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NORADRENERGIC MODULATION OF RETINOGENICULATE TRANSMISSION IN THE CAT

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SUMMARY

1. Relay neurones were extracellularly recorded from the A-layers of the dorsal lateral geniculate nucleus (dLGN) of the anaesthetized cat. The noradrenergic influence on retinogeniculate transmission was investigated through microiontophoretic techniques in a total of 140 dLGN relay cells using three experimental approaches: (i) the effects of agonists for α_1-, α_2- and β-adrenoceptors were separately analysed; (ii) the noradrenergic influence was related to the global state of activity of the relay neurones, which was associated with discrete patterns of the electroencephalogram (EEG); (iii) distinct phases of visual responses evoked from the area of the retinal receptive field, and of binocular and lateral inhibitory responses, were evaluated before, during and after the action of noradrenergic agonists.

2. The spontaneous generation of high-frequency bursts of spikes in dLGN relay neurones, associated with periods of highly synchronized, δ-like patterns of the EEG, was selectively suppressed by the β-adrenoceptor agonist isoprenaline or the α_1-adrenoceptor agonist phenylephrine. Single action potentials, occurring at a low frequency between bursts, were significantly less affected. Depending upon the ejection level of the adrenoceptor agonists, burst activity was suppressed by 23–73%, compared with a reduction in single spike firing in the range 7–24%. The suppression of burst firing occurred in all functional types of dLGN relay neurones (X, Y; on, off), enhanced burst activity was observed in less than 1% of the cells.

3. On-going tonic sequences of action potentials (around 15 Hz), occurring during periods of EEG activity characterized by lower amplitudes and higher frequencies, were separately affected by adrenoceptor agonists. Isoprenaline had no significant effect, phenylephrine induced a global reduction of spike firing with no obvious relation to the ejection level, and the α_2-adrenoceptor agonist clonidine inhibited action potential generation in a near dose-dependent manner.

4. Visual response properties were investigated during periods of less synchronized states of EEG activity. Responses to visual stimulation of the retinal receptive field centre were not significantly influenced by isoprenaline, while phenylephrine or clonidine attenuated the phasic and the tonic response component in all functional

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types of relay neurones and independent of the stimulus contrast being used. At low ejection levels, slight facilitatory effects were observed with isoprenaline (65% of neurones that were tested) or phenylephrine (15%). The inhibitory influence of the antagonistic surround area of the receptive field appeared unaltered during action of isoprenaline or phenylephrine.

5. Binocular and long-range lateral inhibition were selectively modulated by adrenoceptor agonists in more than 90% of the neurones that were tested. Application of isoprenaline resulted in a significant *decrease* (average 7 spikes s^{-1}) in amplitude and duration of the late phases of inhibitory responses, thereby reducing the relative strength of late inhibition by about 45%. By contrast, phenylephrine induced a significant *increase* (average 5 spikes s^{-1}) in the strength of late inhibitory responses.

6. In a sample of neurones, the influences of adrenoceptor stimulation on visual responses during periods of δ-like, synchronized EEG activity were directly compared with those changes in visual responsiveness which were associated with the naturally occurring shift in the EEG to patterns of lower amplitudes and higher frequencies. The shift in the EEG was accompanied in the dLGN with a *suppression* of burst firing, a strong *increase* in the tonic component of visual responses from an average of 10 to an average of 45 spikes s^{-1}, and a significant *reduction* averaging 67% in the late phases of binocular and lateral inhibition. These changes were largely mimicked by microiontophoretic application of isoprenaline.

7. We conclude that the noradrenergic influence provides an important basis for the faithful transfer of visual signals through the dLGN during periods of increased arousal by preventing burst discharges and controlling the late phases of globally organized inhibitory mechanisms without interfering with the antagonistic centre–surround organization of the receptive field area. The suppressant influence of α_2-adrenoceptors may reflect the existence of a regulatory system, which limits the effects of the ascending brainstem system in the dLGN.

INTRODUCTION

The state-dependent gating of visual information through the dorsal lateral geniculate nucleus (dLGN) is controlled by ascending inputs from the upper brainstem core (for recent reviews see Steriade & McCarley, 1990; McCormick, 1992). The major brainstem–thalamic projection system comprises cholinergic fibres from the pedunculopontine and lateral dorsal tegmental nuclei, serotonergic fibres from the raphe nuclei, and a noradrenergic projection from the locus coeruleus. The shift from periods of synchronized electroencephalographic activity, such as occurs during drowsiness or slow-wave sleep, to states of a desynchronized electroencephalogram (EEG) is accompanied by increased activity of these brainstem neurones, and experimentally induced activation of the brainstem system mimics the events occurring during natural arousal. The ascending influence induces a shift in overall neuronal activity in the thalamus from rhythmically or non-rhythmically occurring burst firing to the generation of more tonic sequences of fast action potentials (McCarley, Benoit & Barrionuevo, 1983), and which may allow a more faithful transfer of synaptic information (Steriade & McCarley, 1990). In the dLGN, the influence of acetylcholine greatly facilitates visual responsiveness, due to a direct

excitation of relay cells (Sillito, Kemp & Berardi, 1983; Eysel, Pape & Van Schayck, 1986; McCormick & Prince, 1987) and a concomitant reduction of inhibitory influences (Eysel *et al.* 1986; Francesconi, Müller & Singer, 1988), resulting from an inhibition of the γ-aminobutyric acid (GABA)-containing local interneurones (McCormick & Pape, 1988) and of the recurrent GABAergic projection from the perigeniculate nucleus (Godfraind, 1967). On the other hand, topographically more precise inhibitory mechanisms are enhanced during the action of acetylcholine, presumably resulting in an improvement in the spatial and temporal acuity of responses within the area of the visual receptive field (Sillito *et al.* 1983). Compared with acetylcholine, the implication for visual responsiveness of the noradrenergic input to the dLGN is less well understood. Microiontophoretic application of noradrenaline revealed suppressive effects on spontaneous and visually evoked activity in the cat dLGN (Phillis, Tebécis & York, 1967; Pape & Eysel, 1987), whereas electrical stimulation of noradrenaline-containing neurones in the feline locus coeruleus was found to facilitate the responsiveness of geniculate relay cells (Nakai & Takaori, 1974). Similar studies in the rat dLGN demonstrated a predominantly facilitatory action of noradrenaline (Rogawski & Aghajanian, 1980; Kayama, Negi, Sugitani & Iwama, 1982). Recent experiments in thalamic neurones *in vitro* revealed distinct postsynaptic effects mediated via stimulation of different subtypes of adrenoceptors (reviewed in McCormick, 1992). For example, the activation of β-adrenoceptors in dLGN relay neurones modulates a highly voltage-dependent membrane conductance, thereby selectively dampening burst activity, and presumably also reducing the influence of inhibitory mechanisms (Pape & McCormick, 1989). The additional depolarization towards threshold for firing of fast action potentials through activation of α_1-adrenoceptors in relay cells is thought to further improve the faithfulness of sensory signal transmission (McCormick & Prince, 1988).

The present study was undertaken to improve our understanding of the functional significance for visual information processing of the noradrenergic projection to the dLGN. The conflicting interpretations of noradrenaline-mediated influences reached in former studies in the dLGN *in vivo* may partly result from (i) the mixed activation of different adrenoceptor subtypes, (ii) the different overall state of activity of the neurones (i.e. burst activity *versus* tonic firing of action potentials), or (iii) the different paradigms of visual stimulation that were used. Therefore in the present study, using microiontophoretic techniques in the cat dLGN *in vivo*, (i) the effects of agonists for the α- and β-binding sites were investigated separately, (ii) the global state of activity of the recorded neurones in the dLGN, associated with discrete patterns of the EEG, was continuously monitored and related to noradrenergic influences, (iii) distinct types of visually evoked responses, including those to light spots of different diameter projected into the area of the classical receptive field, binocular and lateral inhibition, were separately investigated before, during and after the action of noradrenergic agonists.

The results indicate that activation of α_1- and β-adrenoceptors results in an effective limitation of burst firing and a selective modulation of late phases of binocular and long-range lateral inhibition in the dLGN, thereby providing a state of activity which enables the faithful transfer of visual signals without interfering with the antagonistic organization of the dominant receptive field area. The influence

of β-adrenoceptor stimulation in particular imitates some of the changes in visual responsiveness associated with the naturally occurring shift in the state of the EEG from synchronized patterns to periods of activity characterized by higher frequencies and lower amplitudes. In addition, our findings document a prominent suppressant influence of α_2-adrenoceptor stimulation in the cat dLGN, and which may help to explain the inhibitory action of noradrenaline observed in former studies.

A preliminary report on the action of microiontophoretically applied noradrenaline in the cat dLGN has been published in abstract form (Pape & Eysel, 1987).

METHODS

Anaesthesia and general procedures

Experiments were carried out on adult cats of both sexes (body weight 2·5–4·0 kg). In nine cats, surgery was performed under initial anaesthesia with ketamine hydrochloride (20–25 mg kg^{-1}, I.M.; Ketanest, Parke-Davies, Germany) and xylazine (1 mg kg^{-1}, I.M.; Rompun, Bayer, Germany). Anaesthesia was then continued by artificial respiration with N_2O–O_2 (70–30%) and halothane (0·2–0·4%; Fluothane, ICI-Pharma, Germany) with the cats paralysed by alcuronium chloride infusion (0·15 mg kg^{-1} h^{-1}; Alloferin 10, Hoffmann-La Roche, Germany) through the femoral artery. In two cats, anaesthesia was induced by 36 mg kg^{-1} sodium pentobarbitone (I.P.; Nembutal, Rousselot, France) and maintained by continuous infusion of 2–4 mg Nembutal kg^{-1} h^{-1} added to the relaxant. In this case artificial respiration was maintained with compressed air. The end-expiratory CO_2 was kept at about 3·8%, the body temperature at 38·0 °C, and the mean arterial blood pressure maintained above 90 mmHg throughout the experiments. The local anaesthetic Xylocaine (2%; Astra Chemicals, Germany) was applied to all wound margins and pressure points. Blood pressure, heart rate and EEG pattern were continuously monitored, and the level of anaesthetic was increased (halothane 0·8–1%) during any indication of stress of the animal. Atropine sulphate (1%; Atropin-Pos, Ursapharm, Germany) and phenylephrine hydrochloride (5%; Neosynephrin-Pos, Ursapharm, Germany) were applied topically for mydriasis and retraction of the nictitating membranes. The corneae were protected with zero power contact lenses. Craniotomies were performed for epidural EEG registration (silver ball electrode, area 17), for lowering two concentric, bipolar stimulation electrodes bilateral to the optic chiasm, and for vertical access to the lateral geniculate nucleus.

Recordings and microiontophoresis

Five-barrelled glass micropipettes broken to a total outer tip diameter of 6–9 μm (DC resistance of single barrels 10–35 MΩ) were used for microionotophoresis (Neurophore-2-system, Medical Systems Corp., NY, USA) and recordings. The recording barrel and one barrel used for current balance were filled with 3 M NaCl, the three remaining barrels were filled with quisqualic acid (Quis, 15 mM in 165 mM NaCl, pH 7·0, Tocris Neuramin Ltd, UK) and two of the following substances (all of the hydrochloride form, diluted to 50, 100 and 200 mM in aqueous solution or saline, and set to a final pH 4·0): isoprenaline (Iso, Sigma, Germany) phenylephrine (Phe, Sigma), clonidine (Clo, Sigma), yohimbine (Yoh, Sigma) and RX821002 (RX, 2-(2-(2-methoxy-1,4 benzodioxanyl))2-imidazoline hydrochloride, Research Biochemicals Inc., MA, USA). Leakage of drugs from the electrode tip was prevented by retaining currents of +12 nA for Quis and −12 nA for the other substances. Ejection currents of opposite polarity ranged from 5 to 100 nA. Since agonists were applied in different concentrations and with different ejection currents, we defined five groups of '*ejection levels*', with each ejection level representing the multiplication of concentration and ejection current as shown in Table 1. Effects of agonists were analysed according to these five groups, and in the results we will refer to these group numbers.

Visual stimulation and data collection

Visual stimuli were generated by a Picasso cathode ray image generator (Innisfree, Cambridge, MA, USA) and presented on an oscilloscope screen (Tektronics 608) 0·5 m in front of the cat's eyes. Light spots of variable diameter (0·2–5 deg) were used to elicit receptive field centre or centre–surround responses and large-field phase-reversing gratings (24 × 20 deg, spatial frequency

0·25–0·5 cycles deg^{-1}, temporal frequency about 1 s^{-1}) were used to elicit binocular and long-range lateral inhibition (see Figs 5 and 6). The background illumination was 1 cd m^{-2}, and the depth of modulation for both types of stimuli was 0·9.

After conventional electronic amplification, analog single unit action potentials were selected through a window discriminator (Model 121, WPI Instruments, CT, USA), converted to −5 V pulses and fed on-line via a laboratory interface (Model 1401, Cambridge Electronic Design, UK)

TABLE 1. Groups of ejection levels, defined by the combination of ejection current and concentration of the agonist

Group	Ejection current (nA)	Agonist concentration (mM)
1	5	100
2	5	200
	10	100
3	50	50
	20–30	100
	10	200
4	75–100	50
	40–50	100
	20–30	200
5	75–100	100
	40–50	200

into a personal computer (AT-286). Spike trains were collected and averaged as peristimulus-time histograms (PSTHs) with a bin width of 5 ms (except for the time histograms of spontaneous activity: 15 ms), or as spike-interval histograms (INTH) with a temporal resolution of 1 ms. Cell responses to flashing spots were averaged from twenty-five trials (PSTH), those to phase reversing gratings from fifty or one hundred trials. INTHs were calculated from records of a duration of 1–2 min.

Cell classification and retinal deafferentation

Based on response latency to electrical stimulation of the optic chiasm and/or linear summation tests (Shapley & Hochstein, 1975) geniculate cells were classified as X- or Y-type. In some cases, additional conventional tests were used (Cleland, Dubin & Levick, 1971). To isolate long-range lateral inhibitory mechanisms in the dLGN (see Eysel *et al.* 1986), the retinal receptive field area of the cell under study was irreversibly destroyed by photocoagulation (Xenon photocoagulator, Model Log-2, Clinitex Inc., MA, USA). The size of the retinal lesions was estimated from fundus inspections and fundus plots on a tangent screen. Lesions ranged from 3 to 5 deg in diameter.

RESULTS

The actions of the α_1-adrenoceptor agonist phenylephrine, the α_2-agonist clonidine, and the β-agonist isoprenaline were studied in a total of 140 relay cells, recorded in layers A and A1 of the dLGN in eleven cats. As reported in former studies (reviewed in Steriade & McCarley, 1990; McCormick, 1992), dLGN neurones generated two different patterns of spontaneous activity, high-frequency bursts of discharges and more tonic sequences of spikes, which were closely related to characteristic states of the electroencephalogram (EEG). During maintained anaesthesia with N_2O–O_2–halothane, burst activity in the dLGN was associated with a low-frequency–high-amplitude, δ-like pattern of the EEG. The interburst frequency in the dLGN was within the frequency range of the EEG waves (1–4 Hz), and we frequently observed

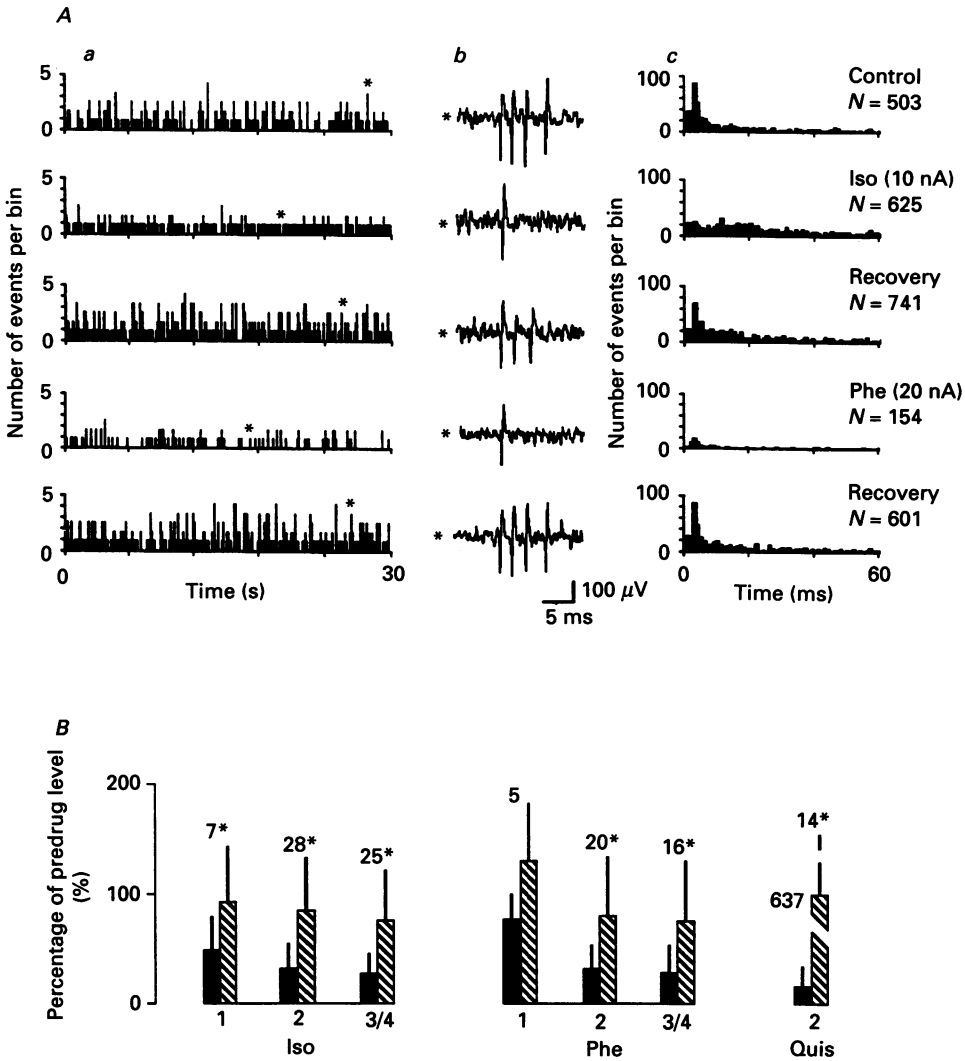

Fig. 1. Selective suppression of burst discharges in the dLGN during stimulation of adrenoceptors. *A*, effects of isoprenaline (Iso) and phenylephrine (Phe) on burst activity in an X-off cell, documented as time histograms (*a*), original recordings (*b*) and spike-interval histograms (INTH; *c*). In the time histograms, a single event per bin (bin size 15 ms) indicates a single action potential, a larger number of events per bin represents burst discharges (asterisks indicate examples shown in original recordings; see text for further details). In the INTHs (bin width 1 ms), burst activity is represented by the accumulation of short interspike intervals (1–5 ms; *N* indicates the total number of spike intervals analysed). Microiontophoretic application of Iso or Phe (ejection currents in nanoamps as indicated) results in a strong and reversible suppression of burst activity. *B*, quantitative representation of Iso and Phe effects on spontaneous burst discharges and single spike activity for three different ejection levels (1, 2, 3/4; see Methods). The number of burst discharges (■), and single spikes (▨), were calculated from short (1–5 ms) and longer (> 5 ms) interspike intervals in INTHs, normalized with respect to the predrug level (100%). The number of recordings and the standard deviation are indicated. Note

that a dLGN neurone rhythmically generated burst discharges in synchrony with the EEG δ-like waves (see e.g. Steriade, Curró Dossi & Nuñez, 1991). Spontaneous changes in the EEG to patterns of lower amplitude, dominated by higher frequencies but not totally free of slow waves (see e.g. Ikeda & Wright, 1974), were accompanied by a shift in neuronal activity in the dLGN to more tonic sequences of spike discharges (Fig. 4*A* and *B*; see also McCarley *et al.* 1983). During barbiturate anaesthesia, burst firing in the dLGN associated with waxing and waning periods of EEG synchronization was the prevailing pattern of activity (Steriade & Deschênes, 1984). Since changes in the global pattern of activity in the dLGN and the related state of the EEG itself produced significant variations in the amplitude and time course of visually evoked responses (Livingstone & Hubel, 1981; Funke & Eysel, 1992), particular care was taken to relate the effects of exogenously applied noradrenergic agonists to the mode of neuronal activity in the dLGN.

Adrenoceptor activation suppresses burst activity in the dLGN

Thirty relay cells (thirteen X-, eight Y-cells, nine non-classified cells) were studied when spontaneous burst discharges occurred in the dLGN associated with stages of a synchronized δ-like EEG during N_2O–O_2–halothane anaesthesia, or periods of EEG synchronization during barbiturate anaesthesia. The effects of microiontophoretically applied isoprenaline and phenylephrine were investigated in a total of sixty recordings and forty-one recordings, respectively. An example for an X-off cell is shown in Fig. 1*A*. Spontaneous activity is documented in time histograms, each representing a single sweep of 30 s duration (Fig. 1*Aa*). Since one burst discharge typically contained 3–5 spikes with an interspike interval of around 3 ms, a bin width of 15 ms was chosen for most effective representation of one burst discharge within one bin. Thus, a single event per bin in the time histogram most probably indicates a single action potential, while larger numbers of events per bin represent burst discharges. As is evident from the examples of the original recordings and from the time histograms, the microiontophoretic application of either isoprenaline or phenylephrine resulted in a strong suppression of burst firing. Single action potentials, which typically occurred at a low frequency (around 1 Hz) between bursts, were significantly less affected. This rather selective depression of burst activity is most evident from spike-interval histograms (INTHs), documenting the frequency distribution of interspike intervals calculated from a period of 1 min (Fig. 1*Ac*). The accumulation of short intervals around 3 ms, indicating high-frequency burst activity, was strongly reduced during application of either isoprenaline or phenylephrine. Concomitant with a reduction in the total number of bursts, the number of action potentials per burst decreased. This suppressant influence on burst activity of isoprenaline or phenylephrine occurred in all types of relay cells in the dLGN that were analysed (X, Y; on, off), and irrespective of the type of anaesthesia that was used. Enhanced burst activity was observed in only one out of 101 recordings.

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that Iso or Phe suppressed burst activity at all ejection levels, while single spike activity was significantly less affected (asterisks, $P < 5\%$, Student's t test). Effect of quisqualic acid (Quis) shown for comparison.

For a more quantitative estimation, INTHs were calculated from all recordings, and the number of short (1–5 ms, indicating burst activity) and longer (> 5 ms, indicating single spike firing) interspike intervals were determined before and during application of adrenoceptor agonists. As is shown in Fig. 1*B* for three different ejection levels (Groups 1–4), isoprenaline and phenylephrine depressed high-frequency burst activity, while the generation of single spikes was significantly less affected at all ejection levels that were tested.

Action of adrenoceptor stimulation on the visual response of dLGN cells

The influence of adrenoceptor stimulation on spontaneous or visually evoked single spike firing in the dLGN was analysed during periods of EEG pattern characterized by lower amplitudes and higher frequencies. During these states, dLGN relay cells spontaneously generated single spikes at an average frequency of about 15 Hz. Excitatory visual responses were elicited by a flashing spot of light located within the retinal receptive field, with the phase of the stimulus set for adequate stimulation of the class of relay neurone (on/off) under study. In fifty-three cells (thirty X-, twenty Y-cells, three unclassified cells), isoprenaline ($n = 34$ cells), phenylephrine ($n = 43$) and clonidine ($n = 15$) were applied with different ejection levels. The action of the agonist was analysed for pre-stimulus activity (200 ms prior to visual stimulation), and for two components of the visually evoked excitatory response, i.e. the phasic peak and the tonic-sustained period in the peristimulus-time histograms (PSTHs, Fig. 2). Visual response rates were obtained after subtraction of pre-stimulus ('spontaneous') activity. Differences in the action of adrenoceptor agonists on the different classes of relay cells in the dLGN (on, off; X, Y) were not detected, and thus the results were pooled.

Microiontophoretic application of the β-agonist isoprenaline elicited very weak, if any effects on single spike activity. On average, isoprenaline caused a slight facilitation of excitatory visual responses at low ejection levels (65% of the recordings, ejection level 2–3), while a slight depressant action on spontaneous and visually evoked firing occurred at the highest ejection levels that were used (Fig. 2*A* and *D*). Application of the α_1-agonist phenylephrine resulted in a global reduction in spike firing, with no obvious relation to the ejection level (Fig. 2*B* and *D*). Slight facilitatory effects on visually evoked activity were observed in six out of forty-one recordings (ejection level 2–3). As previously reported from our laboratory in preliminary form (Pape & Eysel, 1987), microiontophoretic application of noradrenaline evoked a very similar, global suppression of spike firing in the cat dLGN. The α_2-agonist clonidine clearly inhibited prestimulus and stimulus-evoked activity in a near dose-dependent manner. Clonidine was the only agonist tested, which effectively attenuated the phasic component of the visual response (Fig. 2*C* and *D*). These influences of the adrenoceptor agonists were not affected by variation of the stimulus contrast between a just-threshold level and 0·9 (as investigated in four X- and three Y-cells).

Since the strong suppressant effect of clonidine or noradrenaline indicated an inhibitory influence of α_2-adrenoceptors on geniculate activity, we tested the effects of two different antagonists of the α_2-binding site, namely yohimbine and RX 821002 hydrochloride (RX; Berridge, Gadie, Lane, Roach, Strachan, Tulloch & Welbourn, 1985). Although different ejection levels were used in different cells, we were unable

to reproducibly antagonize responses to clonidine, or to influence the action of noradrenaline or phenylephrine, with either yohimbine ($n = 22$) or RX ($n = 24$). Application of RX at low ejection levels resulted in a moderate antagonistic action in two cells, while higher ejection levels of yohimbine or RX had a rather unspecific, inhibitory effect (data not shown).

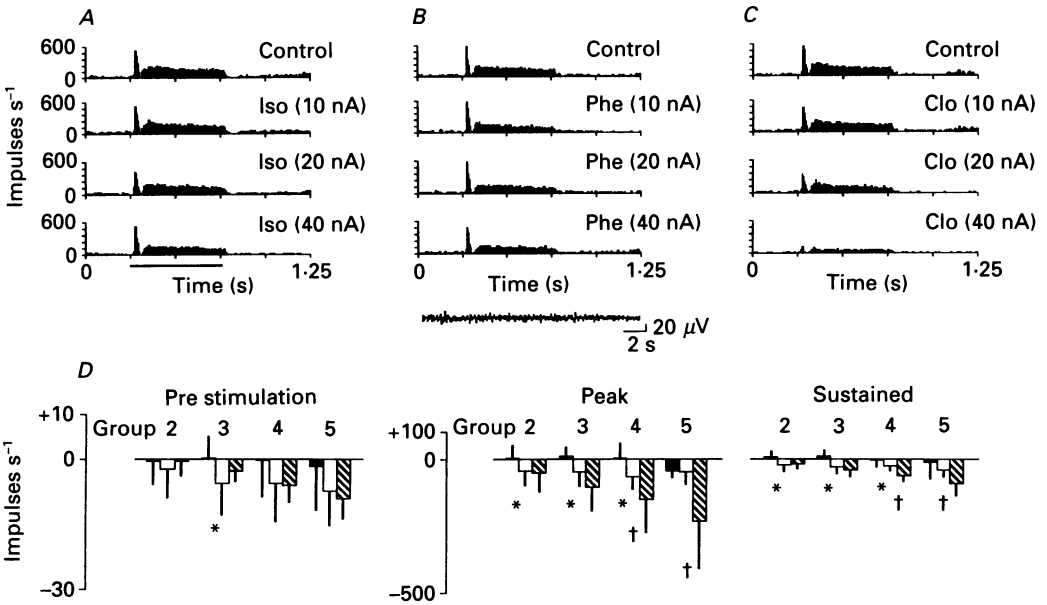

Fig. 2. Action of adrenoceptor agonists on visual responses to stimulation of the retinal receptive field centre with a flashing spot of light. All recordings were obtained during periods of a less synchronized, lower amplitude pattern of the EEG (see original trace below *B*). *A–C*, PSTHs (bin size 5 ms) of visual responses in an Y-on cell before and during microiontophoretic application of isoprenaline (Iso), phenylephrine (Phe) and clonidine (Clo) with different ejection currents (indicated in nA). The on-phase of the light spot is indicated by the bar below the histograms in *A*. *D*, quantitative representation of the relative change (in impulses per second) in peak and tonic-sustained components of the visual response and in activity prior to stimulation during application of Iso (■), Phe (□) and Clo (▨) with different ejection levels (2, 3, 4 and 5). Note the lack of influence of isoprenaline, the attenuation of activity through phenylephrine with no obvious relation to the ejection level, and the suppressant effect of clonidine, which is clearly related to the ejection level. *, $P < 0{\cdot}01$ for difference between Iso and Phe; †, $P < 0{\cdot}01$ for difference between Clo and Phe.

Number of measurements is given below.

	Group			
	2	3	4	5
Iso	13	20	17	9
Phe	19	22	27	11
Clo	12	15	12	4

In a sample of fourteen cells (eight X-, five Y-cells, one unclassified), the actions of phenylephrine and isoprenaline on the receptive field centre–surround mechanism were systematically investigated. A flashing spot of light was located in the receptive

field centre to elicit centre responses, and it was then increased stepwise in diameter for increasing stimulation of the antagonistic surround. A typical experiment in an X-on cell, represented as PSTHs, is shown in Fig. 3*A* and *B*. Under control conditions, an increasing size of the flashing spot of light resulted in a reduction of

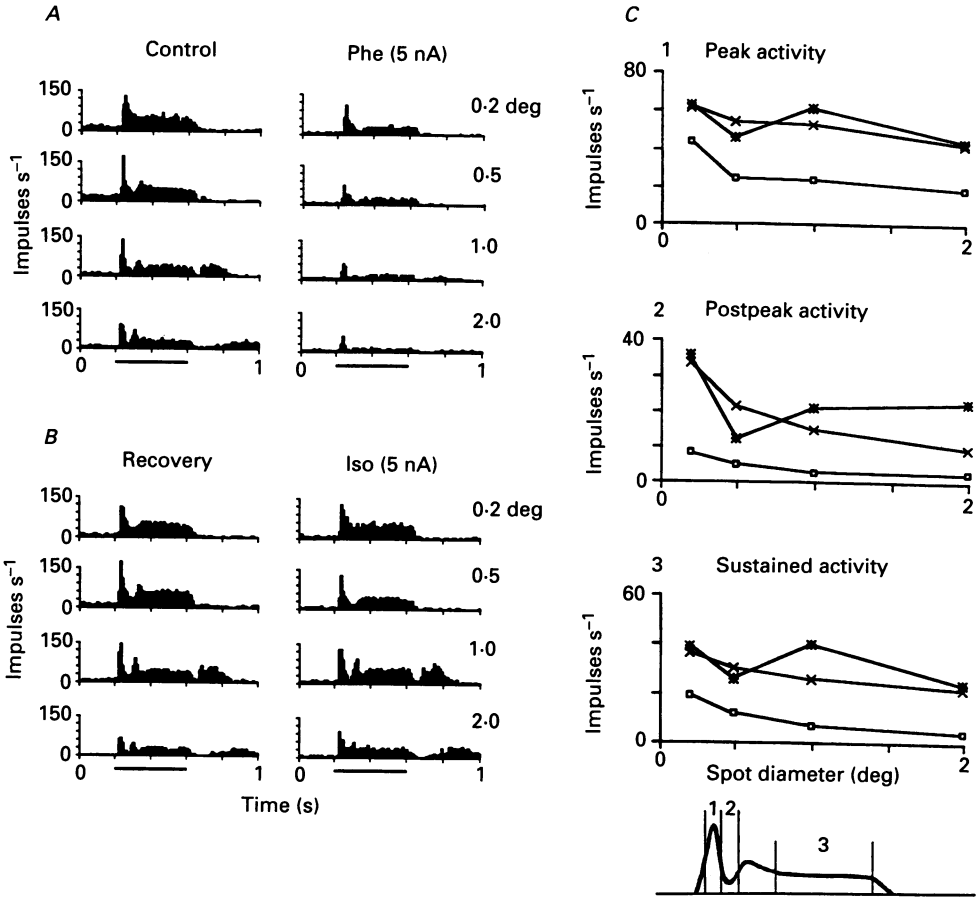

Fig. 3. Lack of modulatory influence on centre–surround antagonism of adrenoceptor stimulation. *A* and *B*, PSTHs (bin size 5 ms) of visual responses in an X-on cell to flashing spots of light of increasing diameter (indicated in degrees of visual angle) centred in the receptive field, before and during application of Phe and Iso. *C*, three different phases were distinguished in the visual response profile, the peak (phase 1), postpeak (2), and sustained response phase (3), as is shown in the schematic diagram (see text for further details). The spike rates at the different phases are plotted against the diameter of the light spot before (×), and during action of Phe (□) and Iso (*). Note that Iso did not significantly modulate the response profile, while Phe exerted a global, suppressant influence at all spot sizes tested.

the phasic peak response (termed response phase 1), an inhibitory period following the peak response (phase 2), and a decrease in the sustained response component (phase 3), indicating the inhibitory influence of the antagonistic surround of the

receptive field. A more quantitative representation of these response characteristics is shown in the diagrams of Fig. 3*C*, where the spike rates at the different phases are plotted against the diameter of the light spot. Microiontophoretically applied phenylephrine inhibited peak, postpeak and sustained activity at all spot sizes that were tested, indicating a global, suppressant influence with no change in centre–surround antagonism (Fig. 3*A*). These effects of phenylephrine appeared similar to those of noradrenaline, as previously reported from our laboratory (Pape & Eysel, 1987). Isoprenaline had no effects on the centre response, and the slight modulation of response phases following the peak response observed at larger spot sizes were non-significant (Fig. 3*B*).

In twelve neurones (six X-, six Y-cells) we were able to compare the influence of adrenoceptor stimulation on visual responses during periods of δ-like, synchronized EEG with those changes in visual responsiveness associated with the naturally occurring shift in the EEG to patterns of lower amplitudes and higher frequencies. The shift in the state of the EEG was accompanied in the dLGN with a shift from burst firing and phasic visual responses towards more tonic sequences of spikes and a strong facilitation of the tonic component of the visual response (Fig. 4*A* and *B*). The tonic response component significantly ($P < 0{\cdot}0001$) increased from an average of 10 ± 9 spikes s^{-1} during synchronized, to 45 ± 21 spikes s^{-1} during less synchronized patterns of the EEG. This change in visual response characteristics was largely imitated by microiontophoretic application of isoprenaline, which facilitated the sustained tonic component of the visually evoked response (Fig. 4*A* and *C*). The phasic component of the response was reduced during ejection of either isoprenaline or phenylephrine, indicating a strong contribution of burst discharges to the phasic visual response occurring during synchronized periods of the EEG (see above).

Binocular inhibition

Binocular inhibition (Singer, 1970) was elicited by stimulation of the non-dominant eye with a phase-reversing, square-wave-modulated grating (see Fig. 5*A*). Each phase reversal caused a prominent inhibitory response, which was separated into an early (E) and a late (L) component, the latter of which appeared in the decaying phase of the early component (Fig. 5*A*). The background activity of the cells under study was elevated (50–80 impulses s^{-1}) by continuous application of quisqualic acid, an agonist of excitatory amino acid receptors of the non-*N*-methyl-D-aspartate subtype (Watkins & Olverman, 1987), thereby allowing us to estimate the strength and time course of the inhibitory response as the reduction in background firing rate. By carefully adjusting the ejection level for quisqualic acid, the level of background activity was kept constant during control and application of adrenoceptor agonists. In this manner, we investigated the action of isoprenaline ($n = 16$) and phenylephrine ($n = 26$) on binocular inhibition in twenty-eight dLGN relay neurones (fourteen X- and fourteen Y-cells).

As is shown in the example in Fig. 5*B*, application of isoprenaline resulted in a significant *decrease* in strength of the late phase of binocular inhibition. This disinhibitory effect of isoprenaline was observed in fifteen out of sixteen cells that were tested, one cell showed no response, and the average reduction in inhibition was six spikes s^{-1} ($P < 0{\cdot}005$, Fig. 5*D*). By contrast, ejection of phenylephrine induced a

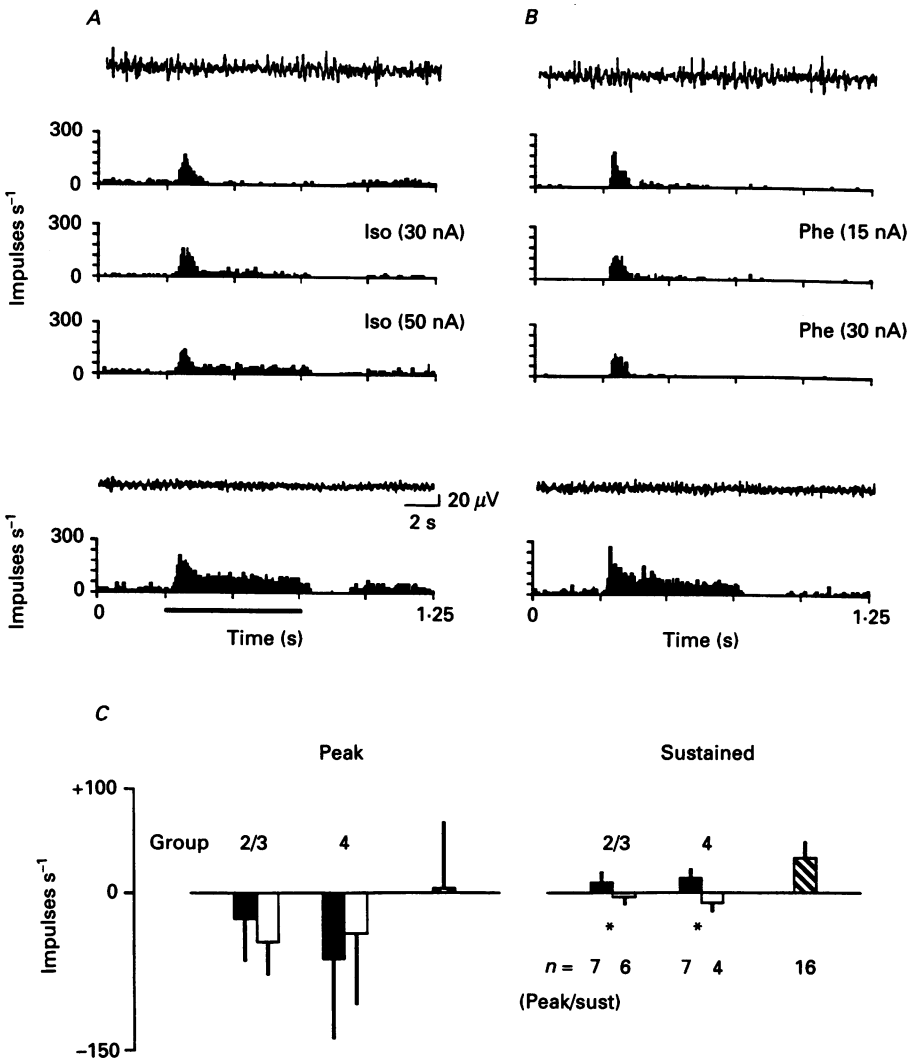

Fig. 4. Stimulation of β-adrenoceptors imitates changes in visual responsiveness associated with shifts in the state of the EEG. During periods of synchronized, δ-like EEG activity (upper traces represent original recordings of the EEG), visual stimulation of the receptive field centre evokes phasic responses (upper PSTHs) in an X-off (*A*) and Y-off cell (*B*). The naturally occurring shift in the state of the EEG to patterns of less synchronized, low amplitude activity (lower traces of the EEG) is associated with a strong increase in the tonic-sustained response component in both cell types (responses to visual stimulation during less synchronized EEG periods are represented in the bottom PSTHs). Microiontophoretic application of isoprenaline (Iso, ejection current indicated in nA) largely mimics these changes in the visual response profile, while phenylephrine (Phe) attenuates the response with no indication of an increase in the tonic component. *C*, changes in peak and tonic-sustained component of the visual response occurring during microiontophoretic application with different ejection levels (2/3, 4) of Iso (■) or Phe (□) and during the shift of the EEG from δ-like to less synchronized, non-δ-like patterns (▨), as averaged from a larger number of cells (as indicated, *n*). Note the highly significant

significant *increase* in the late component of binocular inhibition in twenty-four out of twenty-six cells (Fig. 5*C*), had no effect in one cell and a weak disinhibitory influence in a further cell. On average, late phases of binocular inhibition were increased by six spikes s^{-1} ($P < 0.005$; Fig. 5*D*). Typically, responses recovered to near control values after 10–30 min following cessation of drug application. The influence of the α_2-agonist clonidine on binocular inhibition could not be quantitatively evaluated, due to its strong inhibitory action. Two further observations are worth mentioning: (i) the early phase of binocular inhibition was not significantly affected by isoprenaline or phenylephrine (Fig. 5*D*). The small change observed in early inhibitory strength is probably due to the effects of adrenoceptor activation on the partly overlapping late phase of binocular inhibition; (ii) X-cells exhibited on average a significantly stronger late phase of binocular inhibition than Y-cells ($P = 0.015$, ten X-, sixteen Y-cells; data not shown). This difference was obscured during states of the EEG associated with higher frequencies and lower amplitudes, and which resulted in a substantial reduction in the late phase of inhibitory responses in both cell classes (see below).

Long-range lateral inhibition

Long-range lateral inhibitory mechanisms in the dLGN were activated by visual stimulation (phase-reversing grating) of the dominant eye, after the direct, excitatory retinal input had been eliminated by a photocoagulation of the classical receptive field area on the retina (Eysel *et al.* 1986). Application of quisqualic acid was used to keep the background firing level at 50–80 impulses s^{-1}. Under these conditions, each phase reversal of the grating evoked a clear inhibitory response, detectable as an early (E) and late (L) component of decreased spike activity (Fig. 6*A*). The influence of adrenoceptor agonists on this long-range inhibition was investigated in a total of fourteen relay cells (three X-, six Y-cells, five unclassified). Ejection of isoprenaline resulted in a highly significant *decrease* in the late phase of inhibition in twelve cells, and it had no effect in two cells (Fig. 6*B*). Long-range inhibition was reduced on average by ten spikes s^{-1} ($P < 0.005$; Fig. 6*D*). By contrast, phenylephrine induced a significant *increase* in the late inhibitory component averaging four spikes s^{-1} ($P = 0.05$) in seven out of eight cells that were tested, and it was ineffective in one cell (Fig. 6*C* and *D*). As was found for binocular inhibition (see above), the early phase of long-range inhibition was not significantly affected (Fig. 6*D*); the minor changes that were observed may result from the influence of the adrenergic drugs on the partly overlapping late phase of inhibition. The possible influence of the α_2-agonist clonidine could not be investigated, due to its strong suppressant effect.

Changes in the state of the EEG affects binocular and long-range lateral inhibition

In a smaller sample of dLGN relay neurones, we were able to evaluate directly the influence on binocular and long-range lateral inhibition of a naturally occurring change in the pattern of the EEG from synchronized, δ-like waves to periods of

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difference (*, $P < 0.001$, Student's t test) between the increase in the tonic-sustained component of the visual response obtained with Iso and during shifts to a non-δ-like EEG compared with Phe.

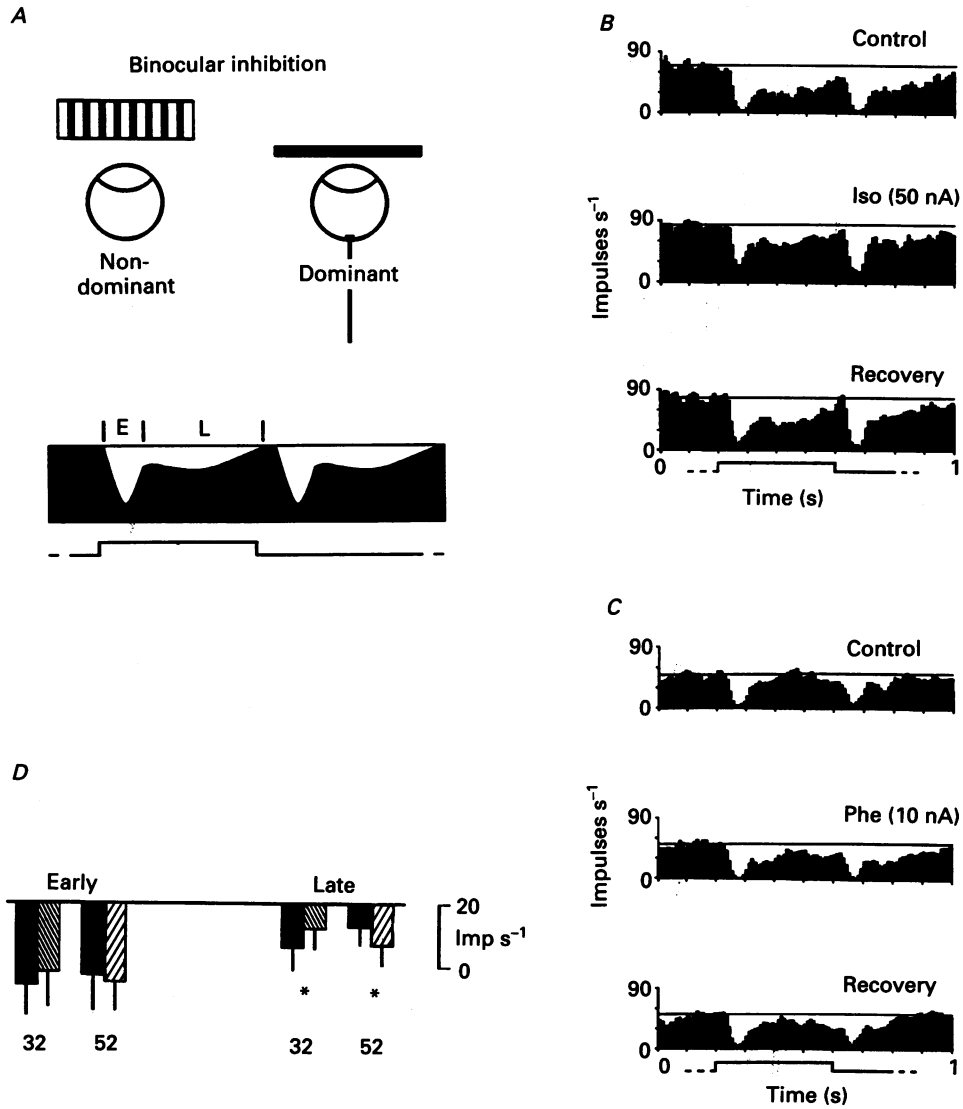

Fig. 5. Stimulation of adrenoceptors selectively modulates the late phase of binocular inhibition. Binocular inhibition was elicited by monocular stimulation of the non-dominant eye with a phase-reversing grating (square-wave modulated, contrast 0·9), and the inhibitory responses, represented as PSTHs, were separated into an early (E) and a late (L) phase, as is illustrated in the schematic diagram in *A*. Microiontophoretic application of isoprenaline (Iso, 50 nA) results in a reduction in the late phase of inhibition (*B*; X-on cell), while phenylephrine (Phe, 10 nA) slightly increases the late phase of inhibitory response (*C*; Y-off cell). The quantitative analysis from a larger number of neurones (*D*) demonstrates that the late component of inhibition is significantly *decreased* with Iso (▨) (* $P < 0{\cdot}5\%$, Student's *t* test) and *increased* with Phe (▨) (* $P < 0{\cdot}5\%$) (control (■)), whereas the early response component is unaffected. The strength of inhibitory responses was calculated as the reduction in spike activity (in impulses per second) from prestimulation levels (indicated by lines in the PSTHs; bin width is 5 ms).

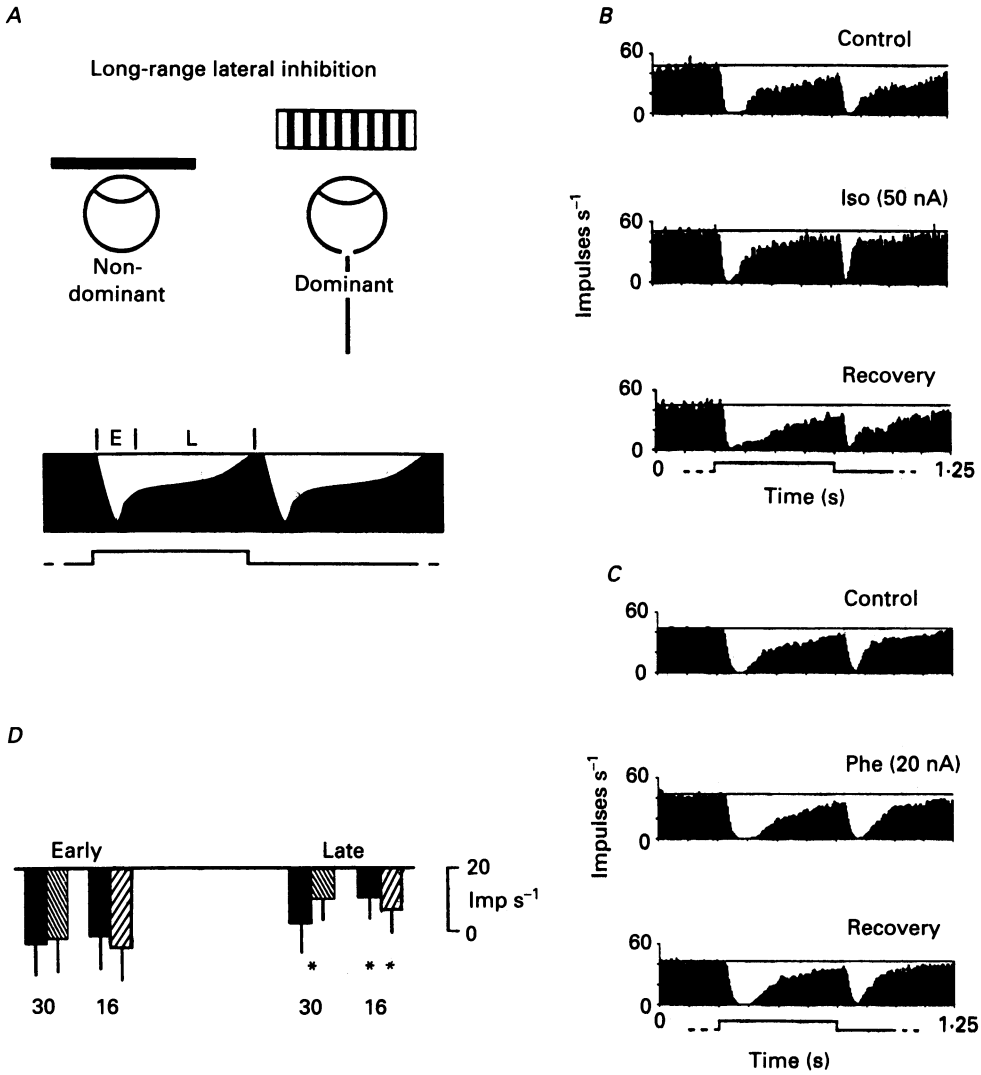

Fig. 6. Long-range lateral inhibition is selectively modulated by adrenoceptor activation. Presentation of data as in Fig. 5. Note that long-range lateral inhibition was evoked by monocular stimulation of the dominant eye (phase-reversing grating, square-wave modulated, contrast 0·9) after elimination of retinal inputs from the classical receptive field area (*A*, see Methods for details). Isoprenaline decreases (*B*, X-on cell), while phenylephrine increases (*C*, Y-on cell) the late phases of inhibitory responses. The quantitative analysis from a larger number of cells (*D*) demonstrates the unaltered early phase and the significantly (*, $P < 0{\cdot}005$; **, $P < 0{\cdot}05$; Student's *t* test) modulated late phase of long-range lateral inhibition after activation of adrenoceptors. Control (■), isoprenaline (▧), phenylephrine (▨).

activity characterized by higher frequencies and lower amplitudes. As is shown in Fig. 7, the shift in the EEG caused a significant *decrease* in the late phase of binocular (Fig. 7*A* and *B*; eight X-, five Y-cells; average decrease by 10 spikes s^{-1}, $P < 0{\cdot}005$) and long-range lateral inhibition (Fig. 7*C* and *D*; one X-, four Y-cells; average

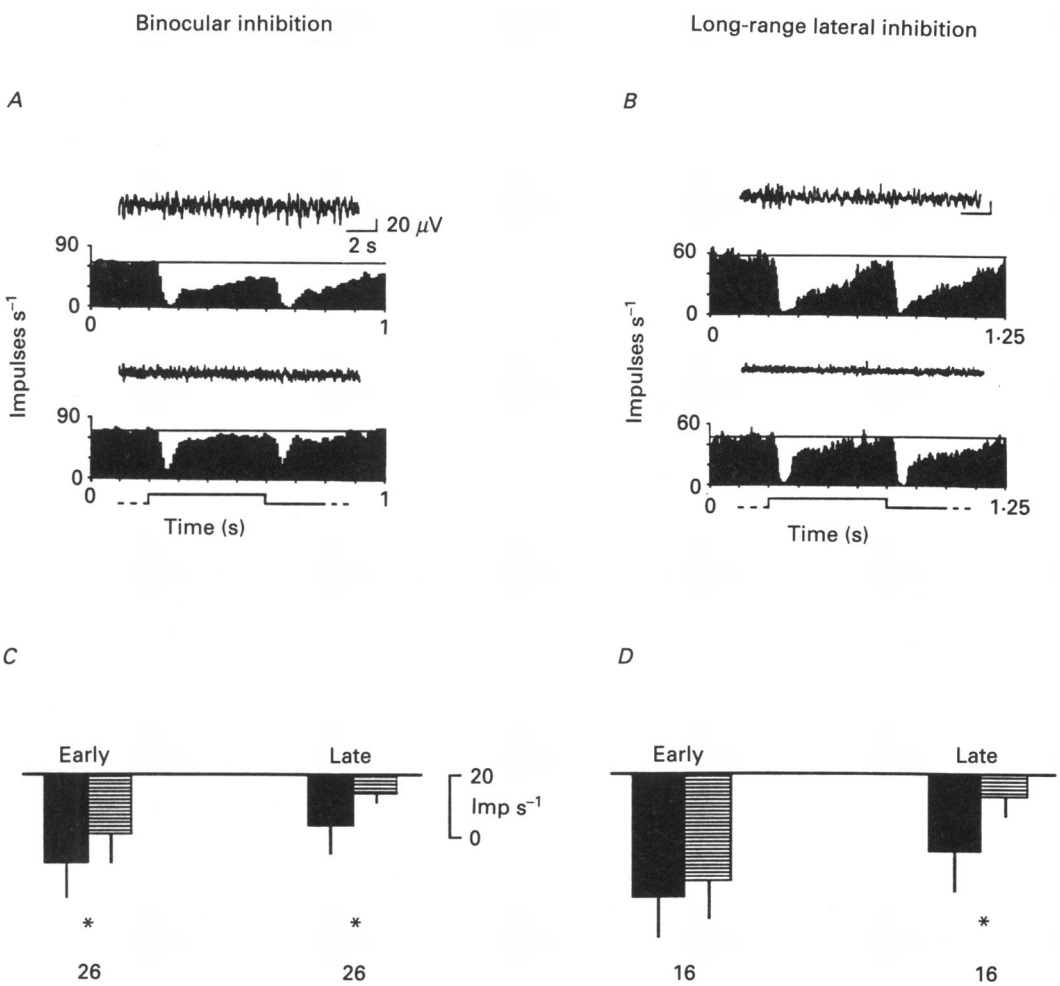

Fig. 7. The state of the EEG influences binocular (*A* and *C*) and long-range lateral inhibition (*B* and *D*) in the dLGN. The inhibitory responses represented in the upper histograms in *A* (X-on cell) and *B* (Y-on) were evoked during synchronized, δ-like patterns of the EEG (see original traces above histograms), while the inhibitory responses represented in the lower histograms were evoked by the same visual stimuli after the EEG had spontaneously shifted to less synchronized patterns of lower amplitude (see original traces). Note the strong decrease in strength and duration of the late phase of binocular and long-range lateral inhibition associated with the shift in the state of the EEG. The quantitative analysis, averaged from a larger number of neurones (as indicated) demonstrates the highly significant decrease in strength of binocular (*C*) and long-range lateral inhibition (*D*) associated with the naturally occurring shift in the state of the EEG from δ-like (■), to less synchronized, non-δ-like (▤), patterns of activity. See Figs 5 and 6 for details of stimulus parameters and data representation. *$P < 0{\cdot}005$.

decrease 17 spikes s^{-1}, $P < 0.005$), resembling that observed during activation of β-adrenoceptors (see above). The early inhibitory component was substantially less affected. From these results we conclude that the state of the EEG predominantly influences the late components of inhibitory responses in the dLGN, thereby partly explaining the wide variation in the time course of inhibition and the effects of adrenoceptor activation recorded in different cells under different experimental conditions.

DISCUSSION

The present study evaluates the modulatory influence of the ascending noradrenergic brainstem system on retinogeniculate signal transmission during distinct modes of overall activity in the dLGN. During functional states characterized by clustered burst discharges in dLGN relay neurones, and which were associated with synchronized, δ-like patterns of the EEG, the stimulation of β-adrenergic receptors through isoprenaline resulted in (i) a significant reduction in the generation of burst activity, and (ii) a facilitation of the tonic component of responses to stimulation of the visual receptive field area, associated with a reduction in the late phase of long-range lateral and binocular inhibitory influences. This influence of β-adrenoceptor activation partly mimicked the change in the responsiveness of dLGN relay neurones observed during the naturally occurring shift in the EEG to a less synchronized, higher frequency pattern of activity. The latter state was associated with tonic sequences of action potentials in dLGN relay neurones, and application of isoprenaline under these conditions did not result in a further effect on spontaneously generated activity or characteristics of responses to stimulation of the visual receptive field centre–surround area. The microiontophoretic application of phenylephrine, stimulating predominantly α_1-adrenoceptors, resulted in a suppression of burst discharges in dLGN relay neurones during periods of synchronized EEG, while the late phases of long-range lateral and binocular inhibitory influences were increased. The generation of tonic sequences of action potentials was attenuated by noradrenaline (Pape & Eysel, 1987) or phenylephrine in a rather unselective manner, independent of the ejection level that was used. This effect may be best explained by an involvement of α_2-adrenoceptors (see below), whose stimulation by the selective agonist clonidine resulted in a prominent suppression of the different patterns of spontaneous and visually evoked activity in the dLGN.

Noradrenergic influence on the overall state of activity in the dLGN

In previous studies, various effects of the noradrenergic system were reported to occur in the dLGN, depending upon the experimental approach and the species that was used (see Introduction). The diverging results may indicate species differences or technical limitations of the method being used, e.g. local concentrations of noradrenaline exceeding the physiological range during microiontophoresis, activation of ascending brainstem fibres other than those containing noradrenaline during electrical stimulation, or an interplay between different pre-and postsynaptic mechanisms activated by the increase in the extracellular level of noradrenaline in the dLGN. On the other hand, studies using the slice preparation *in vitro* revealed

distinct postsynaptic effects of noradrenaline mediated by different adrenoceptor subtypes in the dLGN, with no indication of differences between rodents and cat (reviewed in McCormick, 1992). In particular, the activation of β-adrenoceptors in dLGN relay neurones modulated a mixed sodium–potassium conductance activated by hyperpolarization, termed I_h, thereby selectively dampening burst activity and presumably also reducing the amplitude and/or the duration of hyperpolarizing membrane responses (Pape & McCormick, 1989). The activation of α_1-adrenoceptors evoked a decrease in membrane conductance for K^+ ions, resulting in a depolarization of the membrane towards firing threshold and thus a facilitation of tonic spike activity (McCormick & Prince, 1988).

The present findings demonstrate in the dLGN of the cat *in vivo* that stimulation of β-adrenoceptors through microiontophoretic application of isoprenaline indeed suppressed the generation of burst discharges, generally occurring during periods of synchronized, δ-like patterns of the EEG. By contrast, tonic sequences of action potentials, associated with periods of less synchronized, lower amplitude EEG, were not significantly affected by isoprenaline. Burst discharges in thalamocortical relay neurones are known to occur during membrane hyperpolarization to values negative to the normal resting potential and to represent calcium mediated action potentials with a low threshold of activation, which in turn trigger high-frequency sets of Na^+–K^+-mediated spikes (Jahnsen & Llinás, 1984; Steriade & Deschênes, 1984). During depolarization of the membrane, the Ca^{2+} action potential inactivates and more tonic sequences of independent Na^+–K^+ spikes ('single spike firing') are generated (Jahnsen & Llinás, 1984; Steriade & Deschênes, 1984). Although in the present study Ca^{2+}-mediated action potentials were not directly measured, we were able to separate burst activity from single spike firing by the extremely short inter-spike interval of 1–5 ms within a typical burst response. This approximation will slightly overestimate the occurrence of burst activity, because single spikes occurring in the frequency range typical of bursts (e.g. visually evoked peak responses up to 600 Hz, Fig. 2*C*) are counted as bursts. The order of magnitude of the resulting error was estimated by analysing the effect of microiontophoretically applied quisqualic acid, an agonist for excitatory amino acid receptors of the non-*N*-methyl-D-aspartate subtype (Watkins & Olverman, 1987). Activation of these receptors will evoke a strong depolarization of the membrane and hence a near-complete suppression of burst discharges due to an inactivation of the underlying Ca^{2+} spike. Using the above approximation, single spike firing was found to increase by more than 600% during action of quisqualic acid (Fig. 1*B*), and the remainder of burst activity of less than 15% may indicate the error resulting from incorrect identification of Ca^{2+}-mediated burst discharges. On the other hand, the slight reduction of single spike activity might be due to the blockade of Ca^{2+}-mediated responses that triggered only one action potential.

The application of the α_1-agonist phenylephrine resulted in a suppression of burst activity in dLGN neurones, which appeared similar to that of isoprenaline. This inhibition of Ca^{2+}-mediated burst activity may be expected from the α_1-mediated decrease in membrane K^+ conductance and associated depolarization observed in the cat dLGN *in vitro* (McCormick & Prince, 1988). However, the interpretation of the action of noradrenaline is complicated by the finding in the cat dLGN *in vivo* that

the generation of single spikes was inhibited by microiontophoretically applied noradrenaline (Phillis *et al.* 1967; Pape & Eysel, 1987) or by phenylephrine in a rather unselective manner, independent of the ejection level that was used (this study). Although at present we cannot provide a satisfactory explanation for these different results obtained *in vivo* and *in vitro*, on-going activity of noradrenergic fibres may be different in the two different preparations, presumably resulting in a difference in the endogenous concentration or noradrenaline in the dLGN. This in turn will affect responses to noradrenaline due to the non-linear occupancy–response relationship of α_1-adrenoceptor agonists (Ruffolo, Nichols, Stadel & Hieble, 1991), the possible interaction between the distinct adrenoceptor subtypes (Nakamura, Tsujimura & Nomura, 1991), and the regulation of the number and the state of desensitization of adrenoceptors (Bylund & U'Pichard, 1983).

The suppressant noradrenergic influence in the cat dLGN may be due to an activation of α_2-adrenoceptors, based upon the following findings: (i) microiontophoretic application of the α_2-selective agonist clonidine (Ruffolo *et al.* 1991) resulted in a suppression of single spike activity in the dLGN, the magnitude of which was clearly related to the ejection level that was used; (ii) besides a high density of α_1- and a moderate density of β-adrenoceptors (reviewed by McCormick, 1992), autoradiographic studies demonstrated the existence of α_2-binding sites in moderate to high densities in the dLGN (Unnerstall, Kopajtic & Kuhar, 1984), (iii) the activation of α_2-adrenoceptors in the rat dLGN *in vitro* induced an increase in membrane K^+ conductance and associated hyperpolarization (Coulter, Huguenard & Prince, 1990), probably resulting in an inhibition of single spike activity. These data indicate a depressant effect on geniculo-cortical activity of an activation of α_2-adrenoceptors, and which may introduce a regulatory mechanism by functionally counteracting with the facilitatory action of α_1-adrenoceptor stimulation in the dLGN. It remains to be investigated, whether pre-, post- or extrasynaptic α_2-receptors are involved (Bylund & U'Prichard, 1983; Starke, Göthert & Kilbinger, 1989), whether the suppressant effect of exogenous phenylephrine is due to a direct action on α_2-adrenoceptors (Curet & DeMontigny, 1988) or an α_1-adrenoceptor-mediated modulation of the regulatory system, and whether the net effect of the noradrenergic brainstem system is controlled through the effective concentration of noradrenaline at the different binding sites under physiological conditions in the dLGN.

Noradrenergic modulation of visual responsiveness in the dLGN

The possible modulation by noradrenaline of visual information processing in the cat dLGN was investigated on four different aspects of visually evoked responses in the present study: responses to stimulation of the retinal receptive field centre, centre–surround antagonism, binocular inhibition, and long-range lateral inhibition. Besides a global suppressant effect of noradrenaline, and which is probably mediated through the α_2-adrenoceptor system (see above), the more specific centre–surround response properties appeared unchanged during application of noradrenaline (Pape & Eysel, 1987), isoprenaline or phenylephrine, indicating a lack of modulatory action of the noradrenergic brainstem system on the processing of visual signals within the classical receptive field area. The primary targets of noradrenergic influences appear

to be the inhibitory mechanisms between signals arriving to the dLGN from the two eyes, and inhibitory processes functionally ranging over wide areas in the dLGN, as is indicated by the selective modulation through phenylephrine and isoprenaline of the late phases of binocular and long-range lateral inhibition. Long-range inhibition has been shown to act over lateral distances of up to 1 mm in the dLGN, and it is probably recurrently mediated by GABAergic neurones located in the perigeniculate nucleus (Eysel *et al.* 1986). Binocular inhibition in the dLGN may also partly rely on the recurrent pathway via the perigeniculate nucleus (Guido, Tumosa & Spear, 1989; Uhlrich, Cucchiaro, Humphrey & Sherman, 1991), and it is interesting to speculate that the noradrenergic brainstem system is capable of controlling the recurrent inhibitory loop to the dLGN. In any case, the decrease in strength and duration of inhibitory responses during action of isoprenaline observed in the present study provides direct *in vivo* evidence of a disinhibitory influence of β-adrenoceptor activation in the dLGN. Disinhibition in the dLGN after stimulation of β-adrenoceptors was proposed from recent findings *in vitro*, which demonstrated a decrease in amplitude and duration of hyperpolarizing membrane responses due to β-adrenergic modulation of I_h (Pape & McCormick, 1989). The decrease in late periods of inhibitory influence is probably reflected in the facilitation of the tonic component of visual responses to stimulation of the dominant receptive field area, which was observed with application of isoprenaline predominantly during periods of a highly synchronized EEG activity (Fig. 4*A*). Microiontophoretic application of phenylephrine resulted in an increase in strength and duration of binocular and long-range lateral inhibitory responses in the dLGN, thereby functionally antagonizing the β-adrenergic influence and supporting the idea of a highly regulated system of noradrenergic modulation in the dLGN.

The state of the EEG and the noradrenergic influence in the dLGN

The shift from periods of synchronized EEG activity, such as occurs during certain stages of slow-wave sleep or drowsiness, to the desynchronized EEG pattern of the aroused or attentive state is associated with tonic depolarization and an abolition of burst activity in thalamocortical relay cells, which appears to enable the faithful transmission of synaptic signals through the thalamus (reviewed in Steriade & McCarley, 1990). In the dLGN, periods of less synchronized EEG activity are associated with an increase in the ratio with which retinal signals are transferred to relay neurones, a facilitation of the tonic component of visual responses, a reduction in inhibitory influences, and an improvement in the faithfulness of processing visual contrast information (Livingstone & Hubel, 1981; Funke & Eysel, 1992; reviewed in Singer, 1977; Steriade, Paré, Hu & Deschênes, 1990). These state-dependent modes of thalamocortical activity appear to be largely controlled by ascending inputs from the upper brainstem core, of which noradrenergic fibres arising in the region of the locus coeruleus comprise an important part (reviewed in McCormick, 1992). The activity of these noradrenergic neurones has been found to vary with the behavioural state of the animal, in that their tonic discharge rate is low during slow-wave sleep and highest during waking (Aston-Jones & Bloom, 1981), presumably resulting in a varying release of noradrenaline in the thalamus. The present study demonstrates that stimulation of adrenoceptors partly mimics the changes in spontaneous activity and visual response properties in geniculocortical relay neurones occurring during

the shift from δ-like to less synchronized patterns of the EEG: dampening of high-frequency burst discharges, facilitation of the tonic component of visual responses, and disinhibition of late phases of binocular and long-range lateral inhibitory mechanisms. It is important to note that these effects were predominantly mediated through the β-specific agonist isoprenaline, indicating an important function particularly of β-adrenoceptors in controlling the state-dependent gating of visual information through the thalamus.

In conclusion, the ascending noradrenergic brainstem system appears to provide an important basis for the faithful transfer of visual signals through the dLGN during periods of increased arousal by preventing burst discharges and controlling the late phases of more globally organized inhibitory mechanisms without interfering with the antagonistic organization of the classical receptive field area. These modulatory effects reflect a highly regulated system of noradrenergic influences, presumably controlled by the local concentration of noradrenaline at different adrenoceptor subtypes in the dLGN. Ascending cholinergic influences may act in concert with the noradrenergic system in that they further improve the processing and transmission of visual information through a direct depolarization of geniculocortical neurones and a selective modulation of long- and shorter-range inhibitory processes in the dLGN (see Introduction; Curró Dossi, Paré & Steriade, 1992). Indeed, slow oscillatory burst firing in dLGN neurones, which has been found to provide an important element in the generation of sleep δ-waves, was suppressed and replaced by tonic activity after stimulation of the mesopontine cholinergic nuclei (Steriade *et al.* 1991). Since the output of the noradrenergic fibres is much higher during waking than during rapid eye movement (REM) sleep, and the mesopontine cholinergic neurones are under the inhibitory control by the noradrenergic neurones of the locus coeruleus (as reviewed by Hobson, 1990), the contribution of the noradrenergic system may help to distinguish between the two stages of desynchronized EEG activity, wakefulness and REM sleep, and which are associated with particular integrative properties of the brain.

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