 35348 (0.5 mM) to block NMDA, $GABA_A$ and $GABA_B$ receptors respectively, low-strength paired stimuli delivered to the Schaffer-collateral commissural fibers at an interval of 60 ms evoked two excitatory postsynaptic potentials of different amplitudes, the second being larger than the first one. In four cells, GHB (600μM) significantly decreased the amplitude of both the first [from 3.2 ± 0.4 to 2.2 ± 0.4 mV] and the second EPSP [from 7.1 ± 0.9 to 5.8 ± 1.0 mV] (Fig. 4A).

The ratio of the amplitude of the second excitatory postsynaptic potential over the first was calculated before, during and after GHB application. In all tested cells (n = 4), PPF of the AMPA/kainate-mediated responses remained stable during the control period at the mean value of 2.1 ± 0.05. Application of 600 μM GHB for 15 min

significantly increased the PPF mean value to 2.7 ± 0.09, to recover during the washout, from $2.1 + 0.04$ [$F(2,9) = 19.708$, $P < 0.002$].

4. Discussion

The first major result of the present study is that in CA1 neurons, GHB decreases the peak amplitude of both NMDA and AMPA/kainate-mediated excitatory postsynaptic potentials without significant change of passive membrane properties such as resting membrane potential or input resistance. The effective concentrations of GHB used in this study (100–600 μM) are in the range of those measured in the rat brain after systemic administration of pharmacologically effective doses (200–400 mg/kg) of the drug that reduced voluntary ethanol intake (Lettieri and Fung, 1979; Fadda et al., 1988).

GHB reduction of both NMDA and AMPA/kainate-mediated excitatory postsynaptic potentials was reversible on washout and was obtained in the presence of CGP 35348 (0.5 mM), a specific $GABA_B$ receptor antagonist. The effectiveness of CGP 35348 in our model is reflected by the suppression of the late phase of the inhibitory postsynaptic potentials evoked by Schaffer-collateral commissural stimulation. The presence of the $GABA_B$ receptors antagonist, CGP 35348 (0.5 mM), during GHB superfusion could explain why we never observed hyperpolarization of the resting membrane potential and a decrease in the input resistance as described by other authors (Olpe and Koella, 1979; Kozhechkin, 1980; Xie and Smart, 1992a).

This study demonstrates, for the first time, a depressant effect of GHB on both NMDA and AMPA/kainate receptor-mediated component of the excitatory postsynaptic potentials recorded in hippocampal slices with $GABA_B$ receptors blocked by CGP 35348. Indeed, a GHB-induced depression of the excitatory and inhibitory synaptic potentials in CA1 region of the hippocampus has been previously described (Xie and Smart, 1992a,b; King et al., 1997). This effect was obtained at higher concentrations of GHB (1–10 mM) than those used in the present study and it was reversibly blocked by the selective $GABA_B$ antagonists, CGP 35348 and CGP 36742, suggesting that GHB can also activate presynaptic $GABA_B$ receptor to reduce excitatory and inhibitory transmitter release. At high concentrations, GHB can saturate and probably desensitize GHB receptors (Maitre, 1997).

The second major finding of the present work is that the reduction of the amplitude of the NMDA and AMPA/kainate-mediated excitatory postsynaptic potentials by GHB was blocked by NCS-382 (500 μM), a GHB receptor antagonist (Maitre et al., 1990). This result suggests that GHB depressant effect is mediated by the activation of GHB receptors.

The result, that PPF increases during the depressant effect of GHB on AMPA-mediated EPSPs, suggests a presynaptic location of GHB receptors. It seems likely that GHB may act presynaptically to reduce neurotransmitter release; GHB receptors are mostly found on nerve terminals (Maitre et al., 1983b). A presynaptic mechanism of GHB action is also consistent with the observations that K^+-evoked release of both GABA and glutamate was attenuated by GHB and reversed by the specific GHB receptor antagonist, NCS-382 (Banerjee and Snead, 1995).

We found that NCS-382 (500 μM) does not change membrane properties of pyramidal neurons nor altered synaptic transmission per se, providing evidence that NCS-382 did not cause nonspecific damage to the slice.

In recent years, it has been proposed that GHB might prevent ethanol withdrawal syndrome in both laboratory animal and in man by mimicking ethanol actions in the central nervous system (Fadda et al., 1989). Indeed, GHB and ethanol share pharmacological and biochemical actions. Previous electrophysiological studies have shown that ethanol reduced NMDA-mediated neurotransmission in both hippocampus and nucleus accumbens (Lovinger et al., 1990; Nie et al., 1993; Nie et al., 1994). The GHB-induced reduction of both NMDA and AMPA/kainate-mediated EPSPs observed in our study further supports the hypothesis that GHB may have ethanol-like actions.

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