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Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulations in the rat auditory cortex

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Abstract. We investigated the relationships between cortical arousal and cholinergic facilitation of evoked responses in the auditory cortex. The basal forebrain (BF) was stimulated unilaterally, while cluster recordings were obtained simultaneously from both auditory cortices in urethane-anesthetized rats. The global electroencephalogram (EEG; large frontoparietal derivation) and the local EEG (from the auditory cortex) were recorded. The BF was stimulated at two intensities, a lower one which did not desynchronize the EEG and a higher one which did. Twenty pairing trials were delivered, during which a tone was presented 50 ms after the end of the BF stimulation. At low intensity, the pairing procedure led to a transient increase in the ipsilateral tone-evoked responses. At high intensity, the pairing increased the ipsilateral evoked responses up to 15 min after pairing. Such effects were not observed for the contralateral recordings. Systemic atropine injection prevented the facilitations observed ipsilaterally. BF stimulations alone did not induce any increased evoked response either at low or at high intensity. These results show (1) that a tone, presented while the cortex is activated by cholinergic neurons of the BF, evokes enhanced cortical responses, and (2) that the duration of this facilitation is dependent on the stimulation intensity. These results are discussed in the context of neural mechanisms involved in general arousal and cortical plasticity.

Key words: Basal forebrain – Nucleus basalis – Auditory cortex – EEG desynchronization – Sensory plasticity – Rat

Introduction

Cholinergic activation has long been associated with cortical arousal (Mitchell 1963; Phillis and Chong 1965; Celesia and Jasper 1966; Longo 1966; Szerb 1967; Jasper and Tessier 1971). Recent data supporting this relationship between acetylcholine (ACh) activity and brain-activated states are reviewed in Steriade and McCarley (1990) and in Steriade and Buzsàki (1990).

The major source of cholinergic input to the entire cortical mantle comes from several groups of neurons within the basal forebrain (BF; Divac 1975; Wenk et al. 1980; Fibiger 1982; Mesulam et al. 1983b; Woolf 1991). More specifically, the projections to the neocortex seem to originate mainly from the ventromedial aspect of the globus pallidus, the dorsal aspect of the substantia innominata (SI), and even some neurons embedded among the fibers of the internal capsule. This area, described as the Ch4 sector of the cholinergic system in both rodent and primate (Mesulam et al. 1983a,b), includes the nucleus basalis magnocellularis (NBM). The projections from the NBM to the neocortex are ipsilateral and to a certain extent topographically organized in such a way that different areas of the neocortex are innervated by different subsets of NBM neurons (Wenk et al. 1980; Bigl et al. 1982; Price and Stern 1983; Rye et al. 1984; Saper 1984; Luiten et al. 1987).

Several lines of evidence show that the NBM plays an important role in the cholinergic control of neocortical activation. Damaging the NBM by neurotoxic lesions results in decreased cholinergic activity in the neocortex and in slower electroencephalogram (EEG) rhythms, with apparent reduction of desynchronized patterns (Stewart et al. 1984; Buzsàki et al. 1988; Riekkinen et al. 1992). Conversely, electrical stimulation of the NBM results in increased release of ACh in the neocortex (Casamenti et al. 1986; Kurosawa et al. 1989), and in neocortical EEG desynchronization (Belardetti et al. 1977; Casamenti et al. 1986). Lastly, there is a strong correlation between the discharge rate of the NBM neurons and neocortical activation (Detari and Vanderwolf 1987; Buzsàki et al. 1988).

On another hand, over the last few years, different results have suggested an important role for the cholinergic projections from the BF in the normal physiology and plasticity of the sensory cortices. First, cortical ACh de-

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pletion by neurotoxic BF lesion leads to weaker evoked responses in the visual (Sato et al. 1987a) and somatosensory (Juliano et al. 1990; Jacobs et al. 1991) cortices. Similar ACh depletion is also able to prevent the sensory plasticity normally observed after peripheral manipulations (Juliano et al. 1991). Second, in anesthetized animals, BF stimulation delivered before a sensory stimulus enhances the cortical responsiveness to this stimulus. In the somatosensory cortex, repeated pairing of BF stimulation with a cutaneous stimulus can enhance the stimulus-evoked activity; in some cases this enhancement outlasts the period of pairing up to tens of minutes (Rasmusson and Dykes 1988; Tremblay et al. 1990; Webster et al. 1991). In the auditory cortex, Metherate and Ashe (1991) showed that stimulation of the BF can enhance the evoked potential elicited by auditory thalamus stimulation. All these results fit nicely with the large amount of data showing that iontophoretic applications of ACh modulate cortical processing in the visual (Sillito and Kemp 1983; Sato et al. 1987b; Murphy and Sillito 1991), somatosensory (Donoghue and Carroll 1987; Metherate et al. 1987; Lamour et al. 1988; Metherate et al. 1988a), and auditory modalities (Ashe et al. 1989; McKenna et al. 1989; Metherate and Weinberger 1989, 1990).

So far, the nature of the relationship between the BF cholinergic activation that induces cortical arousal, on the one hand, and the BF cholinergic activation that promotes facilitation of sensory processing and plasticity, on the other hand, has not been elucidated. To what extent the effectiveness of BF stimulation in facilitating cortical processing is linked with cortical arousal induced by BF stimulation is unknown. One possibility is that facilitation of cortical processing occurs only if the BF stimulation induces a cortical arousal. The alternative is that facilitation of cortical processing can occur even if the BF stimulation does not desynchronize the cortical activity. In this latter case, we can wonder whether the facilitation is the same as that observed under cortical activation i.e., if it has the same magnitude, affects the same proportion of neurons, and lasts the same duration.

The present study is an attempt to answer these questions. Stimulation of the BF in the area of the NBM was performed in urethane-anesthetized rats, while tone-evoked responses were recorded in the primary auditory cortex. The intensity of stimulation was adjusted to obtain (or not) a desynchronization of the EEG. BF stimulation was paired with tone presentation. Simultaneous recordings were performed in both auditory cortices. As the BF cholinergic projections are unilateral, the contralateral data constitute an internal control of the state of the preparation and can also assess the specificity of the effects induced by BF stimulation. Furthermore, to verify the cholinergic nature of the effects observed, a subset of recordings was collected under atropine. Finally, to determine whether stimulation of the BF could by itself facilitate the sensory responses, additional recordings were collected first in a protocol using BF stimulation alone, then in a protocol using paired presentations of BF stimulation and tone.

Materials and methods

Subjects and preparation

Adult male Wistar rats ($n=25$), weighing 290–390 g, were used as subjects. They were anesthetized with urethane (1.5 g/kg i.p., two thirds of this dose being followed by one third of it 15 min later; supplements of 0.2 g were occasionally given during the experiment). The animal, placed on a heating pad that maintained the body temperature around 37° C, was secured to a stereotaxic frame with blunt hollow ear bars. After a sagital incision was made, a local anesthetic (Xylocaïne) was liberally applied on the wound. Craniotomies were performed unilaterally above the location of the basal forebrain (1.8–2.8 posterior and 3.0–3.6 lateral to bregma, according to the atlas of Paxinos and Watson (1982). These coordinates were selected because anatomical data showed that the BF neurons projecting to the temporal cortex are located in the caudal aspect of the NBM (Wenk et al. 1980; Bigl et al. 1982; Lamour et al. 1982; Rye et al. 1984; Saper 1984; Luiten et al. 1987). Craniotomies were also performed bilaterally above the auditory cortices. The dura mater was resected and the location of the primary auditory cortex was evaluated according to the patterns of cerebral vasculature described in the literature (Kelly and Sally 1988). Two silver spheres were inserted between the bone and the dura around the midline, rostral to lambda and to bregma, to record a global EEG.

Recording and stimulation techniques

Cluster recordings were collected for two reasons. First, we wanted to be able to select a tonal frequency eliciting comparable neuronal discharges in both auditory cortices. Unit recordings are far better than evoked potentials to detect a tonal selectivity, and a lot of mapping studies have used indifferently both single unit and cluster recordings to reveal the frequency selectivity in the auditory system (Imig and Morel 1985; Langner and Schreiner 1988; Redies et al. 1989; Clarey and Irvine 1990). Second, owing to the length of our protocol (see below), we chose to record small clusters instead of single units, since the probability of holding two units simultaneously in each cortex for several hours is quite low.

Two recording electrodes, made of Teflon insulated tungsten wire (50 μm, A-M System), were lowered under electrophysiological control into each cortex. The neuronal activity was amplified (Grass model P511 K), filtered (500–10 000 Hz), displayed on an oscilloscope, then sent to a voltage window discriminator to select the largest spikes (signal to noise ratio at least 3:1). The output pulses, collected by a microcomputer 200 ms before the BF stimulation up to 200 ms after tone offset, were used to generate an on-line display of each evoked response (10 ms bin) for two channels of neural activity (one from each cortex). Off-line analysis allowed building of standard peristimulus time histograms (PSTHs) and quantifying the tone-evoked responses on each channel, by selecting temporal windows after tone onset. The global EEG (bandpass 1–90 Hz), as well as the local EEG recorded via the electrodes in the auditory cortex ipsilateral to the stimulating electrode, were sent to a polygraph (Grass model 7P511J).

The stimulating electrodes were bipolar concentric electrodes (300 μm external diameter). They were connected to a constant-current stimulator via an isolation unit placed close to the stereotaxic frame. A homemade electronic circuit grounded the input of the preamplifier from 1 ms before until 1 ms after the stimulation, to avoid its saturation.

Experimental protocol

The frequency of the tone (between 1 and 16 kHz) used during the protocol was chosen to evoke neuronal discharges as similar as possible in both auditory cortices (the recording electrodes for one

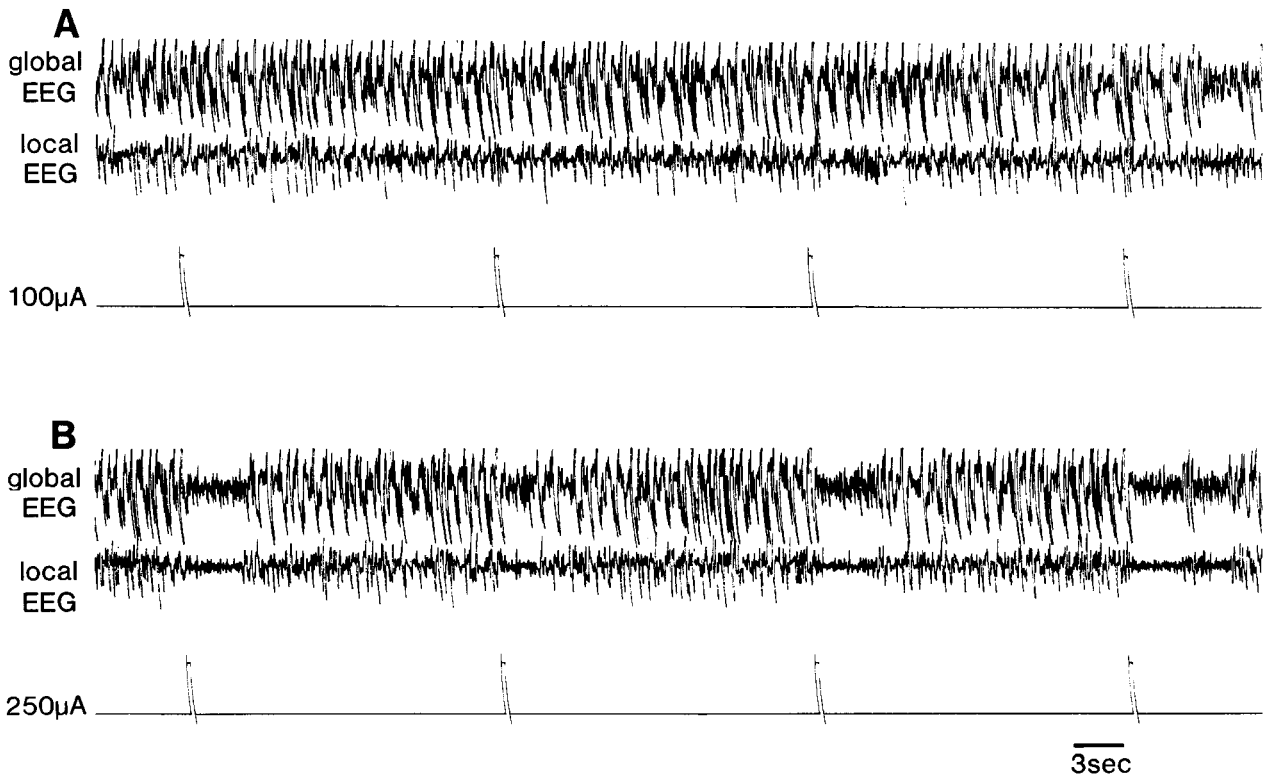

Fig. 1. Effects of basal forebrain stimulation on the local and global electroencephalogram (EEG) during pairing trials between BF stimulation and tone. At low intensity (100 μA), there were no changes in the two EEGs (**A**), while at high intensity (250 μA) there was a clear desynchronization of both EEGs at each pairing trial (**B**) The threshold for EEG desynchronization was in this case 150 μA. The results obtained on the tone-evoked responses for this recording are presented in Fig. 6A

side, or occasionally both, were moved until this was obtained.) The tone was 200 ms in duration (including 2 ms rise/fall time) and 70 dB sound pressure level (SPL) in intensity (as measured at the extremity of the hollow ear bar by a B&K sound level meter).

Once clear auditory responses, with a latency less than 30 ms, were obtained from the recording electrodes in both cortices, the stimulating electrode was slowly lowered. Starting at −6.0 below the dura, BF stimulations (300 ms, 100-Hz, 0.1-ms pulses) were delivered to adjust the final location of the stimulating electrode. A clear desynchronization of the EEG derived from the ipsilateral auditory cortex was required at the final placement (between −6.5 and −7.5 below the dura). Special care was taken to determine the threshold intensity allowing desynchronization of the local EEG. Two intensities of stimulation were then selected: the lower one (low BF stimulation) was at least 20 μA below the threshold for desynchronizing the local EEG; the higher one (high BF stimulation) was at least 100 μA above the threshold for desynchronizing the local EEG. At this high intensity, the global EEG was also desynchronized. Thus, no changes could be visually detected on the local or on the global EEG when using the low BF stimulation, while the high BF stimulation induced clear and reliable EEG desynchronization at each trial (see Fig. 1).

The standard protocol was started by ten tone alone presentations. The tone, delivered bilaterally, was presented with an intertrial interval (ITI) of 20 s. The low BF stimulation was then paired with the tone for 20 trials, during which the onset of the tone occurred 50 ms after the end of the BF stimulation. The responsiveness to the acoustic stimulus was measured immediately and 15 min postpairing by ten tone-alone presentations. During both the pairing trials and the postpairing tests, the ITI was the same as before pairing. Fifteen minutes later, the same protocol was repeated, except that the high BF stimulation was used during the pairing trials. The total time of this standard protocol was 75 min. All stimulus presentations (tone, BF stimulation) were controlled by an Apple IIe computer.

For eight animals, this whole standard protocol was repeated after systemic atropine sulfate injection (2–20 mg/kg i.p.). The injection took place at least 60 min (up to 90 min) after completion of the standard protocol; the recording session started 15 min after the atropine injection. The tone, the intensities used for the BF stimulations, and the ITI were in all aspects identical to those used in the normal condition.

In a separate group of animals ($n=5$), the whole protocol was first carried out using 20 BF stimulations alone, delivered in the absence of the tone, instead of the 20 BF stimulation-tone pairings. Sixty to ninety minutes later, the standard protocol was repeated, this time involving 20 BF stimulation-tone pairings. The same BF intensities of stimulation were used in each case.

Data analysis

During the off-line analysis, we focused on the "on" excitatory responses that occurred within 30 ms after tone onset, since sustained responses are rather unusual in the primary auditory cortex. However, the global amount of activity evoked during the whole tone duration was also analyzed and is reported. To take into account possible changes in spontaneous activity occurring during the protocol, the evoked responses were computed by subtracting the number of spikes per bin occurring during the 200 ms preceding the onset of the BF stimulation from the number of spikes per bin occurring during the first 30 ms of tone. All the statistical analyses were performed by comparing the tone-evoked responses obtained during and after the pairing procedure with those obtained immediately before the pairing procedure.

Table 1. Number of animals used, and number of ipsilateral and contralateral recordings obtained in normal conditions and after atropine administration. No contralateral recordings were performed during stimulations of the basal forebrain alone; and this paradigm was not tested under atropine

		Normal conditions		Atropine	
		Number of animals	Number of recordings	Number of animals	Number of recordings
Pairing tone with BF stimulation	Ipsilateral recordings	20[a]	23	8	8
	Contralateral recordings	20[a]	21	8	8
BF stimulation alone	Ipsilateral recordings	5[b]	10	–	–
	Contralateral recordings	–	–	–	–

[a] In these 20 animals one ipsi- and one contralateral recording were obtained simultaneously, except in 2 cases where two ipsi- and one contralateral electrodes were recorded simultaneously and 1 case where two ipsilateral and two contralateral electrodes were recorded at the same time

[b] In these five animals two ipsilateral electrodes were recorded simultaneously

Histology

At the end of each experiment, the animal received an overdose of pentobarbital (100 mg/kg), then was perfused (intracardiac perfusion) with 0.9% saline followed by 10% formalin. The brain was removed and kept in 10% formalin for several weeks. Subsequently, the brains were sectioned on a freezing microtome (60 μm-thick serial coronal sections). The sections were stained with cresyl violet for Nissl preparation and for one animal half of the sections were processed for acetylcholinesterase reactivity.

Results

The data presented here are from 23 ipsilateral and 21 contralateral simultaneous recordings; 8 ipsilateral recordings were subsequently collected after atropine injection (see Table 1). Ten additional ipsilateral recordings were collected in a protocol where BF stimulations alone were used instead of paired presentations of BF stimulation and tone. All recordings exhibited clear, short-latency, tone-evoked responses before any BF stimulation. Only clusters consisting of few waveforms (less than five) were included in the data, and recordings that did not show a stable signal-to-noise ratio across the protocol were discarded from the analysis.

The mean intensity was 62 ± 8 μA (range 25–140 μA) for the low BF stimulation, and 245 ± 17 μA (range 140–420 μA) for the high BF stimulation.

Pairing at low-intensity stimulation

For 22 of 23 ipsilateral recordings, pairing the nondesynchronizing BF stimulation with the tone led to an increase in the short-latency "on" tone-evoked response (A response was considered to be increased or decreased when the percentage of change compared with the prepairing period was greater than 30%). Figure 2 (upper row) shows an example of such an enhancement. Compared with the response before pairing (Fig. 2A), the "on" evoked response was increased during the first (Fig. 2B) and the second (Fig. 2C) block of pairing. It returned to the prepairing level after pairing (Fig. 2D). This is also illustrated in the example presented in Fig. 4A. On the other hand, the majority of the contralateral recordings did not exhibit increased responses during pairing. There were slight increased responses for only 5 of 21 recordings (decreases, $n=5$; no changes, $n=11$). Figure 2 (lower row) shows an example of such an absence of increase on the contralateral recording, while an increased response occurred ipsilaterally. This is also illustrated in Fig. 4B.

The statistical analyses performed on the group data confirmed that during pairing the ipsilateral responses were increased (paired t-test, $t_{(22)}=2.694$, $P=0.01$, and $t(22)=2.217$, $P=0.03$, respectively, for the first and the second block of ten trials). After pairing, the tone-evoked responses no longer differed from the prepairing ones. No significant changes were observed for the contralateral recordings, whether during or after pairing (lowest P value, $P=0.293$).

When the whole tone duration was analyzed, only 10 of 23 ipsilateral recordings exhibited increased evoked activity during pairing (decreases, $n=3$; no changes, $n=10$). On average, there was no significant enhancement of the global amount of activity elicited by the tone either during pairing ($t_{(22)}=1.54$, $P=0.13$; $t_{(22)}=1.06$, $P=0.30$), or after pairing (immediately and 15 min after, $t_{(22)}<1$, n.s.). The contralateral responses were not increased, whether during or after pairing (lowest P value, 0.18).

Pairing at high-intensity stimulation

Surprisingly, less ipsilateral recordings exhibited increased "on" responses during pairing with the high stimulation than during pairing with the low stimulation: only 11 of 23 recordings showed consistent increases (decreases, $n=8$; no changes, $n=4$). Despite this, 17 of 23 showed strong increased responses immediately postpairing (decreases, $n=4$; no changes, $n=2$), and for 14 of 23 the responses were still increased 15 min postpairing (decreases, $n=4$; no changes, $n=5$). Figure 3 shows the effect of pairing at high intensity for the same recording as in Fig. 2. Compared with the response obtained before pairing (Fig. 3A), the "on" response was strongly en-

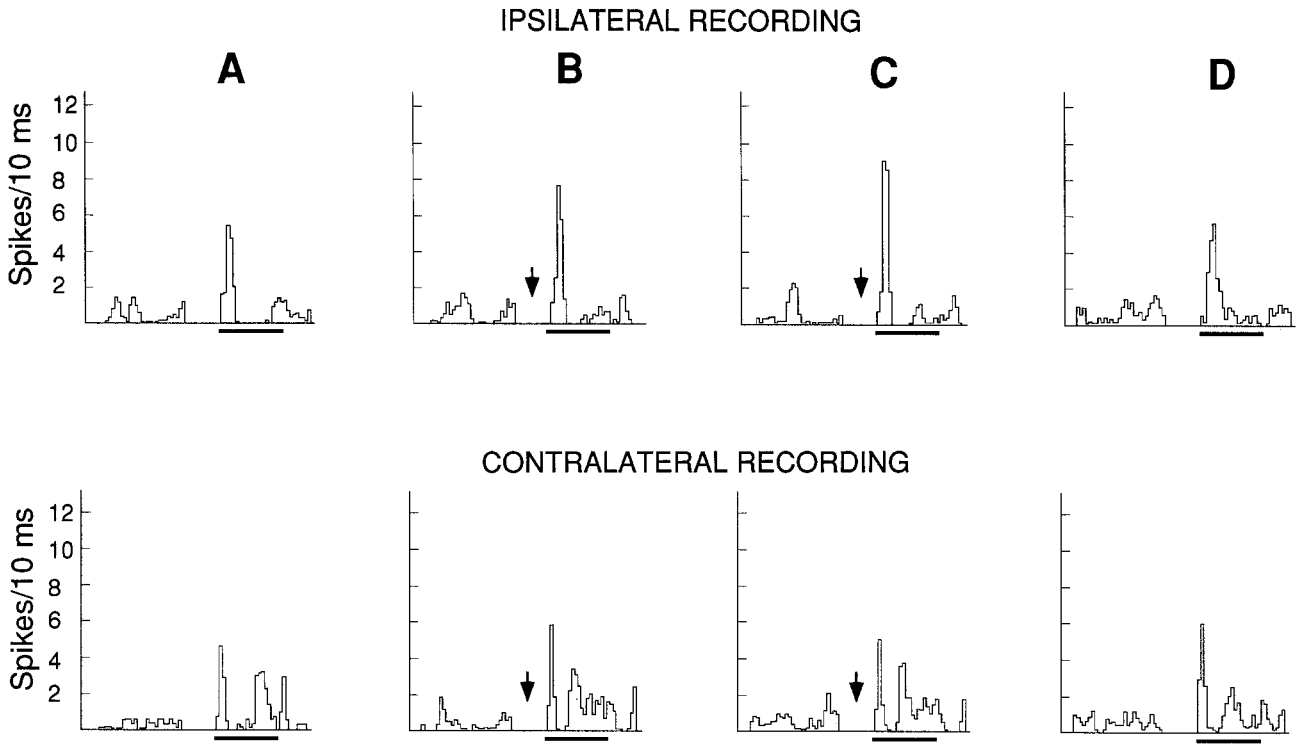

Fig. 2. Histograms (bin width 10 ms) of ipsilateral (*upper row*) and contralateral (*lower row*) neuronal discharges obtained simultaneously before (**A**), during (**B**, and **C**), and post (**D**) pairing with low-intensity BF stimulation (50 μA; *arrows*) The stimulation lasted 300 ms and the input of the preamplifier was grounded from 1 ms before until 1 ms after the stimulation, to avoid its saturation. The *horizontal bars* under the x axes denote the tone (4 kHz) duration (200 ms) Note that compared with the prepairing response (**A**), the ipsilateral tone-evoked response was increased during pairing (**B**, **C**) but not after pairing (**D**). In contrast, the contralateral response was never affected

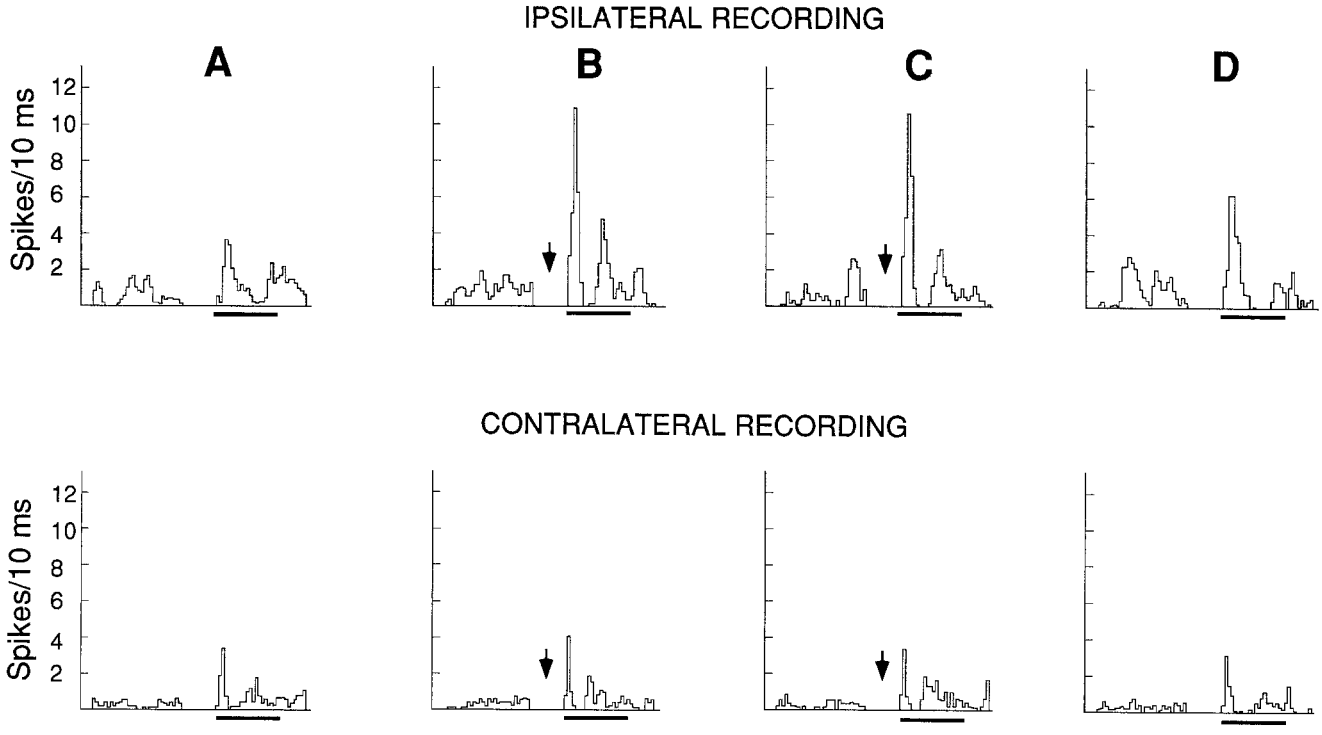

Fig. 3. Histograms (bin width 10 ms) of ipsilateral (*upper row*) and contralateral (*lower row*) neuronal discharges obtained simultaneously before (**A**), during (**B**, **C**), and post (**D**) pairing with high-intensity BF stimulation (300 μA) for the same recording as in Fig. 2. Note that the ipsilateral, "on" evoked response was largely enhanced during pairing (**B**, **C**), and remained increased after pairing. In contrast, the contralateral response was never affected. Conventions the same as in Fig. 2

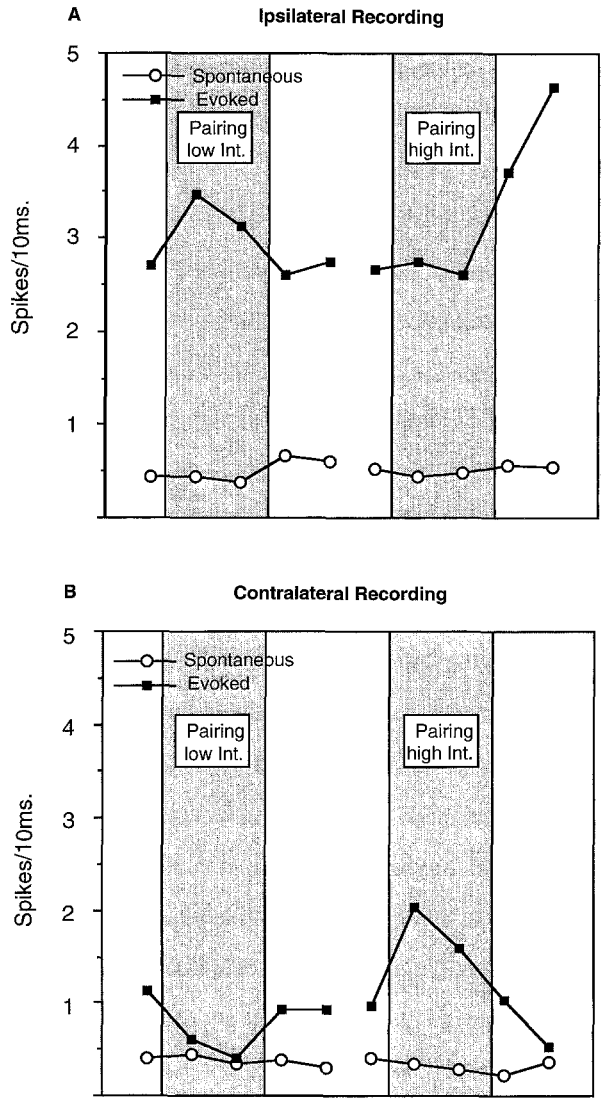

Fig. 4. Effects of pairing on ipsilateral (**A**) and contralateral (**B**) tone-evoked discharges (simultaneous recordings). **A** Using low-intensity BF stimulation (45 μA), the evoked response increased during pairing and returned to the control level immediately after pairing. Using high-intensity BF stimulation (150 μA), the evoked response showed no changes during pairing but was largely increased immediately and 15 min post-pairing. **B** The evoked response was decreased during pairing with low BF stimulation. Using high BF stimulation, it was increased during pairing, but returned to the prepairing level immediately after pairing

hanced during the pairing trials (Fig. 3B,C), and this enhancement was maintained both immediately (Fig. 3D.) and 15 min (not shown) postpairing. In another example, provided in Fig. 4, although the pairing at low intensity induced a clear increase in the tone-evoked response, the pairing at high intensity had apparently no effect. However, immediately and 15 min after pairing the responses were clearly facilitated.

Contralaterally, 10 of 21 recordings showed increased responses during pairing (decreases, $n=5$; no changes, $n=6$). In contrast to what was observed ipsilaterally, the proportion of recordings exhibiting increased responses was not larger after pairing: increased responses were present in only 9 of 21 recordings immediately postpairing (decreases, $n=5$, no changes, $n=7$), and in only 7 of 21 recordings 15 min postpairing (decreases, $n=8$, no changes, $n=6$).

The statistical analyses performed on the group data revealed that the increase in the "on" ipsilateral evoked responses detected during the pairing trials did not reach the statistical level of significance when compared with the prepairing responses ($t_{(22)}=1.725$, $P=0.098$; and $t_{(22)}=1.768$, $P=0.092$, respectively for each block of pairing). This is not surprising since only 11 of 23 recordings exhibited consistent increased responses during pairing. Nonetheless, a comparison of the increases obtained at the two intensities for this subset of 11 recordings showed that they were significantly larger at high than at low intensity (2.66 vs 11.06 spikes/bin; $t_{(10)}=2.06$, $P=0.03$). On the other hand, the responses of the whole population of 23 recordings were significantly increased both immediately ($t_{(22)}=3.553$, $P=0.0018$) and 15 min ($t_{(22)}=2.116$, $P=0.0459$) postpairing. The analyses performed on the contralateral recordings did not reveal any significant change either during pairing ($t_{(20)}=1.36$, $P=0.188$; and $t_{(20)}=1.13$, $P=0.271$) or after pairing ($t_{(20)}=1.123$; $P=0.274$; and $t_{(20)}=0.26$, $P=0.79$; respectively for immediately and 15 min after).

When the whole tone duration was considered, 16 of 23 ipsilateral recordings exhibited enhanced evoked activity during pairing. This increase in the total amount of excitation over the whole tone was significant for the two blocks of pairing trials ($t_{(22)}=2.29$, $P=0.03$; and $t_{(22)}=2.67$, $P=0.01$). It was still present immediately ($t_{(22)}=2.54$, $P=0.01$) but not 15 min ($t_{(22)}<1$, n.s.) after pairing. These effects were not observed on the contralateral side, either during pairing or after pairing (lowest P value, 0.17).

Figure 5 summarizes the group data for the "on" evoked responses at low and high intensity for the ipsilateral and contralateral recordings. The changes observed for the evoked responses were not a consequence of changes in spontaneous activity: overall analyses of variance (ANOVA) revealed that there were no significant modifications of the spontaneous pretone activity across the protocol either at low or at high intensity, whether for the ipsilateral (respectively, $P=0.93$ and $P=0.50$) or for the contralateral (respectively, $P=0.54$ and $P=0.19$) recordings.

Pairing under atropine treatment

In eight cases for which a stable signal-to-noise ratio was still observed 1 h after the end of the regular protocol, the experiment was repeated after atropine injection (i.p., mean dose 9.5 ± 3 mg/kg). Figure 6 shows an example of ipsilateral recording obtained under normal conditions and subsequently under atropine treatment. Under normal conditions (Fig. 6A), the "on" response was enhanced during pairing with both the low and the high BF stimulation. This facilitation lasted after pairing at high intensity. In contrast, with atropine (Fig. 6B), no consis-

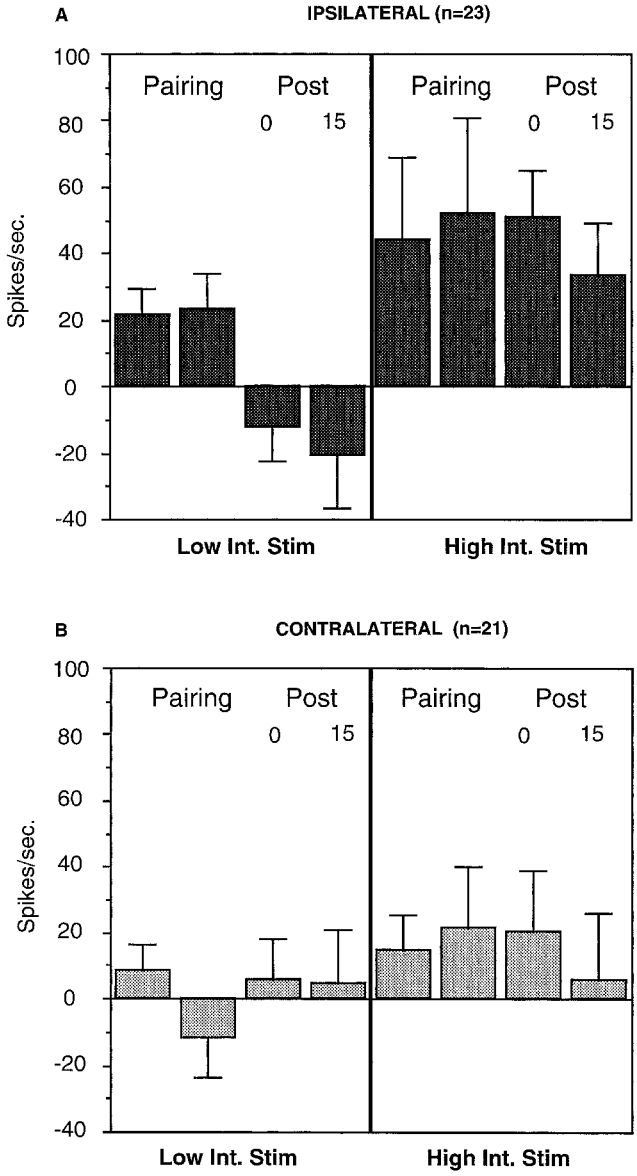

Fig. 5. Group data for 23 ipsilateral (**A**) and 21 contralateral (**B**) recordings. For each recording, the mean "on" evoked response (0–30 ms after tone onset) observed before pairing was subtracted from the mean response observed during and after pairing, to provide a difference (in spikes per second) from the control period. These differences were averaged across recordings and are represented ± SEM. Note that the ipsilateral tone-evoked responses were enhanced during pairing with the low- and the high-intensity BF stimulation, and that they remained increased after pairing with the high BF stimulation

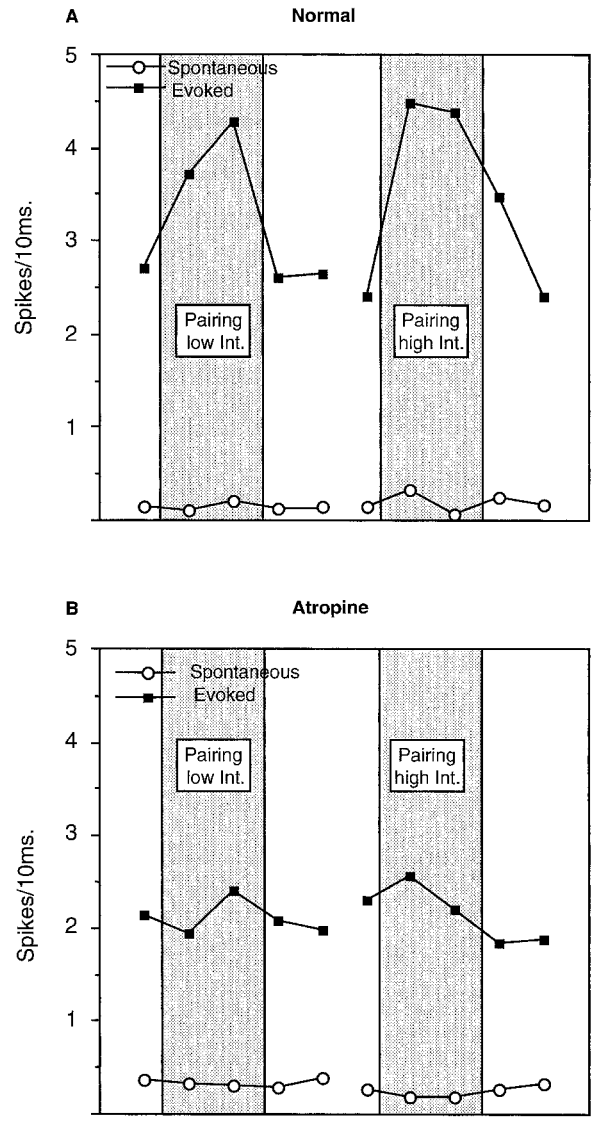

Fig. 6. Ipsilateral facilitation blocked by atropine injection (14 mg/kg). Under normal conditions (**A**), this recording exhibited the usual pattern of effects: a transient increase in the evoked response during pairing with low-intensity BF stimulation, and a long-lasting increase after pairing with high-intensity BF stimulation. These effects were not observed after injection of atropine (**B**) 90 min later

tent changes in the responses were induced by pairing, whether at low or at high intensity.

These eight ipsilateral recordings showed, in normal conditions the same pattern of changes as those described for the whole population (Fig. 7A). The "on" responses were enhanced during pairing at low intensity ($t_{(7)}=5.69$, $P=0.0007$; and $t_{(7)}=2.58$, $P=0.03$; respectively for the first and the second block of pairing), and after pairing at high intensity ($t_{(7)}=3.016$, $P=0.019$; and $t_{(7)}=2.428$, $P=0.045$; respectively for immediately and 15 min postpairing).

Under atropine treatment, the "on" responses obtained before pairing did not differ significantly from those observed in normal conditions (paired t-test, $t_{(7)}=0.075$, $P=0.94$; and ($t_{(7)}=0.588$, $P=0.57$; respectively for each pre-pairing period). However, the effects induced by pairing were greatly reduced with atropine (Fig. 7B). During the pairing at low intensity, only 4 of 8 recordings showed increased responses, the others showed decreased responses. During the pairing at high intensity, 3 of 8 recordings exhibited increased responses (decreases, $n=3$; no changes, $n=2$); after pairing there were only three cases of increased responses immediately after (decreases, $n=3$; no changes, $n=2$) and none 15 min postpairing (decreases, $n=4$; no changes, $n=4$). The statistical analyses performed on the group data failed to

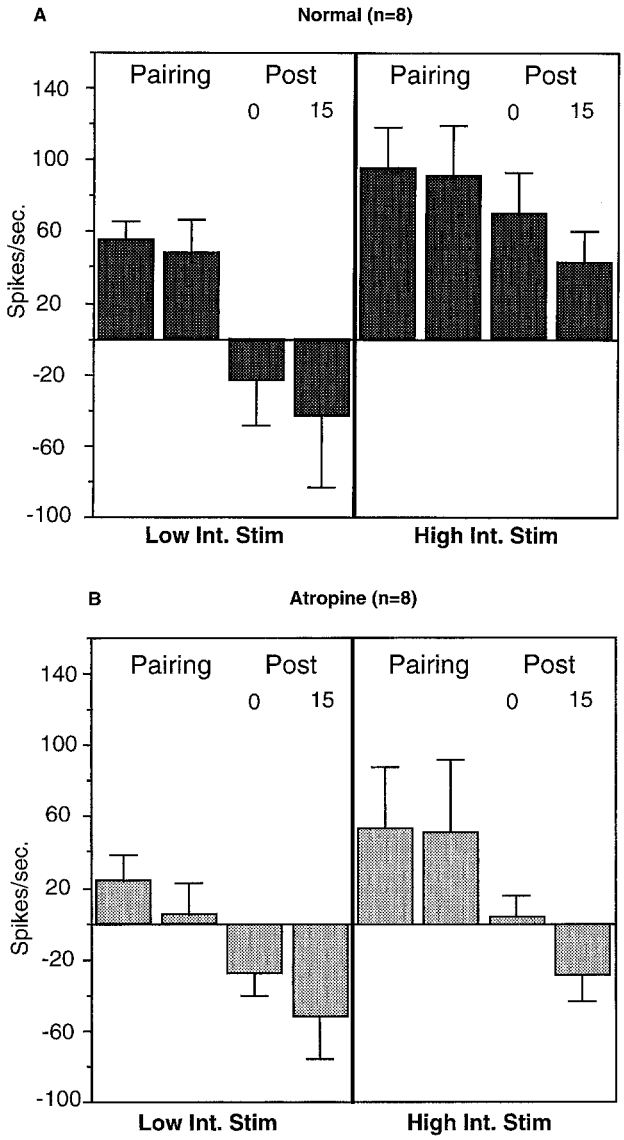

Fig. 7. Group data for the eight ipsilateral recordings collected under normal (**A**) and with atropine (**B**). Under normal conditions, the recordings displayed the pattern of changes of the whole population: transient increase of the "on" responses during pairing at low intensity, and prolonged facilitation of the responses due to the pairing at high intensity. Such effects were absent under atropine treatment

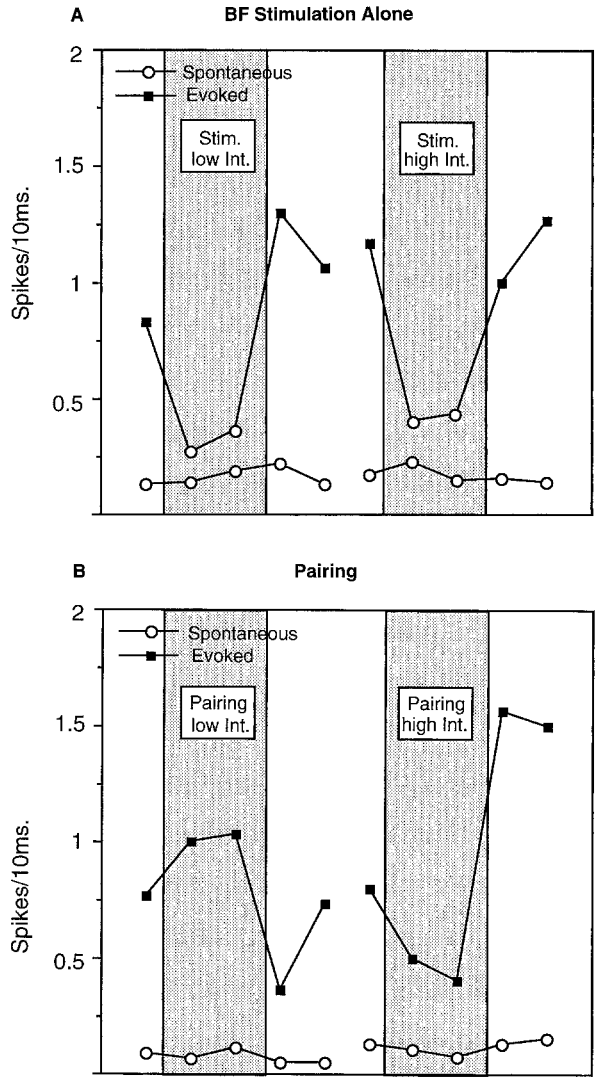

Fig. 8. Differential effects of BF-stimulation alone (**A**) and pairing (**B**) procedures. For this recording, the BF stimulation alone increased the firing rate above the spontaneous level both at low and at high intensity. Note that, using high-intensity stimulation, no prolonged facilitation of the response was present after the BF-stimulation alone procedure whereas it was after the pairing procedure. Note also that although the response increased during pairing with the low-intensity stimulation, it decreased during pairing with the high-intensity stimulation

reveal any significant increase in the responses, whether during pairing at low intensity ($t_{(7)}=1.7$, $P=0.1328$; and $t_{(7)}=0.32$, $P=0.75$), or during pairing at high intensity ($t_{(7)}=1.57$, $P=0.15$; and $t_{(7)}=1.23$, $P=0.25$). In the two cases, after pairing the responses were at the control level. We found no relationship between the dose of atropine used and the amount of change of the evoked response during and after pairing, both at low and at high intensity.

Over the whole tone, there was a clear increase in the total amount of excitation evoked by the tone during pairing when performed with high BF stimulation under normal conditions ($t_{(8)}=2.87$, $P=0.02$; and $t_{(8)}=2.31$, $P=0.03$; for each block of pairing). No such increase was detected with atropine ($t_{(8)}<1$, n.s., in each case).

BF stimulation alone

For ten additional ipsilateral recordings, the protocol was first run using repeated BF stimulations alone instead of pairing trials between BF stimulation and tone. Figures 8 and 9 show recordings obtained in such a protocol. It appears that the "on" responses did not increase after the high BF stimulation alone, whereas they strongly increased after the tone had been paired with the high BF stimulation.

The group data of these ten recordings are presented in Fig. 10. No enhancement of the "on" responses was observed after the low BF stimulation alone ($P=0.22$ and $P=0.99$; for, respectively, immediately and 15 min post-stimulation), nor after the high BF stimulation

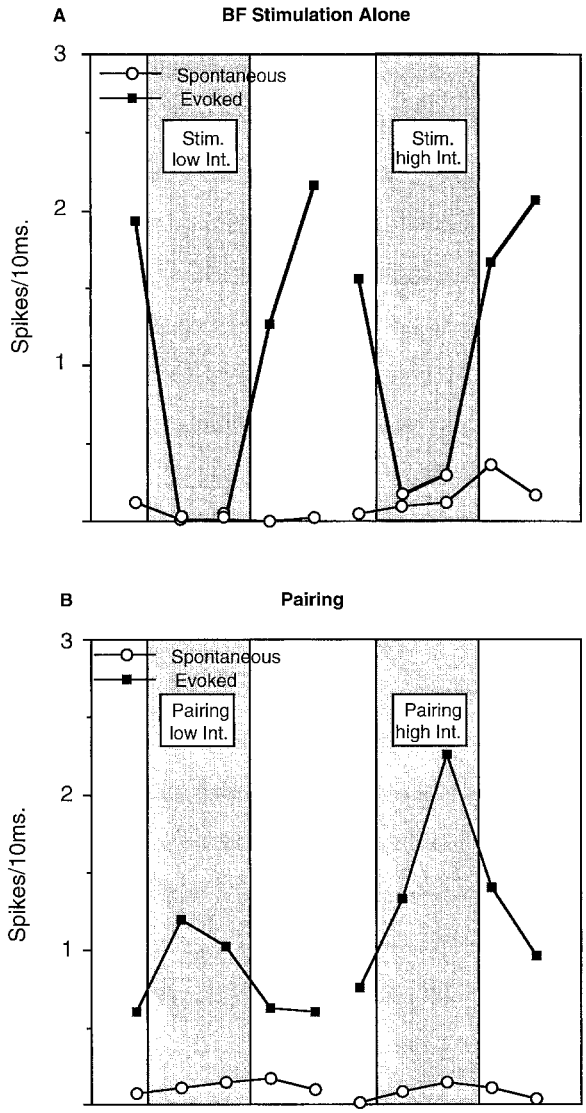

Fig. 9. Differential effects of the BF-stimulation alone (**A**) and pairing (**B**) procedures. For this recording, the BF stimulation alone did not increase the firing rate above the spontaneous level. Note that, using high-intensity stimulation, no prolonged facilitation of the response was present after the BF-stimulation alone procedure, whereas it was after the pairing procedure. Note also that in this case the evoked response was increased during pairing at low intensity and even more so during pairing at high intensity

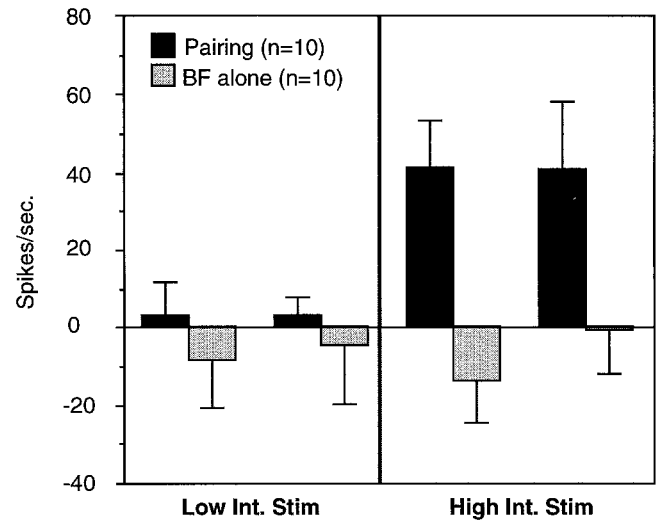

Fig. 10. Group data for the ten ipsilateral recordings collected immediately and 15 min after the BF-stimulation alone (*grey bars*) and the pairing (*dark bars*) procedures. Note that with high-intensity stimulation the "on" responses were increased after the pairing procedure but not after the BF-stimulation alone procedure

alone (respectively, $P=0.49$ and $P=0.75$). In opposition, after pairing with the high stimulation there was a significant enhancement of the "on" responses both immediately ($t_{(9)}=3.41$, $P=0.007$) and 15 min ($t_{(9)}=2.32$, $P=0.045$) postpairing. Note that these recordings exhibited also a clear facilitation of the "on" evoked responses during pairing with the low BF stimulation ($t_{(9)}=3.655$, $P=0.005$; and ($t_{(9)}=5.09$, $P=0.0007$; for each block of pairing).

Finally, we analyzed the neural activity collected during the first 30 ms of recording following the end of the stimulation during the BF alone trials. On average, the BF stimulations increased, although not significantly, the cortical discharges above the level of spontaneous activity (over the 20 trials, $t_{(9)}=1.88$, $P=0.09$; and $t_{(9)}=1.83$, $P=0.10$; respectively for the low and the high intensity). We did not find any significant correlation between the changes of spontaneous activity due to the BF stimulation alone and the changes of tone-evoked response observed during and after the pairing procedure (lowest P value, 0.43). Thus, the fact that the BF stimulation alone enhanced, or not, the spontaneous rate of the cortical discharges, did not allow the prediction of the effects obtained subsequently during pairing. This is exemplified in Figs. 8 and 9. In the case presented in Fig. 8, the activity was increased by the high BF stimulation alone (Fig. 8A), but the tone-evoked response was decreased during pairing (Fig. 8B). In contrast, in the case presented on Fig. 9, the activity was not increased by the high BF stimulation alone (Fig. 9A) but the tone-evoked response was strongly enhanced during pairing (Fig. 9B).

Electrode placements

Figure 11 shows the placements of the stimulating electrodes for 24 of 25 of the animals. They were located in the caudal aspects of the NBM, more precisely in the dorsal part of the SI, at the boundary between the SI and the globus pallidus, or at the boundaries between the SI and the ventromedial part of the internal capsule. For 17 of 23 ipsilateral recordings, we were able to find the electrode tract in the auditory cortex. Based upon the depth in the cortex, we estimated that 14 recordings were from deep cortical layers (below layer IV) and 3 were from superficial layers (above layer IV).

Discussion

Overview of the results

The main findings of the present results can be summarized as follows: both nondesynchronizing (subthreshold)

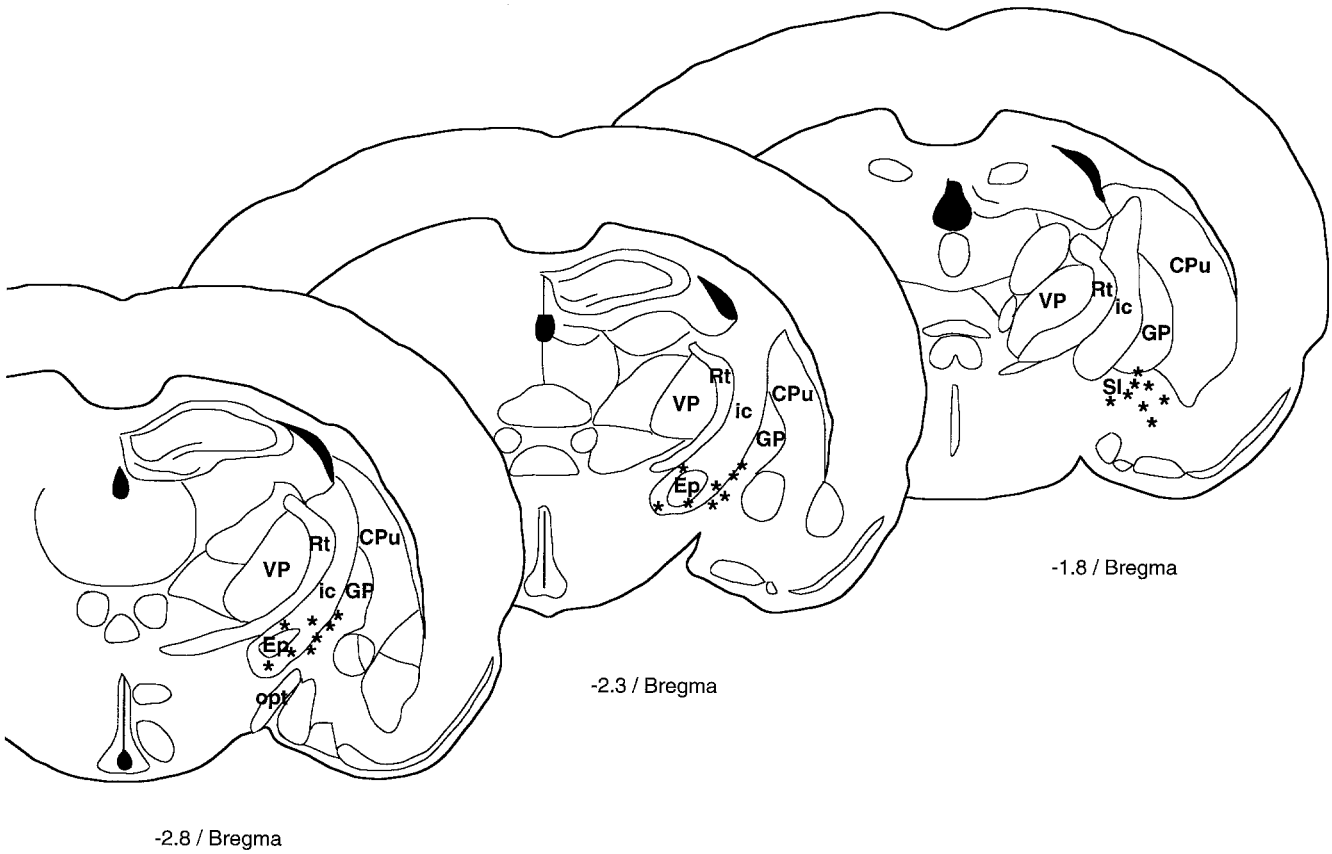

Fig. 11. Schematic representation of the stimulating electrode placements (*asterisks*). At the three anterior levels, anatomical limits between structures were redrawn from the Paxinos and Watson Atlas (1982) *CPu*, caudate-putamen; *Ep*, Entopedundular nucleus; *GP*, globus pallidus; *ic*, internal capsule; *opt*, optic tract; *Rt*, reticular thalamic nucleus; *SI*, substantia innominata; *VP* ventral posterior thalamic nucleus

and desynchronizing (suprathreshold) stimulations of the BF were able to facilitate ipsilaterally the cortical "on" evoked responses when these stimulations repeatedly preceded the occurrence of the tone. The responses returned to the pre-pairing level immediately after pairing when a subthreshold stimulation had been used, while they remained increased up to 15 min after pairing when a suprathreshold stimulation had been used. No systematic increases in the evoked responses were observed contralaterally whether during pairing with the low BF stimulation or after pairing with the high BF stimulation. Such results allow us to rule out the possibility that the effects observed ipsilaterally were a consequence of a change of state of the preparation. To a large extent, the ipsilateral facilitations induced by the pairing procedure were blocked by atropine. Furthermore, when the same BF stimulations were delivered alone, no effects were detected whether with the low or with the high BF stimulation.

Validity of the present findings

Several methodological comments need to be made before interpreting the results further. First, the results show that even a nondesynchronizing stimulation of the BF can enhance the "on" responses in the auditory cortex. This result was observed in the whole population of 23 ipsilateral recordings, on the subset of 8 recordings subsequently recorded under atropine, and on the 10 recordings previously submitted to BF stimulations alone. Such a consistent finding must likely reflect a real effect. Because we did not quantify the power spectrum of the EEG, it could be argued that subtle changes in EEG frequency, not detectable by visual inspection, could have occurred. Even if this possibility cannot be totally ruled out, the main claim here is that BF stimulation which did not induce a local or a global "arousal" (as it is generally defined based upon visual inspection of the EEG) was able to facilitate transiently the ipsilateral tone-evoked responses.

Second, in the present study as well as in all the previous ones, the possibility exists that the activation of fibers of passage by the electrical stimulations could contribute to the observed results. However, chemical stimulations were hardly compatible with the fact that the pairing procedure required control of the exact timing of the BF stimulation with regard to tone presentation. Moreover, the findings (1) that chemical stimulation performed in the same area of the BF also led to EEG desynchronization (Metherate et al. 1992), and (2) that atropine was able to block the facilitations induced by the stimulations (as

in Tremblay et al. 1990; Metherate and Ashe 1991), together suggest that the stimulation was indeed activating cholinergic neurons of the BF, and was increasing cortical responsiveness by an action mediated by muscarinic receptors.

Finally, due to the systemic administration of atropine, the exact location of the involved muscarinic receptors cannot be guaranteed. However, the finding that intracortical application of atropine blocked the BF-induced facilitation of thalamocortical transmission supports the involvement of cortical muscarinic receptors (Metherate and Ashe 1993).

Relations with previous studies and possible mechanisms

Short-term effects. Different types of effects were reported during pairing between a sensory stimulus and BF stimulation. The evoked potentials (EP) recorded by Rasmusson and Dykes (1988) or by Metherate and Ashe (1991) almost systematically increased. On the other hand, the evoked potentials collected by Webster et al. (1991) mostly decreased, while the unit responses recorded by Tremblay et al. (1990) were generally unaffected during the pairing procedure. In the present study, the pairing with a subthreshold BF stimulation induced almost exclusively (22/23 cases) facilitations of the evoked responses. In contrast, a suprathreshold stimulation induced either larger facilitations or decreased responses, which suggests a heterogeneity either at the loci of stimulation or at the cortical recording sites (or at both). Two explanations can be proposed to account for the different effects produced by the BF stimulation.

The first one is based on the existence of noncholinergic neurons in the BF. The limited current spread produced by the low BF stimulations might have activated mostly cholinergic soma, while the larger current spread produced by the high BF stimulations might have activated heterogenous populations of cells. In agreement with that, atropine was totally efficient in blocking the effects observed at low intensity, while it did not block entirely the effects observed at high intensity. It is possible that the high intensity stimulations might have recruited GABAergic neurons of the BF that are known to project also onto the cortex (Fisher et al. 1988; Beaulieu and Somogyi 1991; Freund and Meskenaite 1992). Depending on the precise location of the stimulating electrode, increasing the intensity could have resulted in activation either of a larger proportion of cholinergic neurons or of GABAergic neurons. In the first case one can expect a larger increase in the evoked response, while in the second case a smaller facilitation or even a decrease in the evoked response can be expected.

The second explanation relies on the assumption that increasing the intensity of the BF stimulation increases the amount of ACh released in the cortex. It has been shown that iontophoretic ACh application alters the intensity function of auditory cortex neurons (Metherate et al. 1990). Non-monotonic intensity functions are quite common in the auditory cortex (Brugge and Merzenich 1973; Phillips et al. 1985), and they lead to decreased responses when a high intensity tone is used. To explain why a given amount of ACh applied iontophoretically can facilitate, suppress, or have no detectable effect on the "on" tone-evoked response, Ashe and Weinberger (1991) have proposed the so-called "muscarinic intensity model", in which ACh application mimics an increase in stimulus intensity (see also for details, Ashe et al. 1989). Thus, the high-intensity BF stimulations paired with the tone could have produced the equivalent of presenting a high intensity tone, the consequence being, for neurons having nonmonotonic intensity function, a smaller tone-evoked response.

Long-term effects. As in previous BF stimulation studies (Rasmusson and Dykes 1988; Tremblay et al. 1990; Webster et al. 1991), prolonged facilitations of sensory responses were observed. These prolonged facilitations are consistent with the known physiological effects of ACh on muscarinic receptors. Owing to its slow and long-lasting depolarizing effects on the cortical neurons, associated with an increase in membrane resistance due to decreased K^+ conductances, ACh provides adequate substrate for persistent changes in cells' excitability (Krnjevic and Phillis 1963; Woody et al. 1978; McCormick and Prince 1986; Metherate et al. 1989; Metherate et al. 1992). In agreement with that, long-lasting facilitations of sensory responses were described when pairing iontophoretic applications of ACh with a sensory stimulus[1] (Sillito and Kemp 1983; Metherate et al. 1987; 1988a, b; Lamour et al. 1988).

As in previous studies (Rasmusson and Dykes 1988; Tremblay et al. 1990), long-term facilitations occurred only if the BF was stimulated in conjunction with the afferent volley from the periphery. BF stimulation induced no effects when it had been delivered alone, in the absence of sensory stimulus. Similar observations were reported using iontophoretic ACh applications (Metherate et al. 1987). Thus, an approximate temporal coincidence between neuronal depolarization produced by ACh and neuronal excitation produced by the sensory stimulus seems to be required for enhancement of cortical responsiveness.[2] This is in line with the idea that ACh acts as a permissive agent that facilitates changes in other, non-cholinergic synapses (Singer 1979). Since in some experiments (Metherate et al. 1988b; Tremblay et al. 1990), comparable long-lasting facilitations were observed after combining a sensory stimulus with ACh administration and after combining glutamate with ACh, the mechanism generally proposed for these prolonged effects is that ACh facilitates the glutamatergic (Popowitz

[1]Iontophoretic applications of ACh can induce local EEG changes as well as changes in subthreshold membrane potential fluctuations that seem equivalent to what is observed during arousal, i.e., a shift from low frequency (1–5 Hz) to high frequency (20–40 Hz; Metherate et al.1992).

[2]The requirement for simultaneity is not strict, since the interval between the BF stimulation and the sensory stimulus was 50 ms here but up to 200 ms in Rasmusson and Dykes (1988) which is long compared with the intervals usually used for heterosynaptic facilitation as well as for the so-called long-term potentiation (LTP) phenomenon.

et al. 1988; Hicks et al. 1991; Cox et al. 1992) thalamocortical transmission.

However, this does not explain why the long-lasting facilitation developed after high but not after low BF stimulation. An explanation can be proposed based on the fact that the high-intensity stimulation enhanced the global amount of activity elicited during the whole tone duration while the low-intensity stimulation did not. Thus it is possible that the high-intensity stimulation facilitated a late excitatory postsynaptic potential (EPSP) mediated by glutamate receptors of the *N*-methyl *D*-asparatate (NMDA) type while the low-intensity stimulation only facilitated a fast EPSP, mediated by glutamate receptors of non-NMDA type (Cox et al. 1992). Unequivocal identification of the mechanisms involved in the facilitation produced by the two stimulations is beyond the scope of this study and would probably require the use of selective antagonists of the different types of muscarinic and glutamatergic receptors.

Possible functional significance

Compared with all the previous studies concerning the effect of BF activation on the responsiveness of the sensory neocortex, our goal was to determine the relationships between cortical arousal and facilitation of cortical evoked responses. The use of two intensities of BF stimulation, which differed in their ability to arouse the cortex, leads to the following conclusions:

1. A cholinergic activation of the cortical target cells in the absence of cortical arousal only produces a transient facilitation of the evoked responses (ipsilateral results using low BF stimulation).

2. A state of cortical arousal without a cholinergic activation of the cortical target cells can eventually produce transient facilitation of the cortical processing, but in no case a long-lasting facilitation (contralateral results using high BF stimulation, and ipsilateral results using high BF stimulation under atropine).

3. A state of cortical arousal together with a cholinergic activation of the cortical target cells seems to be the only adequate condition to produce a long-lasting facilitation of cortical processing[3](ipsilateral recordings with high BF stimulation).

This suggests that a nonspecific, diffuse arousal is not sufficient to promote long-lasting cortical plasticity and therefore that the conditions required for cortical plasticity to take place are not strictly identical to those existing during cortical arousal.

If we refer to what is happening in a learning situation, the level of arousal of an animal is probably similar during a conditioning procedure, where the CS predicts the US, and during a pseudo-conditioning procedure where the CS and the US occur randomly. The behavioral responses to the CS are different in these two circumstances, and receptive field determination in the auditory cortex and thalamus before and after training demonstrated that highly selective changes in cortical processing are induced by associative conditioning, while only nonspecific changes of cells' excitability are produced by pseudoconditioning (see Diamond and Weinberger 1986; Bakin and Weinberger 1990; Edeline and Weinberger 1991a,b, 1992). The diffuse activation induced contralaterally by high-intensity BF stimulations, even if paired with tone presentations, could be the equivalent of a general arousal similar to what is happening during a pseudoconditioning procedure. The coactivation of cortical neurons by the tone and the cholinergic input could provide adequate conditions for the selective changes occurring during a conditioning procedure. This idea is developed in a preliminary model of cortical plasticity, which also involves the concomitant action of the tonotopic (MGv) and nontonotopic (MGm) parts of the auditory thalamus (Weinberger et al. 1990). In this model the role of the NBM, which is supposed to be activated by the MGm via the amygdala, is to amplify the input coming from the MGm on the apical dendrites of the pyramidal cortical cells, and thus to produce a widespread enhancement of postsynaptic activation during learning trials. The present data, as well as recent results obtained in awake animals (Hars et al. 1993), show direct support for this model, since they demonstrate that NBM activation is efficient in facilitating evoked responses in the auditory cortex.

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[3]However, these conditions seem necessary but not always sufficient, since 6 of 23 recordings did not exhibit long-lasting facilitation after pairing with the high-intensity stimulation.

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