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Bicuculline enhances the late $GABA_B$ receptor-mediated paired-pulse inhibition observed in rat hippocampal slices

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Abstract

The inhibition of CA1 pyramidal neurones in rat hippocampal slices was studied using extracellular recordings of population spike potential responses to paired orthodromic stimulation. Variation of the interpulse interval allowed the separation of an early phase of inhibition (interpulse interval 5–20 ms), blocked by the $GABA_A$ receptor antagonist bicuculline (1 μM; $n = 11$), and a late phase (interpulse interval 200–400 ms) blocked by the $GABA_B$ receptor antagonist phaclofen (1 mM; $n = 5$) but enhanced by bicuculline ($n = 11$). Similar enhancement was not observed when conditioning response amplitudes were increased by increasing the stimulus strength, rather than bicuculline. Orthodromic stimulation leads to synaptic excitation of both pyramidal neurones and inhibitory interneurones, and may also lead to activation of inhibitory inputs onto interneurones. Bicuculline could prevent inhibition of the interneurones, and hence enhance the late, $GABA_B$ receptor-mediated inhibition. Conversely, the therapeutic administration of benzodiazepines would be postulated to enhance the inhibition of inhibitory interneurones, leading to an iatrogenic decrease in $GABA_B$ receptor-mediated inhibition.

Keywords: GABA receptor; Hippocampus; Epilepsy; Synaptic inhibition; Disinhibition

1. Introduction

The overall transfer function of central nervous system (CNS) neural circuitry involves many separate components acting in unison, and assessments of the overall function from extracellularly recorded population spikes provides a vital overview to complement reductionist studies. The pattern of overall pyramidal cell response to a generalised orthodromic stimulus in the stratum radiatum is an excitatory postsynaptic potential, which can trigger an action potential, followed by two phases of synaptic inhibition (Alger, 1991; Knowles and Schwartzkroin, 1981). The feedback component of this inhibition appears to be due in the main to the basket cell interneurones located on the border of the stratum radiatum and stratum oriens (Lacaille et al., 1987). These cells, and the oriens/alveus interneurones found on the border of the stratum oriens and alveus, receive axon collaterals from CA1 pyramidal cells and also innervate their soma, completing a feedback loop. The dendrites of basket cells and oriens/alveus interneurones can be found in the stratum radiatum and lacunosum moleculare and may also receive excitatory inputs via the Schaffer collateral and commissural fibres in a feedforward manner. Another class of inhibitory interneurones has been identified in the lacunosum/moleculare, which appear to be activated in a feedforward manner and may be responsible for generating inhibition on the dendrites of the pyramidal cell (Alger and Nicoll, 1982; Dutar and Nicoll, 1988b; Lacaille and Schwartzkroin, 1988a,b).

The two temporally distinct periods of synaptic inhibition observed in the neuronal population responses are correlated with two types of inhibitory post-synaptic potentials (I.P.S.P.s). These are produced by the actions of γ-aminobutyric acid (GABA) on two distinct classes of receptor (Hill and Bowery, 1981; Bowery, 1989). Initially $GABA_A$ receptor activation elicits a chloride-dependent I.P.S.P., which may be antagonized by the convulsants bicuculline and picrotoxin (Alger and Nicoll, 1982; Curtis et al., 1971). $GABA_B$ receptor activation elicits a subsequent, late K^+-dependent hyperpolarisation (Alger, 1984; Dutar and Nicoll, 1988a;

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Gahwiler and Brown, 1985; Lancaster and Wheal, 1984) via a pertussis toxin-sensitive G protein (Alger, 1984; Hablitz and Thalmann, 1987; Newberry and Nicoll, 1985). This hyperpolarisation may be antagonized by phaclofen, a phosphonic derivative of the $GABA_B$ receptor agonist baclofen (Kerr et al., 1987; Soltesz et al., 1988), as can the late phase of population response inhibition (Morrisett et al., 1991). The early $GABA_A$ receptor-mediated phase of inhibition appears to involve both feedback and feedforward mechanisms via basket cells and oriens/alveus interneurones (Ashwood et al., 1984; Lacaille et al., 1987). The late phaclofen-sensitive I.P.S.P. appears to be generated on the dendrites of the pyramidal cell and may be a product of a feedforward mechanism involving lacunosum/moleculare interneurones (Alger and Nicoll, 1982; Dutar and Nicoll, 1988a; Lacaille and Schwartzkroin, 1988a,b). In this study we have investigated the hypothesis that GABAergic interneurones responsible for the late $GABA_B$ receptor-mediated I.P.S.P. of pyramidal neurones may in their turn be regulated by inhibitory GABAergic influences, allowing for the possibility of disinhibition.

2. Materials and methods

Preparation of hippocampal slices was as published previously (Andersen et al., 1987). In brief, male Wistar rats (200 g) were anesthetised with halothane and decapitated. The brain was removed and placed in artificial cerebrospinal fluid (ACSF) at 4° C. The ACSF was (concentrations in mM); NaCl 118, $NaHCO_3$ 26, KCl 3, KH_2PO4 1.25, $MgSO_4 \cdot 7H_2O$ 1, $CaCl_2$ 2.5, D-glucose 10, at pH 7.4, oxygenated with 95% O_2-5% CO_2. The hippocampi were dissected out and 500 μm transverse septal slices cut on a McIlwain tissue chopper. Only septal slices were used, as septal-temporal gradients in paired pulse inhibition have been observed, septal slices exhibiting stronger inhibition (Radpour and Wheal, 1987).

Slices were transferred to the recording chamber and perfused with ACSF at a fast flow rate of 10–12 ml min^{-1}. The ACSF was maintained at 32–34° C and oxygenated with 95% O_2-5% CO_2. The drugs used, bicuculline methiodide 1 μM (Sigma) and phaclofen 1 mM (Tocris Neuramin), were diluted into ACSF and perfused through the recording chamber until the changes in population spike recorded had stabilised. A constant voltage stimulus isolation unit (WPI; range 1–30 V) with a bipolar electrode was used to stimulate in the stratum radiatum (orthodromic stimulation). Equivalent, paired pulses were applied every 10 s with interpulse intervals of between 0 and 500 ms. Stimulation intensity was routinely set to the value which produced half-maximal amplitude of the conditioning population spike under control conditions for each set of recordings.

Extracellular recordings were made from the CA1

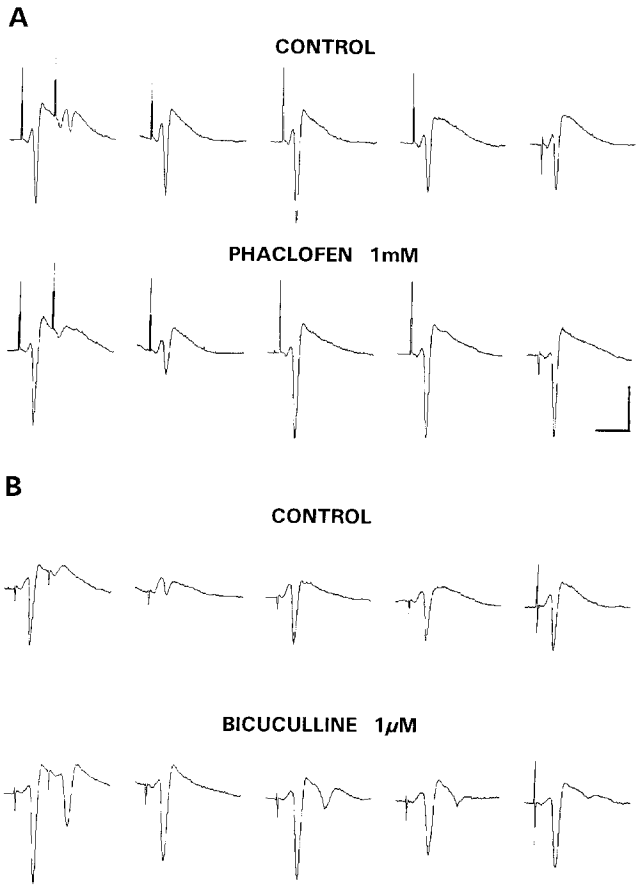

Fig. 1. Effect of GABA receptor antagonists on synaptic inhibition of extracellularly recorded pyramidal cell population spikes. Paired pulse inhibition was observed when an initial conditioning stimulus, which evoked a population spike (first response in leftmost column), was followed by a second, equal, test stimulus after an interpulse interval. Conditioning responses were unaffected by interpulse interval and therefore only one is shown for each set of interpulse interval tests (rows). Leftmost columns show the representative conditioning spike response as a positive-going field E.P.S.P. with a negative-going population spike superimposed. This is followed by the response to a test stimulus for an interpulse interval of 10 ms. Successive columns show test responses for increasing interpulse intervals of 20, 100, 300 and 500 ms. Data were aligned to the recovery phase, effectively removing D.C. offsets. Scale bars represent 2 mV amplitude and 10 ms duration. (A) Effect of phaclofen (1 mM): The top row shows responses to orthodromic stimulation under control conditions. The second row shows the effect of 15 min exposure to phaclofen (1 mM), which had little effect on conditioning responses but prevented the reduction in excitability for an interpulse interval of 300 ms seen in control. The responses recovered on washing. (B) Effect of bicuculline (1 μM): The top row shows responses to orthodromic stimulation under control conditions. The second row shows responses obtained after 30 min exposure to bicuculline (1 μM), with increased conditioning spike amplitudes. Note the increased excitability at 10 ms interpulse interval and the inhibition at 300 ms interpulse interval compared to the conditioning response. The responses recovered on washing.

pyramidal cell layer using glass electrodes containing 3 M NaCl (resistance 4–10 MΩ). Voltage recordings were filtered at 1 kHz, digitally sampled at 10 kHz and stored to disc. Subsequent computerised analysis averaged 6 individual trials for each interpulse interval. The size of the averaged population spike was measured as the difference between the peak and the average of the field-potential values immediately before and after the spike. The amplitudes of the first, conditioning population spike (c) and of the second, test population spike (t) were measured. Inhibition was quantified as the percentage difference between the normalised conditioning and test spike amplitudes $[(c - t/c) \times 100]$. Paired t-tests were used to assess statistical significance and data are presented as mean ± S.E.M.

3. Results

3.1. Paired-pulse inhibition

The time course of pyramidal cell inhibition was monitored by following the initial, conditioning stimulus by a second test stimulus. Conditioning stimuli produced positive-going field E.P.S.P.s with superimposed negative-going population spikes (Fig. 1). The second, test, stimulus produced similar responses, but the relative amplitudes depended upon the interpulse interval. Under control conditions (Fig. 1A) the test spike amplitude was reduced at interpulse intervals of 10–20 ms, but was increased for intervals of 30–100 ms. The test response amplitudes were also reduced for longer interpulse intervals of 200–500 ms. These reductions in population spike amplitude are taken to be reflections of decreased pyramidal cell excitability due to synaptic inhibition.

In order to test the validity of this assumption the dependence of the reduced population spike amplitude on GABAergic transmission was examined pharmacologically. Application of the $GABA_B$ receptor antagonist phaclofen (1 mM) did not induce spontaneous activity and had no consistent effect on the amplitude of individual responses. Phaclofen had no significant effect on the decrease in population spike amplitude for short interpulse intervals of 10–30 ms (Fig. 1A) but prevented the decrease at longer interpulse intervals of 100–500 ms, the implication being that this later phase was due to pyramidal cell inhibition caused by a $GABA_B$ synaptic input. Plotting the pyramidal cell inhibition against interpulse interval more clearly shows the overall patterns of changes (Fig. 2A). The inhibition observed is plotted against interpulse interval for control conditions and the presence of phaclofen (1 mM). As was seen for the raw data, under control conditions there is an early phase of inhibition (interpulse intervals of 10–30 ms), a facilitation (negative values of inhibition) for interpulse intervals of 30–100 ms and a second, late, phase of inhibition for interpulse intervals of 100–500 ms. Phaclofen had no statistically significant effect on this pattern for interpulse intervals of 10–100 ms, but significantly reduces the inhibition for interpulse intervals of 300 and 400 ms ($P < 0.05$).

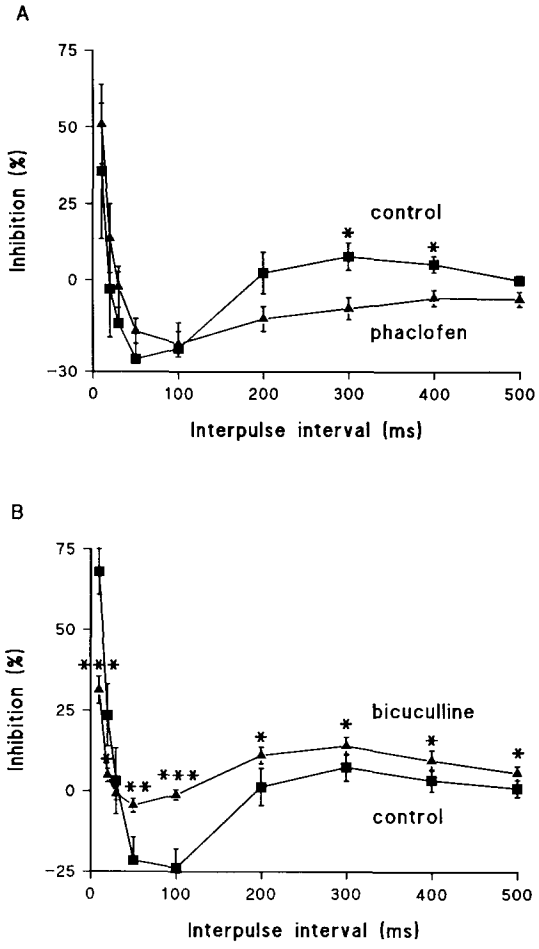

Fig. 2. Effect of GABA receptor antagonists on paired pulse inhibition. Percentage inhibition (calculated as $((c - t)/c) \times 100$) is plotted against the interpulse interval for two sets of experiments under control conditions and in the presence of antagonists. Control data (■) show inhibition at 10 ms interpulse intervals, facilitation at 20–100 ms, and a late component of inhibition at interpulse intervals of 200–500 ms. (A) Phaclofen (1 mM; ▲) had no significant effect on inhibition at short interpulse intervals (10–100 ms), but significantly reduced late inhibition ($^*P < 0.05$, $n = 5$). (B) Bicuculline (1 μM; ▲) significantly reduced inhibition at short interpulse intervals and facilitation at 50 and 100 ms interpulse intervals, but enhanced inhibition at longer interpulse intervals (200–500 ms; $n = 11$). P values from paired t-tests are indicated as $^*P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$.

The role of $GABA_A$ receptor-mediated inhibition in producing the early phase of inhibition was explored with the $GABA_A$ receptor antagonist bicuculline. Initial experiments showed that doses of 5 μM induced

spontaneous activity. Therefore, for these experiments the dose was reduced to 1 μM ($n = 11$). At this concentration bicuculline increased the conditioning spike amplitude (Fig. 1A) showing an increased pyramidal cell excitability. Test spike amplitudes were also increased over all interpulse intervals but particularly at short interpulse intervals of 10–30 ms. The inhibition, quantified as before and plotted against interpulse interval for each experiment, gives an overall picture of changes induced by bicuculline (Fig. 2B). The early phase (interpulse intervals of 10–20 ms) of inhibition is significantly reduced, as is the facilitation for interpulse intervals of 50–100 ms. However, the late phase of inhibition at each point tested (100–500 ms) was significantly enhanced ($P < 0.05$).

3.2. Dependence of bicuculline effect on initial conditions

Bicuculline increased the late inhibition in most experiments (8/11). In the other cases the control value for inhibition was already high and not further increased. This suggested that the effects of bicuculline depended upon the initial (control) state of the system. This was examined by analysis of the correlation between the inhibition under initial (control) conditions, and the decrease in inhibition produced by application of bicuculline (Fig. 3). For the early $GABA_A$ receptor-mediated inhibition (10 ms interpulse interval; ■) there is a clear correlation (linear regression, $r = 0.82$; $P = 0.002$) as would be expected. The more $GABA_A$ receptor inhibition being present, the more available to be blocked. However, a similar correlation (linear regression $r = 0.75$; $P = 0.008$) is also observed for the late inhibition (300 ms interpulse interval; ▲), where the increase in inhibition (negative y-axis values) is greatest where the initial condition showed least inhibition (or facilitation, negative x-axis values).

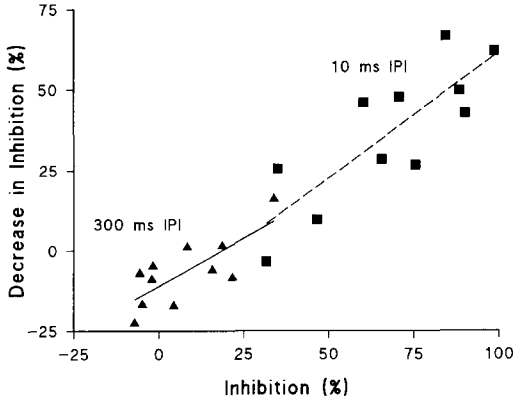

Fig. 3. Dependence of the effect of bicuculline (1 μM) on initial state. The decrease in inhibition produced by application of bicuculline is plotted against the control levels of inhibition for each experiment ($n = 11$). Inhibition at 10 ms interpulse intervals (■) was proportionally decreased by application of bicuculline. The dashed line shows the linear regression ($r = 0.82$; $P = 0.002$). Inhibition at 300 ms interpulse interval was small or negative under control conditions, but proportionally enhanced (negative values of y-axis) by bicuculline ($r = 0.75$; $P = 0.008$).

The mechanism underlying the bicuculline-enhanced late inhibition was tested in 4 experiments by the subsequent addition of phaclofen (1 mM) in the continued presence of bicuculline. The late inhibition (300 ms interpulse interval) was reduced ($-3.1 \pm 0.9\%$) compared to the value in the presence of bicuculline ($9.9 \pm 3.5\%$; $P = 0.02$).

Where control inhibition was high and bicuculline had produced little enhancement, addition of phaclofen reduced inhibition below the control level. Where the control inhibition had been small, and bicuculline had caused an enhancement of late inhibition, phaclofen reversed the change.

3.3. Dependence of late inhibition on stimulus intensity

The bicuculline enhancement of the late inhibition (300 ms interpulse interval) could be effected by the enhancement in conditioning spike amplitude. In order to evaluate this possibility the effect of altering the conditioning population spike amplitude by other means was examined. The amplitude was altered by changing stimulus intensity and early and late inhibition were measured ($n = 11$). Under control conditions, the conditioning spike amplitude increased to a plateau with stimulus intensities above a threshold level, reflecting increasing recruitment of the pyramidal cell population, as would be anticipated. The early inhibition (10 ms interpulse interval) increased from a low value when the stimulus was just above threshold, to a maximum and then decreased as stimulus intensity was further raised.

Bicuculline reduced the inhibition measured at the half-maximal amplitude stimulus intensity. The late inhibition (300 ms interpulse interval) was negative (facilitation) at low stimulus voltages and high stimulus amplitudes but became more positive for half-maximal amplitude stimuli. Application of bicuculline caused greater inhibition than observed at any stimulus voltage under control conditions. The full range of measured inhibitions at 300 ms for any stimulus intensity was -23%–20%, and the corresponding range for application of bicuculline in 3 of these experiments was 0.3%–12%. For the previous set of experiments where bicuculline was tested at half-maximal amplitude stimulus ($n = 11$) the range under control conditions was -7.2%–34%, whereas the full range observed in the presence of bicuculline was 1.5%–30%.

4. Discussion

The observation of two, temporally distinct, phases of synaptic inhibition in response to an orthodromic stimulation of the CA1 pyramidal cells, mediated by $GABA_A$ and $GABA_B$ receptors, confirms previous observations (Karlsson and Olpe, 1989; Alger, 1991; Morrisett et al., 1991). Phaclofen (1 mM) had little effect on conditioning responses (Fig. 1A) or on early inhibition, but significantly decreased late inhibition (300 ms interpulse interval) in experiments where it was observed under control conditions (Fig. 2B). Conforming to the hypothesis that the late inhibition is $GABA_B$ receptor-mediated but not tonically active (Dutar and Nicoll, 1988a; Wojcik and Holopainen, 1992; Bowery, 1993). The phaclofen blockade of this late inhibition argues against a significant role for intrinsic Ca^{2+}-activated K^+ currents in reducing the overall excitability of the pyramidal neurone population.

Bicuculline at high concentrations (5 μM) caused spontaneous repetitive population spikes, and at the lower concentration tested (1 μM) had multiple effects. The conditioning response amplitudes were increased (Fig. 1B), and early inhibition was greatly reduced (10 ms interpulse interval; Fig. 2B). Paradoxically, the facilitation observed in control slices was also reduced (interpulse intervals of 30–100 ms; Fig. 2B), and the late, phaclofen-sensitive phase of inhibition was enhanced (interpulse intervals 300–500 ms).

Paired-pulse facilitation in the hippocampus has been proposed to be produced by disinhibition, reduction of $GABA_A$ receptor-mediated inhibition (Nathan and Lambert 1991). Under control conditions, tonic inhibitory interneurone activity controls conditioning spike amplitude, but after a stimulus which discharges a large percentage of interneurones (feedback and feedforward), there will be a period of synchronous interneurone quiescence which would be observed as disinhibition or facilitation. Bicuculline blocks tonic inhibition, enhancing the conditioning spike, thus disinhibition can no longer produce facilitation. This argues against any significant role for presynaptic Ca^{2+} accumulation in the facilitation observed at the population level. The enhanced late inhibition is not simply related to increased conditioning spike amplitude, as it cannot be mimicked by increasing stimulus strength but could represent a modification of the excitability of the interneurones responsible. Bicuculline reduced the range of inhibitions observed at an interpulse interval of 300 ms, confining it to positive values, preventing facilitation.

There is anatomical evidence of a GABAergic input from the medial septum onto inhibitory interneurones in the rat hippocampus (Halasy et al., 1992) which could be activated by our experimental stimulus in vivo. This pathway in combination with the cholinergic inputs to inhibitory neurones has been postulated to regulate hippocampal excitability and lead to entrainment of the theta rhythm (Stewart and Fox, 1990; Smythe et al., 1992). Bicuculline could be acting to prevent $GABA_A$ receptor-mediated inhibition of these inhibitory interneurones, increasing their probability of firing in response to stimulus, thus allowing an increased $GABA_B$ receptor inhibition. We have not observed the converse pattern of enhanced $GABA_A$ receptor inhibtion in the presence of phaclofen. However, judging from the lack of effect of phaclofen on conditioning responses, there is no tonic $GABA_B$ receptor inhibition of inhibitory interneurones, and any evoked $GABA_B$ receptor inhibition of interneurones may also be antagonised.

The paired-pulse inhibition data effectively illustrate the transfer function of the CA1 pyramidal neurones of the hippocampus. Under control conditions, the system will tend not to follow stimuli repeated at less than 30 ms intervals (30 Hz), which will also control spontaneous activity due to depolarising afterpotentials. However, the system will tend to preferentially follow stimuli repeated at 50–200 ms intervals (20–5 Hz). The pattern of changes in excitability will lead to phase advance of inputs of less than 4 Hz and phase delay inputs of > 10 Hz. Overall, this would appear to give the system the property of reinforcing theta frequency inputs (4–7 Hz), and this may be important to its function.

The simplest explanation for our data would be that the stimuli excite both excitatory and inhibitory inputs to inhibitory interneurones, and that antagonism of $GABA_A$ receptors on these inhibitory interneurones increases their excitability, hence leading to an enhancement of $GABA_B$ receptor-mediated inhibition. These observations could have a clinical relevance, in that anti-epileptic therapies based on enhancing $GABA_A$ receptor function via the benzodiazepine receptor would also be expected to enhance the inhibition of $GABA_B$ receptor-mediated inhibition, possibly reducing its beneficial effects.

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