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Activation of γ-aminobutyric acid$_B$ receptors by baclofen improves visual temporal property of relay cells in the cat lateral geniculate nucleus

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Abstract

The role of γ-aminobutyric acid$_B$ (GABA$_B$) receptors in spatial and temporal properties of the neurons was investigated in the cat dorsal lateral geniculate nucleus (dLGN) using flashing spot and drifting grating stimuli. Iontophoresis of baclofen, the selective GABA$_B$ receptor agonist significantly decreased the spontaneous and visual evoked responses (decreased to 38 ± 7%), in which only the sustained component was suppressed sharply. Baclofen affected neither the center-surround antagonism of receptive fields nor the optimal spatial frequency of stimulating gratings. However, baclofen shortened cells' response duration and elevated their temporal frequencies that evoked the maximum and the half maximum response. In contrast, 2-OH-sacrofen, a GABA$_B$ antagonist showed no significant effect on dLGN cells' spatio-temporal properties. In conclusion, the activation of GABA$_B$ receptors may improve the temporal response properties of dLGN cells' via the sustained pathway, rather than change the spatial properties.

Keywords: Baclofen; γ-aminobutyric acid$_B$ receptor; Lateral geniculate nucleus; Receptive field; Temporal property; Cat

Inhibition is crucial for cells in the dorsal lateral geniculate nucleus (dLGN) in controlling the relay of visual information from the retina to the cortex and participating in the thalamo-cortical oscillations [5,18]. Three types of γ-aminobutyric acid (GABA)-ergic receptor mediated inhibitory post-synaptic potential (IPSP) have been described previously. The early C1-dependent IPSPs are mediated by GABA$_A$ or GABA$_C$ receptors, of which the former plays a key role in sharpening the response properties of geniculate cells such as center-surround antagonism [17] and orientation tuning [19].The GABA$_B$ receptors mediated late IPSPs are relatively slow and differ fundamentally from that of GABA$_A$ receptors. GABA$_B$ receptors are located in pre- and/or post-synaptic membranes, and coupled respectively to various Ca^{2+} and K^+ channels presumably through both a membrane-delimited pathway and a pathway involving second messengers [4,13].

In the primary visual cortex, the GABA$_B$ receptor mediated inhibition enhances the orientation selectivity of the sustained response [1]. The GABA$_B$ receptors have been shown in thalamus, particularly in the dLGN. There is a higher density of GABA$_B$ binding sites in dLGN than in the ventral LGN [3]. GABA$_B$ receptors also participate in the oscillation of dLGN [5,18]. However, in the visual information processing, the role of GABA$_B$ receptors in the spatio-temporal properties of dLGN neurons in vivo is still unclear. The purpose of this study is to elucidate this issue using electrophysiological technique combined with local administration of baclofen (p-chlorophenyl GABA), a selective GABA$_B$ agonist.

Seven adult cats were prepared for single unit recording as described previously [16]. Animals were kept slightly anesthetized and paralyzed throughout the experiments. A computer driven Picasso image synthesizer (Innisfree,

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USA) and a Tektronix 608 display (USA) were used to generate visual stimuli. The position of display could be adjusted to any point in the animal's visual field while maintaining a fixed distance of 57 cm between the display and the cat's eye. The post-stimulus time histograms (PSTHs) of a cell's visual evoked response were averaged for 8–10 times with a computer. The responses to the drifting sinusoidal gratings were defined as the amplitude of the fundamental Fourier component of PSTHs. To the flashing spots, the responses were defined as the peak and count response of the smoothed PSTHs. The detailed methods for recording, data collection, and data analysis were described previously [16].

Three-barrel glass electrodes were lowered into layers A and A 1 of the dLGN. Action potentials of a single neuron were extracellularly recorded through the central barrel of the electrode, which was filled with 3 M NaCl. The recording sites were at least 150 μm apart. In some cases, biocytin (2.5% in 0.05 M Tris, 1 M KC1 (pH 7.2)) was filled in the barrel for injecting to mark the recording site. The second electrode barrel was filled with baclofen (Sigma, 10 mM in 150 mM NaCl (pH 3.5)) for drug iontophoretic administration and fed with a small negative retaining current (10–25 nA) for holding the drug. Current balancing was provided through the third barrel containing 175 mM NaCl. Neuron response data were not collected until 5 min after the onset of the baclofen iontophoresis. The recovering time was about 5 min.

The $GABA_B$ agonist baclofen reduced, in a dose-dependent way, the visual responses of the dLGN neurons in the cat. The cells' spontaneous and visual evoked responses decreased with the iontophoretic current increase. Higher current (40 nA) baclofen injection reduced the cells' responses to visual grating stimuli to a mean of $38 \pm 7\%$ ($n = 23$) of the control, including six neurons depressed completely. The inhibition mediated by $GABA_B$ receptors is more significant in the dLGN, compared with that (a mean of $49 \pm 5\%$ of the control, l20 nA) in rat superior colliculus [2].

Fig. 1A shows the PSTHs of a typical cell's responses to flashing spots of increasing diameter before and during baclofen administration. During baclofen injection, the sustained component almost disappeared compared with the control, while the transient component of the visual responses changed little. The most prominent inhibitory effect appeared at about 120 ms and later after the onset of visual stimulus in eight neurons measured, corresponding to the measurement of the $GABA_B$ receptor-mediated IPSC in vitro [3,4]. The typical spot-diameter tuning curves of the same neuron above were shown in Fig. 1B. The neuron responded maximally to a flashing spot of 0.5° in diameter, which corresponded to the size of the cell's receptive field center, and then decayed with increasing diameter due to the surround inhibition. It is noteworthy that both the peak and the count response curves were similar in shape. Although the count response was reduced 2.5-fold by baclofen (open square curves, upper in Fig. 1B), either the diameter of the flashing spot that evoked the maximum response or the time course of the response decreased with increased diameter kept unchanged during baclofen application. This suggests that the center-surround antagonist mechanism of the receptive field is unaffected by the baclofen activation of $GABA_B$ receptors.

To study whether $GABA_B$ receptors contribute to the spatial property of the relay cells, we measured the spatial frequency tuning curves before and during baclofen injection using drifting sinusoidal grating stimuli (Fig. 2). Obviously, baclofen injection reduced the cell's response, but had little effect on the shape of the high part of the spatial frequency-tuning curve. Since a cell's spatial resolution of gratings is closely related to the center mechanism of its receptive field, thus, this is quite in agreement with the above finding that baclofen did not affect the spatial center-surround structure of receptive fields.

Baclofen made the time course of PSTHs narrower, while the peak response changed little, as shown in Fig. 3A. Inter-

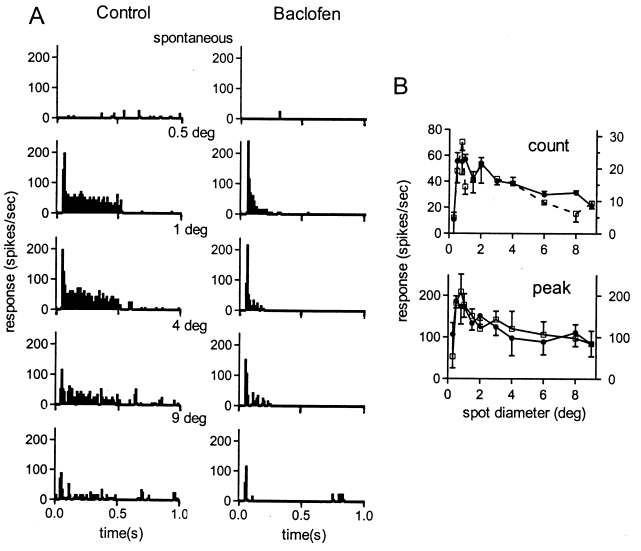

Fig. 1. PSTHs of a dLGN cell's responses to flashing spots of different diameters and diameter tuning curves before and during baclofen administration. (A) PSTHs in 10 ms bin-width averaged from eight responses showing spikes evoked by the repeatedly flashing spot (on 500 ms, off 500 ms) of increasing diameter (numbered from 0.5 to 9°). The left column and the right column show the PSTHs before (the control) and during a 10 min 40 nA iontophoresis of baclofen, respectively. The top row of two PSTHs shows the spontaneous response. (B) Diameter tuning curves showing the count (upper) and the peak (below) responses of the same neuron to different size of flashing spots. The left vertical axis is for the control responses (filled circles), the right vertical for those during baclofen administration (open squares). Note that since the scales in the vertical axis are different, the count responses before and during baclofen are significantly different in quantity indicating a big decrease in sustained response components by baclofen. In contrast, the peak responses are quite similar before and during baclofen. The error bars in the two figures indicate the 95% confidence ranges.

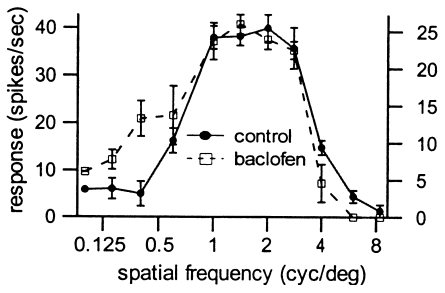

Fig. 2. Effect of baclofen on the spatial frequency tuning curve. Drifting sinusoidal gratings of different spatial frequencies in the optimal orientation and temporal frequency were presented on the receptive field of the neuron. The data were cumulated from the fundamental Fourier component of averaged PSTH of six responses. The scales of left and right sides showed the control (filled circles) and baclofen-injected (open squares) curves, respectively. Though there had been some change at low spatial frequency, the optimal spatial frequency was not affected. The error bars in the figure indicate the 95% confidence ranges.

estingly, the optimal temporal frequency in temporal frequency tuning curves shifted to the right (higher frequency direction) during activation of $GABA_B$ receptors by baclofen presumably due to the shortening of response time course (Fig. 3B). The improvement in temporal frequency property caused by baclofen was prominent (*t*-test, $P < 0.05$) in all seven neurons tested. The histograms in Fig. 3C summarize the effects of baclofen on temporal frequency in these cells. Baclofen significantly increased the optimal temporal frequencies that evoked the maximum responses and the higher frequency that evoked the half maximum response.

We also administrated the $GABA_B$ receptor antagonist 2-OH-saclofen in the dLGN, however, neither the spontaneous nor the visual evoked responses changed significantly during drug application in dLGN. There are some studies suggesting that 2-OH-saclofen exhibits partially agonist properties in rat dLGN, as suggested by Emri [6] though 2-OH-saclofen had electrophysiological effect in many brain areas such as visual cortex [1] and superior colliculus [2] in vivo.

In this study we demonstrated the first evidence that activation of $GABA_B$ receptors by baclofen improved the temporal properties of relay cells of dLGN in the cat without influence to the cells' spatial discrimination, although the sustained response component was reduced. This suggests that the $GABA_B$ receptor-mediated inhibition may play an important role in temporal property within the cat dLGN.

The results showed that $GABA_B$ receptor mediated inhibition was limited to the long latency (>120 ms) sustained response. It is consistent with the notion that the $GABA_B$ receptor operates via a 'slow' G-protein coupled second messenger system [4]. Perceptual and single unit studies have revealed the existence of sustained and transient channels in visual system (for review, see Ref. [12]) Compared with the previous report that bicuculline affected primarily the transient responses of dLGN neurons [7,14] our results suggest that the inhibitions mediated by $GABA_A$ and $GABA_B$ receptors may modulate signals through the transient and sustained pathways, respectively.

Previous work suggested that $GABA_A$ receptors played

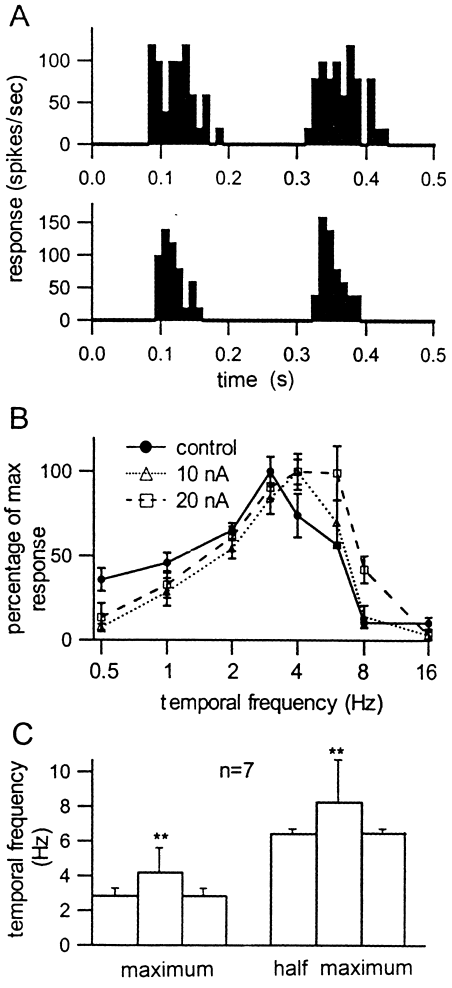

Fig. 3. Effect of baclofen on cells' temporal properties. (A) PSTHs represented in 10 ms bin-width showing spikes evoked by a 4 Hz drifting sinusoidal grating with the optimal orientation and spatial frequency. Upper, control response; below, response during baclofen injection (I0 nA, 10 min). (B) Temporal frequency tuning curves showing the fundamental Fourier component of responses to the optimal drifting gratings presented on the receptive field. The solid line (filled circles) shows the control tuning curve; the dotted line (open triangles) and dash line (open squares) show the tuning curves during the baclofen administrations with 10 and 20 nA currents used, respectively. All the curves were normalized and their maximum responses were 50 (filled circles), 30 (open triangles) and 21.5 (open squares) in spikes/s for the control, the 10 nA, and 20 nA curves, respectively. (C) Two groups of histograms showing the effect of baclofen on the temporal frequencies of gratings that evoked the maximum response and the half maximum responses (mean ± S.D.,). Three columns in each group show the temporal frequencies of the control, during baclofen injection and after full recovery, respectively (left to right). Baclofen significantly increased both the temporal frequencies that produced the maximum and the half maximum responses. ** indicating that data vs. the controls are significantly different at $P < 0.05$ level (*t*-test).

a key role in some receptive field properties of cells in the dLGN, such as surround [17] and orientation bias [10,19]. However, we found that interestingly, baclofen did not clearly affect the transient component of responses, the center-surround antagonism and spatial frequency-tuning curve suggesting that the transient components may carry more spatial information than the sustained one. Our finding that baclofen injection elevated the optimal temporal frequency of cells' responses indicates a kind of nonlinear interaction within the dLGN, and is in agreement with the observation in the visual cortex by Pfleger and Bonds [15].

$GABA_B$ receptors were located either in pre-synaptic or in post-synaptic membranes in many brain areas [3,6,9,11]. Our study could not distinguish whether the effect of baclofen is pre- and/or post-synaptic in the dLGN, however, some evidence suggested that postsynaptic $GABA_B$ receptors were not activated by endogenous GABA in visual pathway [6]. Our observation showed that there were six neurons silenced by baclofen, while the majority of cells still kept some degree of response even when a large injection current was used. The difference implies that the densities of $GABA_B$ receptors on the different neurons may vary significantly. On the other hand, the subtypes of baclofen-insensitive $GABA_B$ receptor [8] may also exist in the relay cells in cat dLGN, as Yamada suggested in other brain areas [20].

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[1] Allison, J.D., Kabara, J.F., Snider, R.K., Casagrande, V.A. and Bonds, A.B., GABAB-receptor-mediated inhibition reduces the orientation selectivity of the sustained response of striate cortical neurons in cats, Vis. Neurosci., 13 (1996) 559–566.
[2] Binns, K.E. and Salt, T.E., Different roles for GABAA and GABAB receptors in visual processing in the rat superior colliculus, J. Physiol. (Lond.), 504 (1997) 629–639.
[3] Bowery, N.G., GABAB receptor pharmacology, Annu. Rev. Pharmacol. Toxicol., 33 (1993) 109–147.
[4] Crunelli, V. and Leresche, N., A role for GABAB receptors in excitation and inhibition of thalamnocortical cells, Trends Neurosci., 14 (1991) 16–21.
[5] Destexhe, A., Spike-and-wave oscillations based on the properties of GABAB receptors, J. Neurosci., 18 (1998) 9099–9111.
[6] Emri, Z., Turner, J.P. and Crunelli, V., Tonic activation of presynaptic GABA(B) receptors on thalamic sensory afferents, Neurosci., 72 (1996) 689–698.
[7] Eysel, U.T., Pape, H.C. and Van Schayck, R., Contributions of inhibitory mechanisms to the shift responses of X and Y cells in the cat lateral geniculate nucleus, J. Physiol. (Lond.), 388 (1987) 199–212.
[8] Guyon, A. and Leresche, N., Modulation by different GABAB receptor types of voltage-activated calcium currents in rat thalamocortical neurones, J. Physiol. (Lond.), 485 (1995) 29–42.
[9] Howe, J.R., Sutor, B. and Zieglgansberger, W., Baclofen reduces post-synaptic potentials of rat cortical neurones by an action other than its hyperpolarizing action, J. Physiol. (Lond), 384 (1987) 539–569.
[10] Hu, B., Li, X.R., Zhou, Y.F. and Shou, T., Effects of GABA antagonist bicuculline on the orientation tuning character of relay cells in dorsal geniculate nucleus (dLGN), Acta Biophys. Sinica, 10 (1994) 121–127.
[11] Le Feuvre, Y., Fricker, D. and Leresche, N., GABAA receptor-mediated IPSCs in rat thalamic sensory nuclei: patterns of discharge and tonic modulation by GABAB autoreceptors, J. Physiol. (Lond.), 502 (1997) 91–104.
[12] Maunsell, J.H. and Newsome, W.T., Visual processing in monkey extrastriate cortex, Annu. Rev. Neurosci., 10 (1987) 363–401.
[13] Misgeld, U., Bijak, M. and Jarolimek, W., A physiological role for GABAB receptors and the effects of baclofen in the mammalian central nervous system, Prog. Neurobiol., 46 (1995) 423–462.
[14] Norton, T.T. and Godwin, D.W., Inhibitory GABAergic control of visual signals at the lateral geniculate nucleus, Prog. Brain Res., 90 (1992) 193–217.
[15] Pfleger, B. and Bonds, A.B., Dynamic differentiation of GABAA-sensitive influences on orientation selectivity of complex cells in the cat striate cortex, Exp. Brain Res., 104 (1995) 81–88.
[16] Shou, T., Li, X., Zhou, Y. and Hu, B., Adaptation of visually evoked responses of relay cells in the dorsal lateral geniculate nucleus of the cat following prolonged exposure to drifting gratings, Vis. Neurosci., 13 (1996) 605–613.
[17] Sillito, A.M. and Kemp, J.A., The influence of GABAergic inhibitory processes on the receptive field structure of X and Y cells in cat dorsal lateral geniculate nucleus (dLGN), Brain Res., 277 (1983) 63–77.
[18] Ulrich, D. and Huguenard, J.R., Gamma-aminobutyric acid type B receptor-dependent burst-firing in thalamic neurons: a dynamic clamp study, Proc. Natl. Acad. Sci. USA, 93 (1996) 13245–13249.
[19] Vidyasagar, T.R., Contribution of inhibitory mechanisms to the orientation sensitivity of cat dLGN Neurones, Exp. Brain Res., 55 (1984) 192–195.
[20] Yamada, K., Yu, B. and Gallagher, J.P., Different subtypes of GABAB receptors are present at pre- and postsynaptic sites within the rat dorsolateral septal nucleus, J. Neurophysiol., 81 (1999) 2875–2883.