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Spinal neuronal inhibition and EEG synchrony by electrical stimulation in subcortical forebrain regions of the cat

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Summary. In cats anaesthetized with sodium pentobarbital and 70% N_2O, single lumbar dorsal horn neurons were excited by controlled noxious radiant heating of glabrous hindpaw skin. The EEG was recorded from the pericruciate cortex and posterior lateral gyrus. Subcortical forebrain sites where electrical stimulation inhibited dorsal horn neuronal heat-evoked responses contralaterally were identified by mapping the caudate nucleus, internal capsule, septum, nucleus accumbens and basal forebrain regions. Inhibitory sites were mainly located in the ventral forebrain (ventral septum, diagonal band, basal forebrain). The caudate nucleus and internal capsule had a low incidence and effectiveness of inhibitory sites. In the basal forebrain, the incidence and effectiveness of inhibitory sites decreased from caudal to rostral regions. There was a rostral limit of inhibitory sites, both medially and laterally. The magnitude of inhibition increased with graded increases in brain stimulation intensity. The mean incremental increase in inhibition was greater for caudal than for rostral basal forebrain sites. Mean stimulus currents for threshold of inhibition and for inhibition to 50% of control heat responses were lower for caudal than for rostral sites. Responses of the dorsal horn neurons to increasing temperatures of noxious skin heating were monotonic linear functions over the temperature range studied (48–53° C). Stimulation in both rostral and caudal basal forebrain decreased the slope of this stimulus-response function, with a greater decrease for caudal sites. Cortical EEG synchronization was evoked by stimulation in the caudate nucleus and rostral basal forebrain. For both regions, most synchronogenic sites did not produce descending inhibition of dorsal horn neurons. The significance of these findings in relation to descending inhibition from other brain regions and stimulation-produced analgesia is discussed.

Key words: Dorsal horn neuron – Descending inhibition – EEG synchronization – Subcortical forebrain – Basal forebrain – Nociception

Introduction

Focal electrical stimulation in regions of the forebrain in several species, including man, can produce analgesia. These forebrain structures are the head of the caudate nucleus (Schmidek et al. 1971; Lineberry and Vierck 1975; Chen et al. 1982), internal capsule (Adams et al. 1974; Fields and Adams 1974), septal area and basal forebrain (Gol 1967; Breglio et al. 1970; Schmidek et al. 1971; Oleson et al. 1980). The mechanisms underlying the analgesic effects of stimulation to these forebrain structures are not known. Stimulation in brainstem regions such as the midbrain periaqueductal gray (PAG) and medullary nucleus raphe magnus (NRM) also produced analgesia; however, the demonstration that this stimulation results in inhibition of spinal dorsal horn cells suggests a descending influence may be an important component of the analgesic effect (Oliveras et al. 1974, 1975; Guilbaud et al. 1977; Willis et al. 1977; Carstens et al. 1980). It has been shown that stimulation in the medial preoptic and septal area of the forebrain produces descending inhibition of nociceptive spinal dorsal horn neurons (Carstens et al. 1982). It is not known, however, if such descending inhibition of spinal neurons can also

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be activated from other forebrain regions that produce analgesia. In the present experiments, therefore, subcortical forebrain structures were electrically stimulated while observing nociceptive responses of contralateral lumbar dorsal horn neurons.

In addition to producing analgesia, stimulation of the caudate nucleus and basal forebrain in the cat results in EEG synchronization and inhibition of behaviors such as eating and attack (Buchwald et al. 1961a, b; Sterman and Clemente 1962a, b; Lineberry and Siegel 1971; Siegel and Wang 1974; Goldstein and Siegel 1980). Stimulation to the same forebrain structures also inhibits the firing of cells in the mesencephalic reticular formation, cerebral cortex, thalamus and hypothalamus (Siegel and Lineberry 1968; Lineberry and Siegel 1971; Siegel and Wang 1974). In this study, therefore, the cortical EEG was monitored for EEG synchronization during caudate and basal forebrain stimulation in order to determine if synchrony at the cortex is associated also with inhibition of spinal dorsal horn cells. The results of this study have (1) identified subcortical forebrain regions where stimulation inhibits the nociceptive responses of dorsal horn neurons, (2) analyzed this descending inhibition quantitatively, and (3) shown a dissociation between forebrain sites inducing EEG synchronization and descending inhibition.

Methods

Animal preparation

Twenty-two female cats (2.1–3.0 kg) were anaesthetized with sodium pentobarbital (35 mg/kg i.p., initially) and maintained during surgery with supplemental doses of sodium pentobarbital (2–3 mg/kg i.v.). Cannulae were inserted into the trachea, a common carotid artery and an external jugular vein. Mean arterial blood pressure, central venous pressure, end-tidal CO_2 and deep body temperature were continuously monitored and maintained within physiologic limits. The lumbar spinal cord was exposed by laminectomy (L4 to L7) and the left posterior tibial (PT) and superficial peroneal (SP) nerves were exposed and placed on platinum hook electrodes. The spinal cord and peripheral nerves were covered by pools of warm paraffin oil. The left hind paw was embedded in paraffin wax and fixed pads upward for stimulation with radiant heat.

The cats were immobilized with an i.v. infusion of pancuronium bromide (0.4 mg/kg/h), with anaesthesia maintained by artificial ventilation with a gaseous mixture of 70% N_2O and 30% O_2 and intravenous sodium pentobarbital supplements (mean 1.78 mg/kg/h). In view of the controversy regarding the anaesthetic adequacy of N_2O in cats (Blakemore et al. 1974; Hammond 1978), the level of anaesthesia was carefully monitored throughout the experiments. Anaesthesia was considered sufficient when pupils were small (slitlike) and no pupillary dilation or blood pressure changes were produced by regular noxious heating of the skin or stimulation of hindlimb nerves at levels suprathreshold for C-fibers. Such autonomic reflexes rarely occurred and were immediately abolished by additional doses of pentobarbital (2–3 mg/kg i.v.). This supports the conclusions of others (Blakemore et al. 1974; Hammond 1978) on the adequacy of this combination of anaesthetic agents.

Recording and stimulation

Extracellular single-unit recordings were obtained from dorsal horn neurons with micropipettes filled with 3 M KCl. Lamina location of neurons was determined by depth from the dorsal cord surface with electrode tracks about mid-way between the midline and the dorso-lateral sulcus. After location by a search stimulus (ipsilateral SP and PT nerve stimulation, 2.5 V, 0.1 ms), neurons which also responded to volleys evoked electrically in SP and/or PT C-fibers (25 V, 0.5 ms) were tested for responsiveness to noxious skin heating from a quartz halogen lamp focused onto glabrous hindpaw skin within the cell's receptive field as determined by mechanical probing. A feedback system from a thermocouple in contact with the center of the heated area accurately controlled the skin surface temperature during heat stimuli (47–53° C for 10 s), applied every 3 min (Beck et al. 1974).

The action potentials were processed through a window discriminator and continuously monitored on an oscilloscope. A ratemeter recorded the maximal frequency (Hz) of neuronal discharges to noxious skin heating (1-s bin width). A microcomputer was used to store histograms of the evoked discharges and to determine on-line the total number of action potentials in the integration period selected, usually 30 s, commencing 5 s prior to the heat stimulus. When a neuron had significant spontaneous activity, this was subtracted during off-line data analysis.

Concentric bipolar center-cathode stimulating electrodes (Rhodes NE-100; 0.2 mm inner diameter, 0.5 mm outer diameter, 0.5 mm protrusion of inner) were stereotaxically positioned in brain sites via stainless steel guide cannulae. Either 2 or 4 electrodes were inserted vertically into the contralateral forebrain at Horsley-Clarke co-ordinates A 13.5 to 17.0, L 0.5 to 7.0, V +8.0 to –5.0 (Snider and Niemer 1961). Electrodes were also placed at brainstem sites previously shown to produce descending inhibition of dorsal horn neurons (Carstens et al. 1980; Gebhart et al. 1983b). These were the ipsilateral mesencephalic PAG at A 1.0, L 1.5, V +1.0 and lateral reticular formation (LRF) at A 1.0, L 4.0, V –2.0 and the medullary NRM at P 6.5, L 0.0, V –8.5 and ipsilateral medullary reticular formation (MRF) at P 6.5, L 3.0, V –8.5. The medullary electrodes were inserted through the cerebellum at 45° to the Horsley-Clarke vertical. For recording the EEG and field potentials evoked by forebrain stimulation, a steel screw was advanced into the cranium sufficiently to lightly contact the dural surface of the pericruciate cortex and posterior lateral gyrus, ipsilateral to the forebrain stimulating electrodes. An indifferent electrode was attached to adjacent muscle.

Brain structures were stimulated at parameters known to produce suppression of behavior (eating behavior, attack behavior elicited by hypothalamic stimulation) and EEG synchronization (Buchwald et al. 1961a, b; Goldstein and Siegel 1980). Constant current pulses (0.2 ms) at 100 Hz in 50 ms trains repeated at 6 Hz were applied for 35 s, commencing 10 s prior to the onset of skin heating. Each forebrain site was first tested for descending inhibitory effects with a stimulus current of 760–950 μA. When an effective site was located, the current was reduced to determine threshold levels.

Histology

At the end of each experiment a DC lesion was made at the brainstem stimulation sites and at two stimulation sites in the forebrain. The brains were fixed, sectioned, and stained for

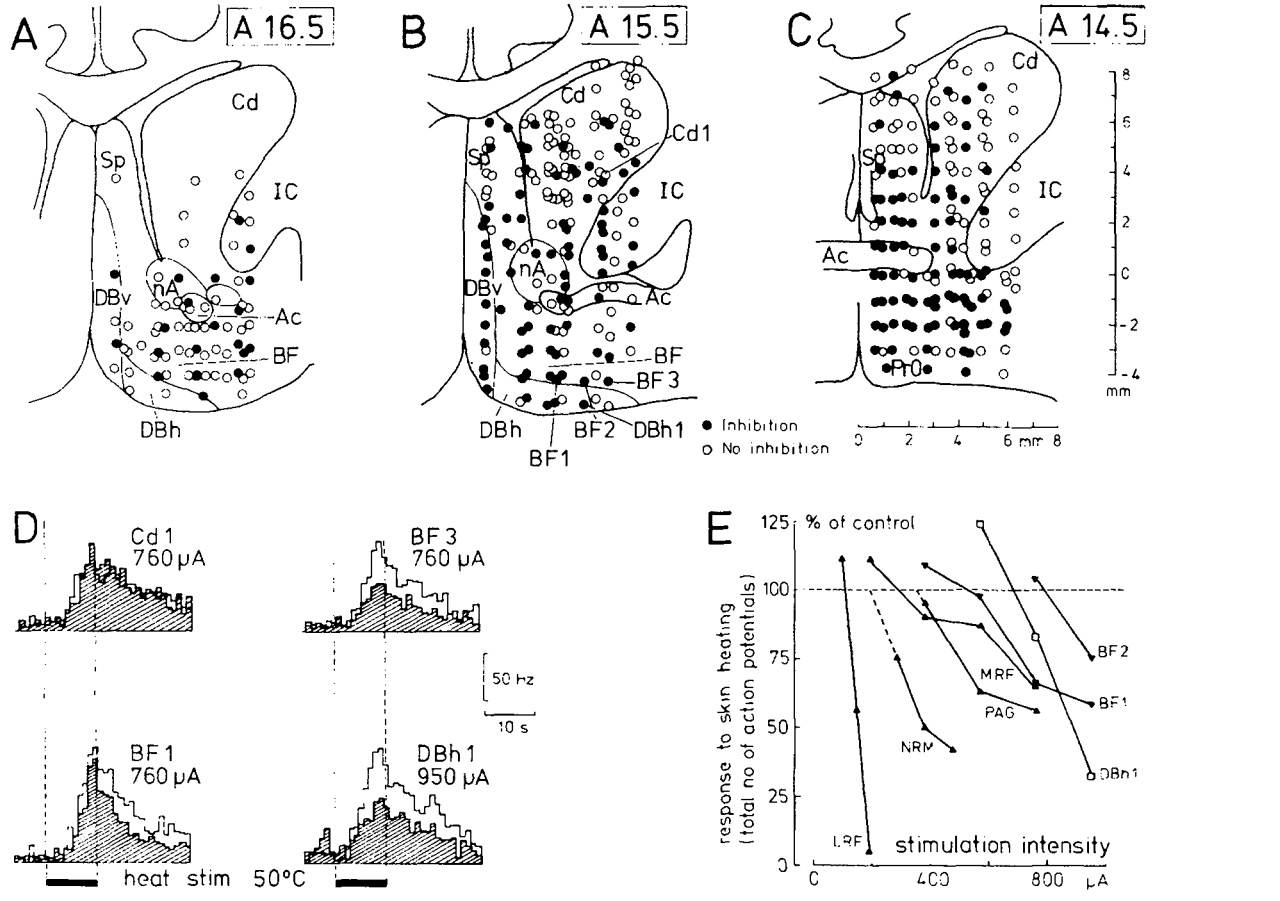

Fig. 1A–E. Frontal section drawings showing stimulation sites in the rostral (**A**), intermediate (**B**), and caudal (**C**) forebrain. The stimulation points were reconstructed from histological section and plotted onto the frontal section above that was closest to the actual rostro-caudal location of the stimulation site. Stimulation sites occurring between A 17.0–16.5 are plotted in **A**; sites between A 16.0–15.5, in **B**; sites between A 15.0–13.5, in **C**.Filled circles, sites where stimulation (760 µA) reduced dorsal horn neuronal responses to noxious skin heatinng to less than 90% of control heat responses; open circles, sites where stimulation did not produce inhibition. The atlas of Snider and Niemer (1961) was used. *Abbreviations:* Ac, anterior commissure; BF, basal forebrain; Cd, caudate nucleus; DBh, diagonal band (horizontal limb); DBv, diagonal band (vertical limb); IC, internal capsule; nA, nucleus accumbens; PrO, preoptic area; S, septum. Stimulation sites for the data in **D** and **E** are indicated (BF_{1-3}, cd_1, DBh_1. (**D**) Peristimulus time histograms (PSTHs) (bin width 1 s) of a lamina IV dorsal horn neuron's responses to noxious skin heating. Heat responses were recorded without (control, unshaded PSTHs) and during (shaded PSTHs) electrical stimulation of forebrain regions at the indicated stimulation intensities. Brain stimulation was commenced 10 s prior to the onset of heating and lasted 35 s. (**E**) Plot of the same neuron's heat responses during stimulation of brainstem or forebrain regions (as a percent of control heat responses) against stimulation intensity (µA)

localization of electrode tracks and lesions to reconstruct the sites of stimulation.

Results

Characteristics of neurons

The effects of electrical stimulation in the forebrain were studied in 38 dorsal horn neurons responding to noxious skin heating. Eight neurons were in lamina IV, 16 in lamina V, 10 in lamina VI and the depth was not noted for 4. Of these 38 neurons, 27 were multireceptive, wide dynamic range or Class 2 neurons (Mendell 1966; Handwerker et al. 1975; Price and Dubner 1977), responding to innocuous cutaneous stimuli such as light touch or hair deflection as well as noxious heat. Seven neurons appeared to be nociceptive-specific or Class 3 neurons (Christensen and Perl 1970; Cervero et al. 1976); they responded to noxious skin heating but no receptive field could be determined by innocuous mechanical stimuli. With the remaining 4 neurons, only noxious heat was tested as a peripheral stimulus. The cutaneous receptive fields of the neurons to mechanical stimuli varied in size from one to all 5 toe pads, sometimes including a large part of the hindpaw.

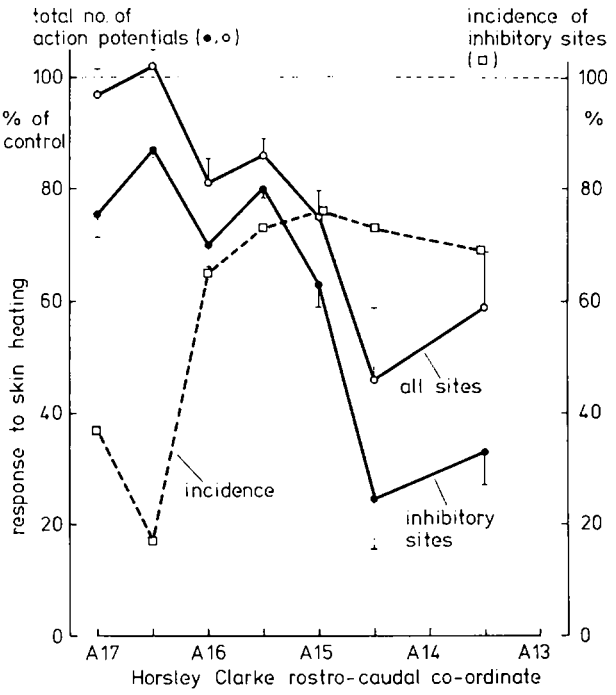

Fig. 2. Incidence and effectiveness of inhibitory sites as a function of rostro-caudal location in the basal forebrain. The plotted circles show the mean dorsal horn neuronal responses to noxious skin heating during basal forebrain stimulation as a percent of control heat responses (total number of action potentials in 30 s). The open circles are the mean responses for all basal forebrain sites tested at each rostro-caudal level; the filled circles are the mean responses for only the inhibitory basal forebrain sites at each rostro-caudal level. Standard error bars are indicated. The plotted squares show the observed number of inhibitory basal forebrain sites as a percentage of the total number of sites tested at each rostro-caudal level

Descending inhibitory effects

The total number of action potentials evoked in a dorsal horn neuron by repeated identical noxious heat stimuli was fairly constant over time. Brain stimulation sites were described as effective in producing descending inhibition if the noxious heat response (number of action potentials) during brain stimulation was reduced to less than 90% of control heat responses obtained just prior to brain stimulation.

Effectiveness of forebrain sites

Inhibitory sites were found in all regions of the forebrain, although spinal inhibition was more readily evoked by electrical stimulation at some sites than at others. Figure 1 provides a diagrammatic summary of the relative effectiveness of forebrain regions in inhibiting noxious heat responses of 38 dorsal horn cells, with a standard stimulus current of 760 μA. The dorsal forebrain, which includes the caudate nucleus and dorsal septal area, had relatively few inhibitory sites. Only 33 of the 117 caudate sites tested (28%) produced descending inhibition: noxious heat responses were reduced to 76 ± 1.7% of control responses (mean for effective sites ± S.E.M.). The ventral forebrain, however, including the ventral septal area, diagonal band, and the basal forebrain area, had many inhibitory sites. Within the vertical limb of the diagonal band, 12 of the 15 sites tested (80%) produced descending inhibition (to 60 ± 9% of control); for the horizontal limb, 6 of 13 sites tested (46%) were effective (inhibition to 66 ± 7.4% of control). In the septal area, 22 of 47 sites tested (47%) reduced heat responses to 77 ± 1.7% of control and 17 of these effective sites were in the ventral part of the septum (Fig. 1). Twelve of 28 internal capsular sites (43%) produced spinal inhibition (to 77 ± 2.1% of control).

The basal forebrain showed a gradient of effectiveness in its rostro-caudal dimension (Figs. 1 and 2). This is obvious when the basal forebrain data are separated into rostral (A 17.0–16.5), intermediate (A 16.0–15.5), and caudal (A 15.0–13.5) segments. The caudal basal forebrain had a greater incidence of inhibitory sites (48 out of 67 sites tested = 72%) than the intermediate basal forebrain region (19 of 28 sites = 68%), which in turn had more effective sites than the rostral region (11 of 43 sites = 26%). The degree of spinal inhibition produced from inhibitory sites also followed this rostro-caudal gradient. With caudal stimulation, noxious heat responses were reduced to 53 ± 3.9% of control levels (mean for effective sites) in contrast to the intermediate and rostral basal forebrain regions where the degree of inhibition was to 74 ± 2.6% and 78 ± 3.8% of control, respectively.

The noxious heat-evoked responses of dorsal horn neurons are inhibited during electrical stimulation in the ipsilateral mesencephalic PAG and adjacent reticular formation (LRF) (Carstens et al. 1980) and in the medullary NRM and adjacent ipsilateral reticular formation (MRF) (Gebhart et al. 1983b). In the present experiments, this was confirmed for one or both mesencephalic sites with all of 24 neurons, and for one or both medullary sites with 23 of 24 neurons tested.

Recruitment of descending inhibition by basal forebrain stimulation

Inhibition of the heat-evoked responses of dorsal horn neurons increased with increasing intensities of

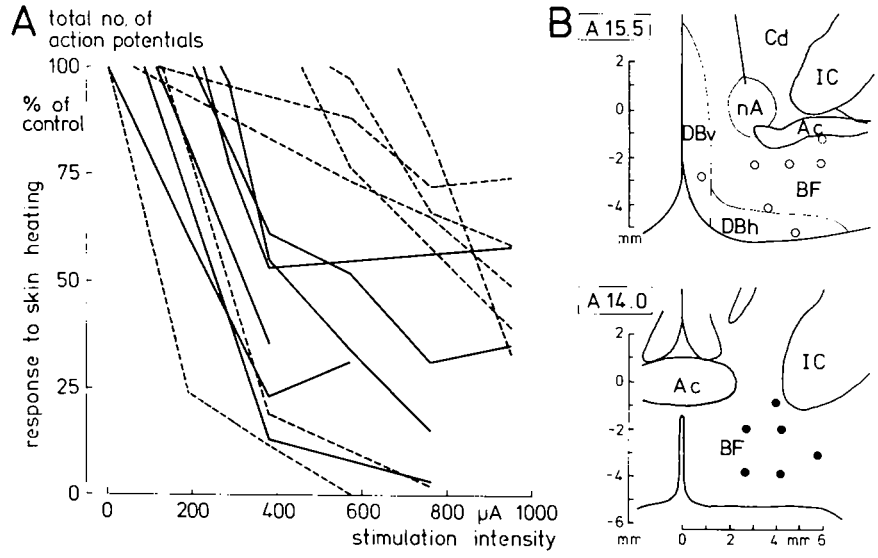

Fig. 3A and B. Descending inhibition produced by basal forebrain stimulation as a function of the intensity of stimulation. In **A**, responses to noxious skin heating are represented on the ordinate as percent of the control heat response (total number of action potentials in 30 s) against the intensity (µA) of basal forebrain stimulation on the abscissa. Lines of recruitment of inhibition connect data points for at least 3 different stimulation intensities. In **B** the histologic location of stimulus sites in the basal forebrain are plotted on frontal section drawings from the atlas of Snider and Niemer (1961). Basal forebrain stimulation sites witin the rostro-caudal range A 15.5–15.0 are represented by broken lines in **A** and open circles in **B**; more caudal sites (A 14.0–13.5) by continuous lines in **A** and closed circles in **B**. Abbreviations as for Fig. 1

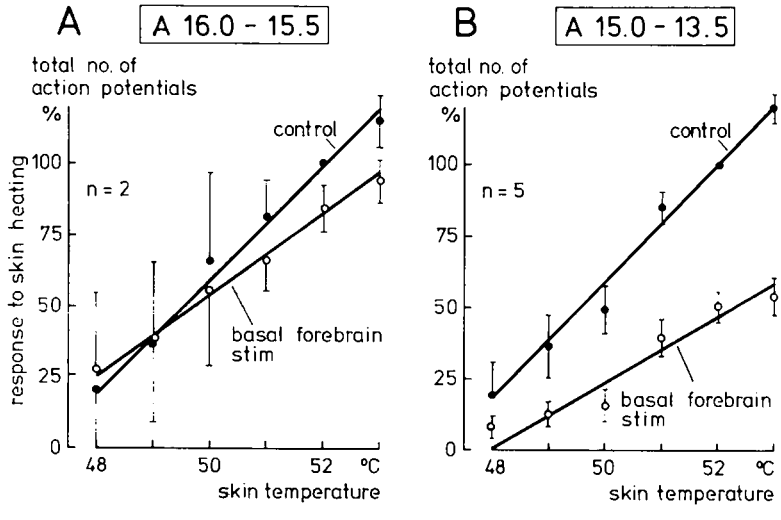

Fig. 4A and B. Effect of basal forebrain stimulation on the intensity coding of graded noxious heat stimuli (stimulus-response function, SRF) by dorsal horn neurons. The data points were obtained by expressing the integrated responses (number of action potentials in 30 s) to skin heating (10 s) as a percent of the control heat response at 52° C (100%). Mean responses at each temperature were then used to plot the regression lines. Each SRF in **A** is a regression line of the mean data from 2 SRFs from stimulation of rostral basal forebrain sites; each SRF in **B** is a regression line of the mean data from 5 SRFs from caudal sites. Closed circles, mean control SRFs (no brain stimulation); open circles, mean SRFs during basal forebrain stimulation. In **A**, correlation coefficient for the control line was 0.80 and for the BFBS line 0.72. The mean slopes for the control SRFS were 20.3 ± 7.6%/° C (± S.E.M.) and during BFBS 14.8 ± 13.47% C/° C. This reduction of the slope is not significant, $p > 0.2$. In **B**, the correlation coefficients of the SRFs were 0.85 (control) and 0.82 (BFBS), the mean slope of the control SRFs (20.8 ± 7.7% C/° C) was reduced significantly ($p \leq 0.05$) to 11.4 ± 5.6% C/° C

basal forebrain stimulation. Figure 3 illustrates this recruitment of descending inhibition for 13 sites in the basal forebrain. For each recruitment line, linear regression analysis was used to calculate (1) the stimulus current for threshold of inhibition (intersection of the recruitment line with the 100% control line), (2) the stimulus current for inhibition to 50% of control, and (3) the increment in inhibition per 100 µA increase in stimulation intensity (the recruitment index, or slope of the line). Extrapolation of some regression lines was necessary to obtain stimulus current values. Data from one regression line were not used, however, since the calculated threshold was less than 0 µA.

The mean threshold for inhibition was 244 µA ± 55 (± S.E.M.; n = 12). However, the thresholds were found to be lower at caudal stimulation sites (mean 132 µA ± 33, n = 6, A 13.5–14.0) compared with more rostral sites (mean 355 µA ± 83, n = 6, A 15.0–15.5). The mean stimulation intensity producing an inhibition to 50% of the control heat response was 622 µA ± 94 (n = 12). Similarly, this value was lower at caudal sites (381 µA ± 50, n = 6, A 13.5–14.0) than at rostral sites (862 µA ± 115, n = 6,

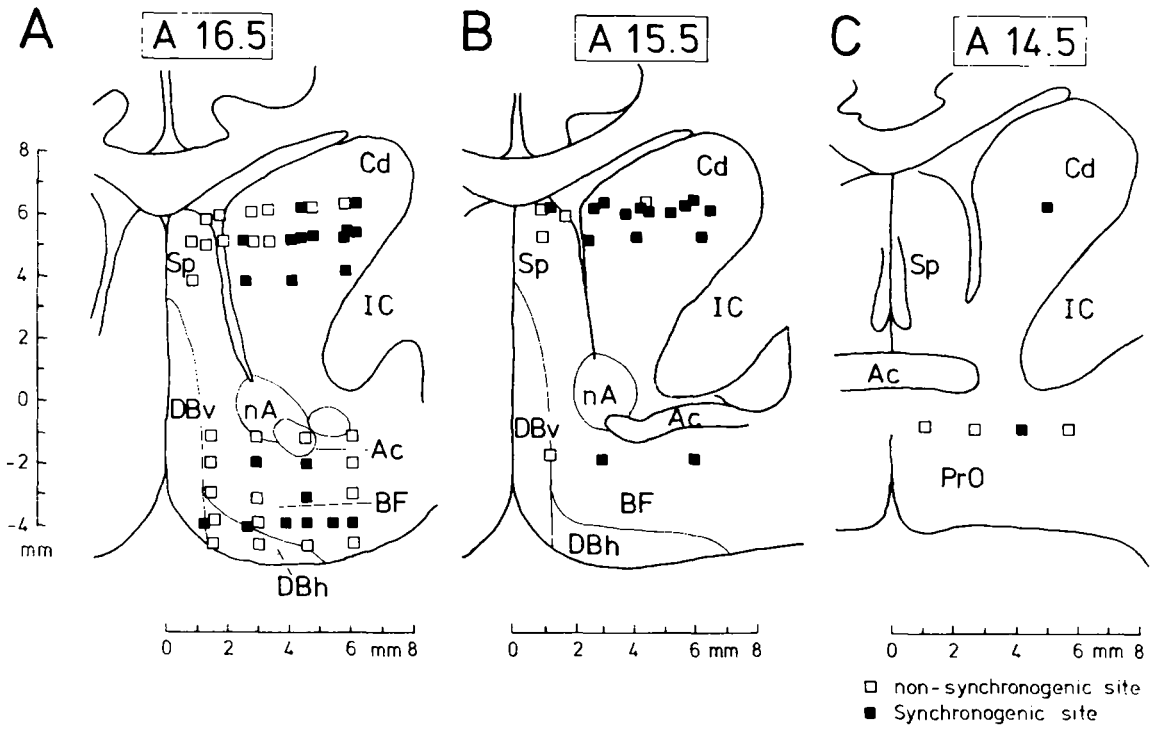

Fig. 5A–C. Frontal section drawings showing stimulation sites in the rostral (**A**), intermediate (**B**), and caudal (**C**) forebrain. The stimulation sites were plotted onto **A**, **B**, or **C** as described for Fig. 1. Filled squares represent synchronogenic sites where stimulation produced EEG synchronization at the cortex; open squares represent non-synchronogenic sites which did not produce EEG synchronization. The atlas of Snider and Niemer (1961) was used. Abbreviations as for Fig. 1

A 15.0–15.5). Differences were also found in the recruitment indices. The mean recruitment index for all sites was 18.7 ± 2.7%/100 μA, but was greater for caudal sites (22.5 ± 2.8%/100 μA at A 13.5–14.0, n = 6) compared with more rostral sites (15.0 ± 4.0%/100 μA at A 15.0–15,5, n = 6). Thus, the recruitment lines are steeper for stimulation at caudal basal forebrain sites and less steep for stimulation at rostral sites (Fig. 3).

Basal forebrain stimulation affects noxious heat intensity coding

The responses of many dorsal horn neurons to noxious skin heating are linearly correlated with temperature (stimulus-response function, SRF) (Carstens et al. 1980). This was confirmed in the present experiments by plotting integrated control responses against the temperature of the noxious heat stimulus (range 48–53° C) (Fig. 4). The response thresholds (extrapolated to the skin temperature-axis) and slopes of each SRF, without (control) and during basal forebrain stimulation (285–950 μA), were calculated by linear regression analysis (not illustrated). Again, rostral and caudal basal forebrain stimulation sites were of different efficacy. Stimulation at rostral sites (A 16.0–15.5, L 5.5–6.0, V –3) reduced the slope of the SRF to 73% of control, whereas at caudal sites (A 15.0–13.5, L 2.5–4.5, V –2 to –4) the decrease in slope was to 53% of control. Regression lines of the mean data for rostral and caudal sites have been plotted in Fig. 4.

Descending inhibition in relation to EEG synchronization

The two regions of the forebrain that have been most intensively investigated for EEG synchronization and behavioral inhibition are the caudate nucleus and basal forebrain.

In 11 of the present experiments, a total of 73 sites mainly located in these two forebrain regions were examined for EEG synchronization (Fig. 5). When stimulated, 25 of the 33 caudate sites (76%) produced typical EEG synchrony. Synchronogenic caudate sites were also tested with the same stimulus paradigm for descending inhibitory effects on dorsal horn neuronal heat responses, but such inhibition was observed with only 4 of the 13 sites examined (31%).

Basal forebrain stimulation also produced EEG synchronization. This was observed with 11 of the 25 sites examined (44%). Many of the sites tested were located in the rostral basal forebrain (Fig. 5). With the same stimulation paradigm, only 2 of 8 synchronogenic sites tested (25%) and 3 of 11 non-synchronogenic sites (27%) also inhibited dorsal horn neurons. Thus, it appears that 2 forebrain regions producing EEG synchronization, the caudate nucleus and the rostral basal forebrain, are relatively ineffective in inhibiting spinal nociceptive responses.

In some experiments the dorsal septum was also examined for EEG synchrony but was found to be ineffective (Fig. 5).

Discussion

Descending inhibition from the subcortical forebrain

The present experiments have identified those regions of the subcortical forebrain where electrical stimulation inhibits the nociceptive responses of contralateral spinal dorsal horn neurons. In the stimulation mapping procedure, many subcortical forebrain structures were examined for descending inhibitory effects on dorsal horn neurons, but the only region clearly effective in the regard was the ventral forebrain, including the vertical limb of the diagonal band and the preoptic-basal forebrain area. This study has also defined the rostral limit of subcortical forebrain sites which exert descending inhibition in the lumbar spinal cord.

The present findings of stimulation-produced descending inhibition of spinal nociceptive responses from the medial preoptic area confirms and extends previous observations (Carstens et al. 1982). In the more dorsal medial septal region, both the incidence and the effectiveness of inhibitory sites decrease (Carstens et al. 1982; the present work). The present study has extended these observations by identifying for the first time effective sites in the lateral basal forebrain also – as far as 7 mm from the midline.

As far as we know, this is the first study which has examined the caudate nucleus and internal capsule for descending inhibition of nociceptive responses in the spinal dorsal horn. In view of the association between inhibition of dorsal horn neurons and analgesia produced by electrical stimulation in brainstem regions such as the PAG and NRM (Oliveras et al. 1974; Willis 1982), it is interesting that these 2 forebrain regions known for stimulation-produced analgesia in man and animals (Lineberry and Vierck 1975; Schmidek et al. 1971; Chen et al. 1982; Adams et al. 1974; Fields and Adams 1974) were relatively ineffective in producing spinal inhibition in the present experiments. Since both regions were systematically stimulated in many locations, it seems unlikely that effective loci within these structures were overlooked in our study. Other differences between these experiments and those reporting analgesia from stimulation in these structures were stimulation technique, species, and the presence of anaesthesia in our study. One explanation for these discrepancies is that the caudate nucleus and internal capsule may influence nociceptive transmission at a higher neural level than the spinal dorsal horn neuron.

Effects of basal forebrain stimulation

The basal forebrain is clearly not uniformly efficacious for stimulation-produced descending inhibition of dorsal horn neurons. This region showed a rostro-caudal gradient of effectiveness, with the rostral part having fewer and less effective sites than the caudal part. Thus, the rostral limit of this forebrain inhibitory region is about A 17.0, both medially and laterally. The caudal limit of this effective region was not presently investigated, but it may be functionally connected to the adjacent lateral hypothalamic area which, when stimulated, also inhibits contralateral dorsal horn nociceptive responses (Carstens et al. 1983). The recruitment of descending inhibition with increasing stimulation intensity highlighted the difference in efficacy between rostral and caudal basal forebrain regions. For the caudal basal forebrain, the stimulus currents for threshold of inhibition and for inhibition to 50% of control, and the recruitment index, were within the ranges previously reported for brainstem sites (PAG, LRF, NRM, MRF) in similar experiments (Carstens et al. 1980; Gebhart et al. 1983a, b). For the rostral sites in the basal forebrain, however, these stimulus currents were greater, and the recruitment index lower, than comparable brainstem values, indicating less powerful inhibition from this forebrain region. Finally, the basal forebrain was not homogeneous in its effects on the intensity coding of nociceptive information by dorsal horn neurons. Caudal sites produced a greater decrease in the slope of the stimulus-response function (SRF) than rostral sites, consistent with the rostro-caudal gradient of this inhibitory region. This reduction in SRF slope was also seen with stimulation in the midbrain PAG (Carstens et al. 1980), medial (Carstens 1982) and lateral (Carstens et al. 1983) hypothalamus, and medial preoptic sites (Carstens et al. 1982). In the present SRF experiments, however, the basal forebrain sites for stimulation were up to 6.0 mm lateral.

It is conceivable that in the rostral basal forebrain, the neuronal elements responsible for the descending volleys are less concentrated than in the caudal basal forebrain. This may explain why relatively high stimulus intensities (with probable current spread) were required to activate descending inhibition from rostral regions.

Pathways for descending inhibition from the subcortical forebrain

The descending inhibition evoked by focal electrical stimulation in the basal forebrain could result from excitation of either cell bodies or fibres of passage or both. In either case, a polysynaptic pathway to the spinal cord is likely since direct basal forebrain-lumbar dorsal horn connections are not known. As discussed above, the caudal basal forebrain may be functionally connected to the lateral hypothalamus which has been shown to project to the mesencephalic PAG (Grofova et al. 1978; Beitz 1982; Mantyh 1982) and adjacent reticular formation (Parent and Steriade 1981) in anatomical studies. The preoptic area of the basal forebrain also projects to the midbrain PAG (Conrad and Pfaff 1976; Beitz 1982; Mantyh 1982), which in turn has a significant spinal projection, both directly (Mantyh and Peschanski 1982) and indirectly via synaptic relays in the medulla. Of the latter, the PAG-NRM connection is well documented, both anatomically (Gallagher and Pert 1978; Abols and Basbaum 1981; Chung et al. 1983) and electrophysiologically (Fields and Anderson 1978; Lovick et al. 1978; Shah and Dostrovsky 1980). Additionally, lateral medullary reticular areas are also important for PAG-induced descending inhibition (Gebhart et al. 1983b; Morton et al. 1984; Sandkühler and Gebhart 1984). Indeed, it appears that the midbrain PAG, by receiving many projections from the forebrain, is crucially positioned for relaying descending inhibitory influences from higher centres to spinal levels (reviewed by Basbaum and Fields 1984). With regard to the present experiments, there seems abundant evidence for pathways from the basal forebrain to the spinal cord.

EEG synchronization and descending inhibition

Cortical EEG synchronization was evoked by stimulation in the caudate nucleus and basal forebrain, confirming previous observations (Lineberry and Siegel 1971; Sterman and Clements 1962a). In these earlier studies, however, this synchrony was closely associated with suppression of behavior and with neuronal inhibition in other brain regions such as the mesencephalic reticular formation (Lineberry and Siegel 1971; Siegel and Lineberry 1968) and thalamus (Siegel and Wang 1974). In the present study, however, the majority of basal forebrain sites tested for EEG synchronization did not produce inhibition in the lumbar dorsal horn. This is related to the fact that the majority of basal forebrain sites tested for EEG synchronization were in the rostral region from where descending inhibitory effects were minimal. There is ample evidence from previous work that both caudal and rostral basal forebrain regions produce EEG synchronization (Lineberry and Siegel 1971; Siegel and Lineberry 1968; Siegel and Wang 1974; Sterman and Clemente 1962a). Thus, the basal forebrain, from the rostral to the caudal extent presently investigated, appears to be homogeneously organized with respect to EEG synchronization, suppression of certain behavioral responses, and inhibition of brainstem unit activity, but not inhibition of spinal nociceptive responses. This dissociation between EEG synchrony and descending inhibition was also observed for the caudate nucleus. Since caudate stimulation can inhibit thalamic neurons (Siegel and Wang 1974), it is possible that the neuronal events producing the analgesic effects of caudate stimulation occur at supraspinal rather than spinal levels.

We propose that the descending spinal inhibitory effects from the basal forebrain are achieved independent of an EEG synchronizing system; whereas the synchronizing forebrain structures that are more closely associated with telencephalic functions, such as the caudate nucleus, modulate complex behavioral responses and nociceptive information by altering neuronal activity in supraspinal regions of the nervous system.

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