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Inhibitory influence of frontal cortex on locus coeruleus neurons

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ABSTRACT **The functional influence of the frontal cortex (FC) on the noradrenergic nucleus locus coeruleus (LC) was studied in the rat under ketamine anesthesia. The FC was inactivated by local infusion of lidocaine or ice-cold Ringer's solution while recording neuronal activity simultaneously in FC and LC. Lidocaine produced a transient increase in activity in FC, accompanied by a decrease in LC unit and multiunit activity. This was followed by a total inactivation of FC and a sustained increase in firing rate of LC neurons. Subsequent experiments revealed antidromic responses in the FC when stimulation was applied to the LC region. The antidromic responses in FC were found in a population of neurons (about 8%) restricted to the dorsomedial area, FR2. The results indicate that there is a strong inhibitory influence of FC on the tonic activity of LC neurons. The antidromic responses in FC to stimulation of the LC region suggest that this influence is locally mediated, perhaps through interneurons within the nucleus or neighboring the LC.**

Firing properties of locus coeruleus (LC) neurons as a function of sensory input indicate that these cells respond initially to novel sensory stimuli of many modalities (1, 2) but habituate rapidly in the absence of reinforcement (3–5). Outside of a formal learning situation, during exploration of a controlled environment, LC units fire when the rat encounters novelty, but the response is usually limited to the first encounter. Our studies in both awake and anesthetized rats show that habituated LC cells resume responding whenever stimulus-reinforcement contingencies are changed—i.e., in early learning trials, reversal, or extinction (3–5). This sensitivity of LC to the significance of a stimulus and particularly its relation to the reinforcement has also been reported by others in rat (6) and monkey (7). These results indicate that LC neurons respond to information concerning the novelty or meaning of the stimulus, and, more importantly, the cells do not respond during repeated presentation of the stimulus. This suggests a modulatory influence, direct or indirect, on excitability of LC neurons from a brain area that responds to highly integrated information.

Another important observation that we have made from recordings in both awake, behaving rats and anesthetized rats concerns the remarkable homogeneity of responding within the nucleus. For example, the same response to a tone can be observed by recording single- and multiunit activity from the same electrode (3, 4). Noradrenaline (NA) is thus released to widespread cortical and subcortical areas by simultaneous activation of many LC cells. The postsynaptic effects of NA on target structures have been widely described: NA acts as a gating factor in thalamic nuclei (8) and somatosensory cortex (9) and promotes tuning in auditory cortex (10) and visual cortex (11). Furthermore, NA plays a permissive role in long-term potentiation in the hippocampal formation (12, 13). These actions of NA highly implicate this system in sensory information processing and memory. Since the release of NA is directly related to the firing pattern of LC neurons, determining factors controlling the excitability of LC nucleus will contribute to the understanding of how the brain selectively processes relevant information.

The present experiments are an attempt to identify extrinsic sources of modulatory control of spontaneous and evoked LC firing rates, which could contribute to the responses to sensory stimuli as a function of significance. The frontal cortex (FC) was studied because neurons in this area have been implicated in habituation and in attentional processes (14) and show differential responses during learning (15). Moreover, this region has been reported to have direct projections to the LC area in rat (16–18) and in monkey (19). In fact, it may be the only cortical area in the rat having direct projections to the LC area (20).

In the first series of experiments, the FC was inactivated by injection of local anesthetic or ice-cold Ringer's solution, and the effect on single- and multiple-unit activity of LC was evaluated. Further experiments tested the possibility that there might be a direct projection from FC to the LC region by looking for antidromic responses of FC neurons to stimulation in the LC.

MATERIALS AND METHODS

Cortical Inactivation. Simultaneous single- and multiunit recordings of neurons in the LC and the FC were taken from 21 male Sprague–Dawley rats weighing 280–380 g. The rats were initially anesthetized with ketamine (120 mg/kg) and maintained under anesthesia with a perfusion of 12 $mg \cdot kg^{-1} \cdot hr^{-1}$ at a constant body temperature of 37°C. The animal was mounted in a stereotaxis apparatus with the head positioned such that bregma was 2 mm lower than lambda. Access to the LC was made through a hole drilled 3.8–4.0 mm posterior to lambda and 1.15 mm lateral to the midline. LC cells, recorded with a tungsten microelectrode (1–3 MΩ), were identified by their broad action potentials, which fire at 0.8–2 Hz; these cells are located just below the fourth ventricle, medial to the large jaw movement-sensitive mesencephalic V trigeminal cells. In three animals the FC injection was first made contralateral to the LC recording site; subsequently, the injection was made ispilateral. An electrode–cannula assembly, consisting of a tungsten electrode glued to a 26-gauge beveled hypodermic needle, was then lowered into the FC, 2.5 mm anterior to bregma and 1.5 mm lateral to the midline, until a stable recording of a few cells, 0.5–3 mm below the surface of the brain, was obtained. The needle was attached to a Hamilton syringe; lidocaine (1% or 2%; Astra, Sodertalje, Sweden) was injected in successive volumes of 0.5–2 μl or slowly infused by a pump (Fig. 1). To assure that any effect of lidocaine was due to its inactivation of the cortical cells, a similar inactivation was achieved in three control experiments where ice-cold Ringer's solution was applied to the surface of the cortex until there was a cessation of electrical activity at the recording site.

Electrical signals from LC and FC were amplified and filtered (band pass, 0.4–3 kHz) and passed through a window discriminator, whose digital output was fed through an inter-

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Abbreviations: FC, frontal cortex; LC, locus coeruleus; NA, noradrenaline.

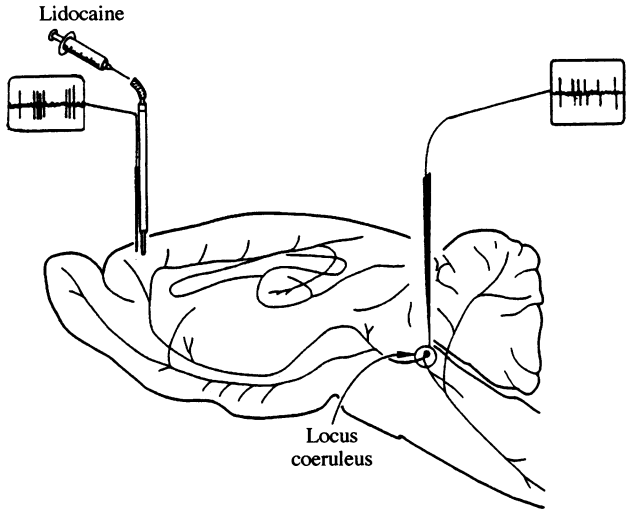

FIG. 1. Schematic representation of electrode and cannula placements for lidocaine injection in FC and recording or stimulating electrode in LC.

face (CED 1401) to a computer. The data were monitored on-line and further analyzed off-line using the SPIKE2 software package.

Antidromic Responses to LC Stimulation. Antidromic responses were studied in 12 rats with the recording electrode in the FC region and the stimulating electrode located in the LC. Recording in FC was made with tungsten microelectrodes, and each experiment consisted of multiple penetrations, so as to explore the whole frontal area. An attempt was made to isolate single units at each recording site. The signal was amplified and filtered as described above, passed through an auditory monitor, and visualized on a storage oscilloscope.

Electrical activity was recorded during implantation, and LC was located as described above. Stimulation was bipolar; the electrodes were of two types: (*i*) concentric, consisting of an inner wire, 250 μm in diameter, inside a 500-μm tube, insulated except for 500 μm at the tip or (*ii*) two etched tungsten electrodes with fine tips glued together so that the tips were less than 500 μm apart. The stimulation consisted of single pulse, 0.2 msec in duration, 100–500 μA in intensity. A persistent response with a fixed latency was considered as possibly antidromically driven, and when this was obtained, high-frequency stimulation was administered and responses were displayed on a storage oscilloscope. Consistent responding to high-frequency stimulation was the second criterion for a response to be considered as antidromically driven. When it was possible to trigger a single unit that was antidromically driven, a collision test was performed. The presence of spontaneously occurring collisions was also noted.

At the end of each experiment, the animal was perfused intracardially with saline and then with 10% formalin. The brain was cut in 60-μm sections and stained with cresyl violet, and electrodes were localized in the FC and brain stem.

RESULTS

Cortical Response to Ice-Cold Ringer's Solution Lidocaine Injections, or Perfusions. Eighteen out of 21 recording electrodes were located in LC. Placements of the electrode–cannula assembly in the FC for successful lidocaine experiments were in the FR2 region (21).

Lidocaine (n = 15) or ice-cold Ringer's solution (n = 3) induced an enduring loss of all electrical activity in the FC. Total inactivation of FC neurons usually occurred after 5 μl of 1% or 2.5 μl of 2% lidocaine, with a corresponding increase in LC firing rate. The relative increase varied, but in every experiment in which the electrode was in the LC, there was a significant increase in the multiunit activity in the presence of cortical inhibition, and this increase was usually, but not always, seen in single-unit records as well (Figs. 2 and 3). Ringer's solution that was warmer than 4°C did not induce an extensive depression of cortical activity and did not induce a change in LC firing rate. The increase over the basal firing rate just preceding the injection was calculated for each animal and was in every case statistically significant as indicated by a t test for correlated samples (in every experiment, $P < 0.001$, in the presence of total depression of FC activity). The mean increase for the 15 rats was 138.92% ± 25%. In the three experiments where recordings were made from the LC contralateral to the injection site, there was no effect of depression of FC activity on the firing rate of the LC cells.

In some experiments (n = 5), lidocaine induced a transient increase in cortical activity. The initial increase in cortical activity followed infusion of a small volume of lidocaine (<1.5 μl) and entrained a significant decrease in the activity within the LC in every case. An example is shown Fig. 3. The mean increase in cortical activity was 31.33% ± 8.68% with a concomitant decrease of 33.20% ± 7.17% in LC activity.

In two control experiments, the recording electrodes were located in the neighboring pontine reticular nucleus, just medial to the ventral subcoeruleus or the dorsomedial tegmental area just ventral to the medial longitudinal fasciculus. In the former case, there was a significant decrease in activity when the FC was depressed by lidocaine injection, and in the latter there was no change in the activity of the cells.

Recording simultaneously from FC and LC neurons, we noted that the cortical neurons sometimes fired in a synchronous pattern. Synchronous activity was seen in the LC but less consistently. The highly synchronized nature of the firing of the FC cells, as well as the bursting mode of firing of the LC unit, can be observed in Fig. 4. When synchronous activity was seen

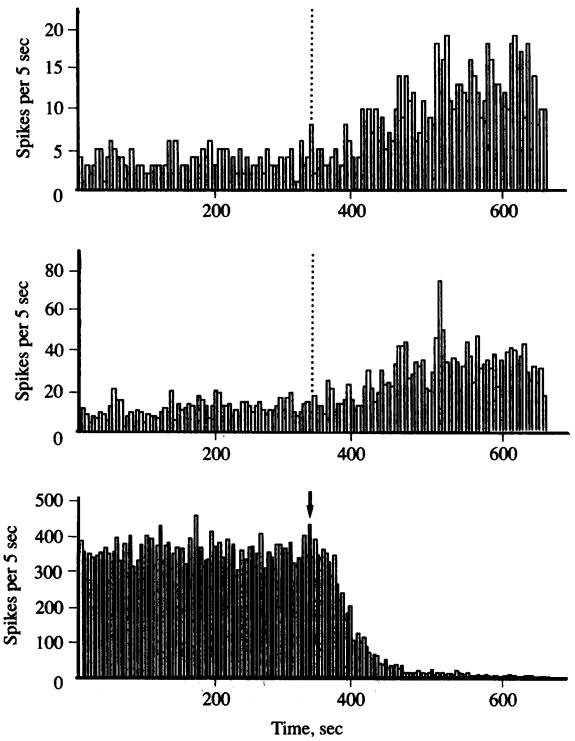

FIG. 2. Cortical and LC activity before, during, and after a 2-μl lidocaine injection (arrow) in FC. A decrease in cortical activity is accompanied by an increase in LC activity. Note the gradual decrease in multiunit firing in the FC (*Bottom*) and the sustained increase in firing of LC cells, as seen in both the single- (*Top*) and multiunit (*Middle*) records.

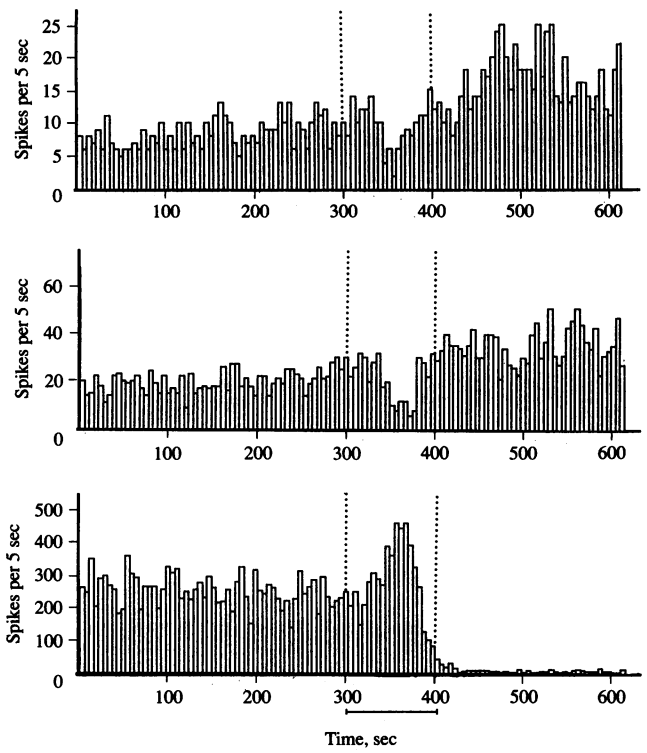

FIG. 3. Cortical and LC activity before, during, and after a 5-μl lidocaine perfusion in FC; the perfusion was made over 100 sec, as indicated by the bar. Note that in this case, before inducing a total depression of firing, lidocaine produces a transient increase in cortical activity (*Bottom*). The change in LC activity is in the opposite direction—i.e., an increase in cortical activity is accompanied by a decrease in LC activity. Subsequent depression of FC is accompanied by a significant increase in LC single-unit (*Top*) and multiunit (*Middle*) activity.

in both structures, they were very often in phasic opposition. A striking example of this is seen in Fig. 4, where the LC unit burst occurs immediately after the FC synchronous multiunit firing and never during firing of the cortical neurons.

Antidromic Responses. Nine rats had stimulating electrodes in LC nucleus, most in the dorsal part. Antidromic responses were obtained from 40 of the 250 recording sites tested, as indicated in Fig. 5. The responses were mostly confined to the FR2 region, as illustrated. All responses were observed 1–2 mm lateral and 0–4 mm anterior to the bregma; these coordinates correspond to the position of the head described above. Responses were observed at all cortical depths. There was no relation between the recording sites and latencies of antidromic responses. Altogether 52 cells were antidromically driven within the population of about 700 recorded throughout the frontal region. The shaded areas in Fig. 5 indicate regions, including over 200 separate recording sites, where antidromic responses were never obtained. They include the entire anterior cingulate, prelimbic, and infralimbic areas along the midline, and the lateral granular area. No antidromic responses were observed in the several recording sites located in the orbital or insular region.

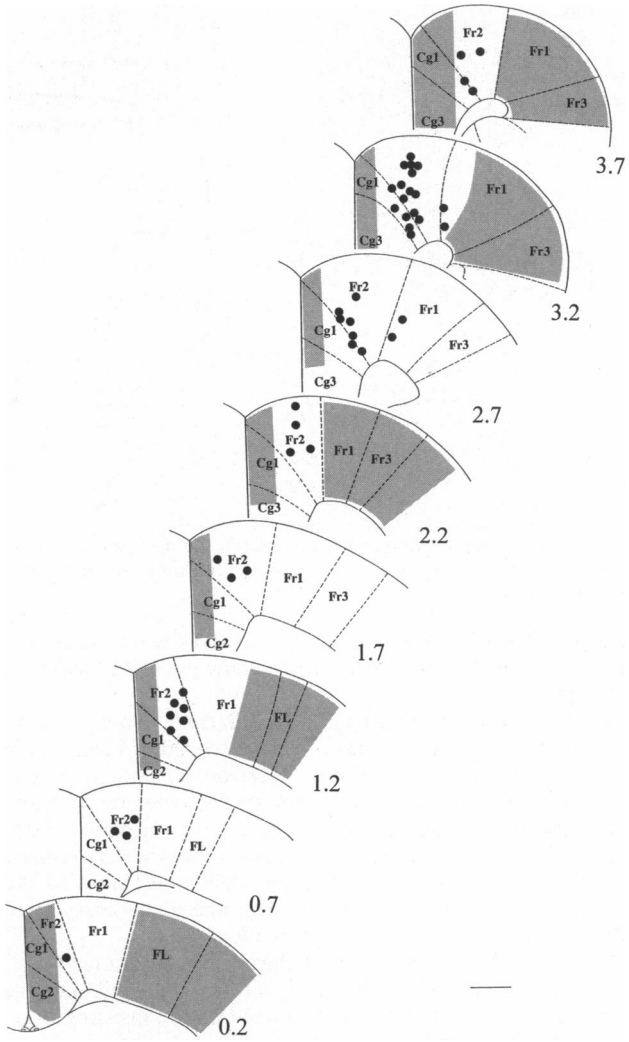

FIG. 5. Area within the medial FC where a population of neurons (±8%) were antidromically activated by the stimulation within LC (filled circles). The gray shading shows the area where no responses to LC stimulation were found. (Bar = 1 mm.) Sections and abbreviations are from Paxinos and Watson (21).

An example of the three criteria for antidromic responses is shown in Fig. 6: the superimposed responses show the fixed latency of 8 msec (Fig. 6*A*), persistent responding at 200-Hz stimulation (Fig. 6*B*), and collision tests showing the absence of a response within 8 msec after an action potential (Fig. 6*C*). In a few cases, there was more than one antidromic response evoked by a single stimulation; Fig. 7 illustrates three responses with latencies of 7.7, 10.8, and 13 msec (four sweeps). The most frequently observed latency for the entire set was 8 msec, indicating a conduction velocity of about 2.5 m/sec; the distribution of the latencies of all responses is shown in Fig. 8.

In one single experiment, where there were clear antidromic responses with the three criteria, the stimulating electrode was found to be anterior to the LC, outside of the nucleus itself. It was situated in a position that would have allowed stimulation

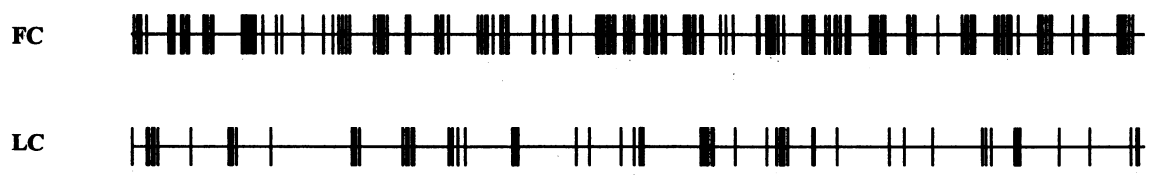

FIG. 4. Synchronous activity in both FC and LC; each deflection represents a single spike. In this particular record, the phases were in total opposition for several minutes. LC firing occurs only during silent periods in FC, usually immediately after a burst of FC activity. (Black bar = 1 sec.)

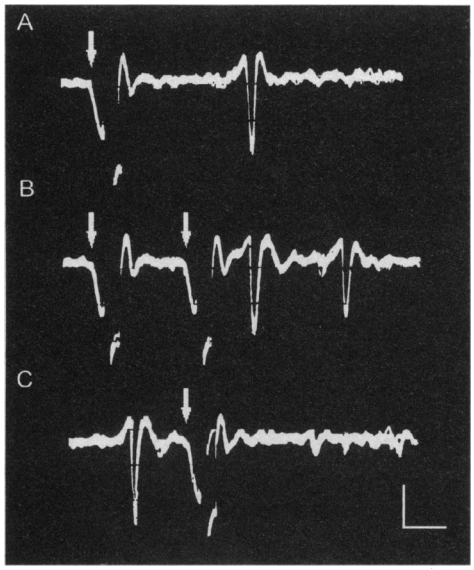

FIG. 6. Antidromic responses evoked in a FC cell by stimulation in LC. (*A*) Fixed latency of evoked spike. In this record, the latency is 8 ms (four superimposed sweeps of the oscilloscope). (*B*) Antidromically driven response to double pulses at 200 Hz. (*C*) Collision test with a spontaneous action potential. There is no evoked spike when the spontaneous spike occurs within 8 ms before the stimulation. (Calibration bars: 0.5 mV, 2 msec.)

of fibers of the dorsal noradrenergic bundle, which contains efferent and afferent fibers of the LC. This was the only case in which antidromic responses were found when the electrode tip was not unambiguously situated within the LC nucleus. In two other rats, the stimulating electrode was in the superior colliculus, and the periolivary nucleus, respectively, and there was no FC response to the stimulation.

DISCUSSION

The results of these experiments clearly demonstrate that the frontal cortex has an inhibitory influence on tonic LC activity. When the neuronal activity of the FC region was suppressed by local injection or infusion of lidocaine, there was a significant increase in firing rate of LC cells in every experiment in which the recording electrode was confirmed to be in the LC nucleus. The effect was seen in multiunit as well as in single-unit records, suggesting that many cells are affected by the FC input. When the FC was inactivated by infusion with ice-cold Ringer's solution, but not with Ringer's solution at more than 4°C, there was a similar increase in tonic firing rate of LC cells, so the effect is not due to the action of lidocaine itself but to the loss of FC inhibitory input.

Effective injection sites were found in a restricted area, corresponding to FR2 of the Paxinos atlas (21), with very few

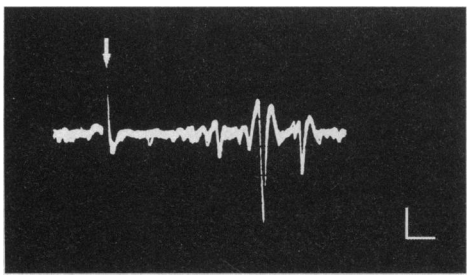

FIG. 7. Antidromic responses evoked in three FC neurons in response to a single stimulation in the LC region with latencies of 7.7, 10.8, and 13 msec (four sweeps of the oscilloscope). (Calibration bars: 0.5 mV, 2 msec.).

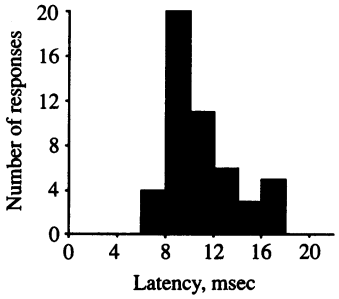

FIG. 8. Histogram of the distribution of the latencies of antidromic responses recorded in FC.

found outside this region. Since there were always slight variations in the geometrical relation between the electrode tip and the cannula, the population of neurons recorded was not always at the same distance from the injection site. Thus the FC electrode can only be considered as a general electrophysiological control for the efficacy of the lidocaine injection/perfusion or Ringer's solution application; no systematic spatial or temporal relationship between FC activation or inactivation and changes in LC firing rates could be determined. In some cases, even after total inactivation of the cortical cells at the recording site, there was no immediate effect on LC firing rates, with subsequent injection producing an increase in LC firing. Thus, within the restricted FR2 area, it was the volume of lidocaine injected that predicted the effect in the LC, suggesting either that the efficacy of the injection in the LC is determined by the size of the population of neurons inactivated within the FC or that it is mediated by areas adjacent to the recording site. In any case, it has been shown that intracortical microinjections of lidocaine, which, while remaining rather circumscribed, have a diffuse effect on cortical metabolism, probably because of interruption of cortico–cortical activity (22). Such an effect would preclude using this approach to accurately map the FC influences on LC. Complementary studies of the effects of electrical stimulation of FC on LC activity could be carried out to perform such a mapping task, although initial attempts have not provided unequivocal results (23). It is possible that such discrete stimulation of FC would not reveal subtle modulatory inputs to LC or the surrounding pericoeruleus region (see ref. 17) in the way that the massive FC inhibition used in the present study clearly does.

Consistent with the idea that stimulation of FC should produce a demonstrable inhibition of LC is the observation that a reliable and significant *decrease* in firing rate of the neurons in LC was seen in the five experiments in which the lidocaine perfusion produced an initial increase in FC activity. The initial excitation of FC after lidocaine is probably due to a greater sensitivity of inhibitory GABAergic interneurons to the effects of lidocaine, thus producing the transient increase in firing of the pyramidal cells (24).

The results of the antidromic stimulation studies reported here contribute more to the question of localization within the frontal region. Those experiments examined over 250 different sites, including ≈700 neurons within the FC. Clear, unambiguous antidromic responses were limited to the medial/lateral agranular field (25), or what Kolb (26) refers to as the medial precentral cortex. Very recent anatomical studies in the rat suggest that cells at the same lateral position but more caudal in the FC project to the pericoeruleus region, just lateral to the LC (17). Failure to find antidromically driven cells in other regions was rather surprising, especially since projections to LC from more extensive dorsal lateral and medial FC in monkey (19) and from insular cortex in the rat (20) have been reported. In any case, negative results can only leave open the question of whether other regions of FC contribute to the functional influence on LC, clearly demonstrated in these experiments.

The results of the LC stimulation studies show that a significant proportion of neurons from a restricted area of FC, ≈8%, are antidromically driven from the LC region and thus have their terminals in the region of the stimulation. Therefore, the influence of FC cannot be exclusively mediated through a distant excitatory projection to an intermediary structure such as the prepositus hypoglosis, a major inhibitory afferent to LC (27), although such a putative FC projection could contribute to the effect. The presence of antidromically driven responses in FC after stimulation of LC points to an excitatory FC input to local inhibitory interneurons in the LC region (28).

Direct projections from the dorsal FC to this region have been suggested by anatomical studies in the monkey (19) and in the rat (16–18). Arnsten and Goldman-Rakic (19) failed to find any other cortical projections to the LC region, and they suggest that this medial prefrontal projection may be one of the few afferents to this noradrenergic nucleus conveying information concerning the significance of stimuli. This was in disagreement with other investigators who have claimed that "there is virtually no forebrain control of this nucleus which itself pervasively innervates most of the forebrain" (27). While some investigators have emphasized the sparse afferent input to the LC nucleus in relation to its diffuse output (27, 29), others have suggested that the long dendritic processes extending well outside the nucleus along the fourth ventricle may receive extensive input with important functional significance (see ref. 28). Finally, there appears to be a small population of glutamic acid decarboxylase-containing interneurons located within the LC itself and in the pericoeruleus region, which should contribute to the regulation of LC activity (28). An excitatory projection of FC neurons on to those cells could mediate the inhibitory influences observed in our experiments. Indeed, very recent studies using anterograde tracing methods show terminals from the FC in the pericoeruleus region, just lateral to the LC nucleus, in a region where there are many glutamic acid decarboxylase positive neurons (17). The present results complement these anatomical studies, by showing unequivocally the functional influence of FC on LC tonic activity.

Studies revealing the high degree of sensitivity of LC responses to changing significance of sensory information, discussed above, would seem to require such a functional input. Experiments in rat, rabbit, and monkey have revealed a population of neurons in FC that is inhibited by sensory stimuli. A striking example of conditioned inhibitory responses to auditory stimuli in FC is given by Pirch and coworkers, in both awake, behaving rats (30) and rats anesthetized with urethane (31). In the awake rats, 19% of the units responded to tones by inhibition; when tones were paired with rewarding stimulation of the medial forebrain bundle, 58% of the FC neurons exhibited a conditioned inhibitory response. The area of FC explored in these experiments was the same region in which we found antidromic responses in the present experiments. In more recent experiments, Gibbs *et al.* (15) reported 16% of neurons in FC of the rabbit were inhibited by tones, habituated rapidly, and then responded again by inhibition to changes in response–reinforcement contingencies. Moreover, these cells exhibited differential responding during conditioning. In monkey nearly half of the neurons in the FC that have delay period responses in a working memory task show inhibitory responses. Some of these neurons displaying "memory fields" are located in the frontal eye field region, which is homologous to the rat medial precentral cortex (32), where the antidromic responses to LC stimulation were found.

If these neurons responding with inhibition during learning or working memory delays represent a population of cells in FC having an inhibitory influence on LC, then the LC neurons would be released from this inhibition during critical periods during learning when release of NA in sensory pathways and forebrain structures would promote selective stimulus processing. These critical periods are precisely when we have observed robust firing of LC cells in response to sensory stimuli (4, 5).

In conclusion, it is clear from the present experiments that the medial precentral region of the FC exerts a strong inhibitory influence on locus coeruleus neurons and that this influence is locally mediated in the LC region. The functional significance of this influence is suggested by the fact that FC neurons in this region are inhibited by conditioned stimuli, which elicit excitatory responses in LC. Further studies are needed to establish the relationship between the firing of FC neurons and LC activity within a particular cognitive context. These experiments lend functional arguments to the anatomical evidence that afferent control of LC is not limited to two medullary nuclei (17, 19, 20, 27): higher control of the all important noradrenergic influence could originate in the FC.

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