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BRAIN STEM AFFERENTS TO THE RAT MEDIAL SEPTUM

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SUMMARY

1. Activity of neurones in the medial septal nucleus and the diagonal band was recorded from urethane anaesthetized rats. Responses of the cells to electrical stimulation of the raphe nuclei and nucleus locus coeruleus (LC) were measured.

2. LC stimulation caused a long latency, 30–100 msec, and long duration, 100–300 msec cessation of spontaneous activity of most recorded neurones. When bursting-type neurones were recorded, the stimulation occasionally caused a synchronized repetitive bursting firing pattern.

3. Pre-treatment with drugs which interfere with catecholamine neurotransmission, i.e. reserpine and 6OHDA, prevented the appearance of cellular responses to LC stimulation.

4. Stimulation of the dorsal or the median raphe nuclei generated more complex and less clear-cut responses. These included several types of long (20–50 msec) and short (2–5 msec) latency responses. These responses were also accompanied in some cells by synchronized repetitive bursting.

5. Interference with serotonin neurotransmission with PPCA or reserpine reduced the detection of long latency responses.

6. Short latency responses accompanied by evoked field potentials were recorded also after stimulation of dorsal tegmental nucleus.

7. Rates of spontaneous firing cells were augmented after monoamine neurotransmission interruption whereas after fornix lesion, when there is supposedly an increased monoamine innervation of the septum, cells fire at lower rates than normal.

8. It is suggested that noradrenaline and serotonin may serve as neurotransmitters in the medial-septum-diagonal band areas.

INTRODUCTION

The septal area constitutes a major relay station receiving afferents from the hypothalamus and limbic midbrain structure and presumably supplying major forebrain structures with a cholinergic input (Raisman,

1966; Lewis & Shute, 1967; Divac, 1975). Its connectivity with the hippocampus and the forebrain has been thoroughly investigated, both anatomically and physiologically (Petsche, Stumpf & Gogolak, 1962; Raiseman, 1966; McLennan & Miller, 1974; DeFrance, Kitai & Shimono, 1973; Divac, 1975). Similarly, the connexions of the reticular formation with the septum have been investigated (Petsche *et al.* 1962; Petsche, Gogolak & Van Zwieten, 1965). Recently, the origin of brain stem afferents to the septum have been delineated with newer histological techniques including anterograde transport of labelled amino acids (Conrad, Leonard & Pfaff, 1974; Pickel, Segal & Bloom, 1974) and retrograde transport of horseradish peroxidase (Segal & Landis, 1974). In conjunction with fluorescence histochemistry (Lindvall & Bjorkund, 1974; Seiger & Olson, 1973; among others) these data suggested that the pontine nucleus locus coeruleus LC and the mid-brain raphe nuclei are the sources of noradrenergic and serotonergic innervation of the septum, respectively. In addition, the dorasal tegmental nuclei of Gudden also seemed to project to the septum (Segal & Landis, 1974). The nature of the monoamine innervations of the septum remained unclear, as well as their possible involvement in the generation of the characteristic bursting of medial septal neurones which are correlated with hippocampal theta rhythm. Earlier studies have demonstrated that septal cells react to the iontophoretic administration of noradrenaline and serotonin by inhibition (Herz & Gogolak, 1965; Segal, 1974). The purpose of the present study is to describe the physiology and pharmacology of the connexions of some brain stem structures with the medial septal nucleus.

METHODS

Experiments were performed on fifty-four adult (200–300 g) male Wistar rats of a local breeding colony. Rats were anaesthetized with urethane (1 gm/kg I.P.) and placed in a stereotaxic frame. Rectal temperature was monitored continuously and maintained at 37–38° C with a heating pad. The skull and dura overlying the cortex were removed, the cortex and corpus callosum aspirated and replaced with mammalian Ringer or, in some cases, with mineral oil. Concentric bipolar stimulating electrodes (tip diameter 100 μm, tip separation 200 μm) were placed stereotaxically in the regions of the nucleus coeruleus and raphe. An additional bipolar electrode (tip diameter 200 μm, tip separation 200 μm) was, in some experiments, placed under visual guidance in the fimbria of the hippocampus. In order to facilitate accurate localization of the electrode only one penetration per stimulating electrode was attempted. A 3 M-NaCl-filled glass micropipette (tip diameter 2–5 μm) or a tungsten micro-electrode was lowered under visual guidance into the medial septal nucleus. Extracellular activity was amplified and filtered (band pass 1–10 kHz) and led via a window discriminator into an Ortec histogram generator for generating inter-spike interval histograms and post-stimulus time histograms. The generated histograms were plotted on a chart recorder. All steps were continuously monitored and occasionally photographed off the face of an oscilloscope.

Stimulation was controlled by a Devices Digitimer which also triggered the formation of histograms by the Ortec histogram generator, and applied square 0·1 msec 0·05–0·5 mA single pulses via a Devices Mark IV battery operated stimulator.

The fornix was sectioned in some rats 1–3 weeks before the experiment. The animals was anaesthetized with Nembutal and placed in a stereotaxic instrument. A microknife (Roboz) was passed 0·5 m behind the bregma from the mid line to 2 mm laterally in a depth of 4·5–5·0 mm. Care was taken to avoid a damage to the sinus. This procedure was sufficient to completely section the fornix.

Stimulation sites were marked by passing small d.c. currents through the tip of the electrodes. Rats were perfused through the heart with buffered formaldehyde, the brain sectioned on a freezing stage and the sections stained with cresyl violet for facilitation of histological localization of electrode placements and, when applicable, the lesion sites. The following drugs were used in the course of the study: reserpine (Sandril, 5–10 mg/kg I.P., E. Lilly Co.), 6-OH dopamine hydrobromide (6OHDA, intracisternal injection of 300 μg, in 50 μl., prepared in 0·1 % ascorbate, Regis), DL-*p*-chlorophenylalanine methyl ester-HCl (PCPA, in saline, 300 mg/kg I.P., Calbiochem), L-DOPA (in saline, 20–40 mg/kg, I.P., Calbiochem), carbidopa (10 mg/kg in saline, with L-DOPA, I.P., Merck), propranolol hydrochloride (1 mg/kg, I.V., Ayerst), picrotoxin (1–2 mg/kg, I.V., K & K).

RESULTS

General

A total of 215 cells were recorded from the medial septal nucleus and the nucleus of the diagonal band, and since there were no apparent differences between the two groups, they were combined. Most of the cells had a characteristic bursting firing pattern consisting of 2–5 spikes in a burst with short interspike interval (20–50 msec) within a burst and long (300–400 msec) interburst interval having a spontaneous firing rate of 10–25 spikes/sec (Fig. 1, top). A second class of cells, that had low spontaneous firing rates (1–15 spikes/sec) and lacked the bursting pattern, were encountered much less frequently than the first group. Finally, there were fast firing cells (15–25 spikes/sec) which exhibited the characteristic bursting pattern only occasionally and might belong to the same family of neurones as the bursting ones.

Responses to fimbria stimulation

The responses of seventeen cells to fimbria stimulation were tested in nine rats. A long duration (20–40 msec) inhibition of spontaneous firing was observed in fifteen of these cells, as previously reported (McLennan & Millar, 1974; Segal, 1974). The inhibited cells were of the bursting type (four cells) or the high frequency firing cell type (ten cells). Two additional cells were excited with rather short, 1–2 msec, latency, and long, 20–50 msec duration. Some bursting cells became synchronized for almost 1 sec by the stimulation (Fig. 2).

Responses to stimulation of nucleus locus coeruleus

The responses of 129 cells to stimulation sites in or near LC were measured in forty-one rats. Of these, eighty-four cells were recorded from normal rats and forty-five cells from 6OHDA and reserpine-treated rats. The results were classified according to the vicinity

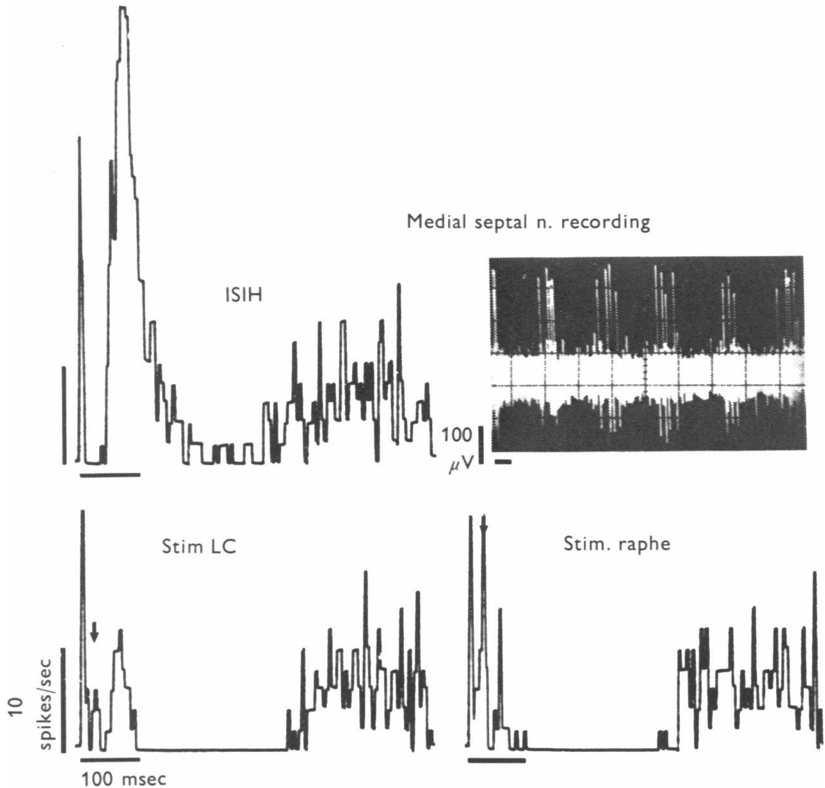

Fig. 1. Responses of a medial septal cell to brain stem stimulation. Top left, an interspike interval histogram (ISIH) of a spontaneously bursting cell, the specimen record of which is presented on the top right. The activity is grouped into two peaks; the shorter latency peak represents the intervals within a burst and the long latency one represents the intervals between bursts. Bottom, two post-stimulus time histograms representing averages of sixty-four repetitions of single pulse stimulation of LC (left), and the median raphe (right). The stimulation was applied 20 msec after on-set of a histogram (arrow). A long latency (60–70 msec) and long duration (200–300 msec) response was generated to LC stimulation whereas a similar long duration but shorter latency response was generated to the stimulation of the raphe nuclei. Abscissa bar = 100 msec for bottom histograms, 10 msec for top histograms. Ordinate = 10 spikes/sec.

of the stimulating electrode to the centre of the LC (Fig. 3). When the stimulating electrode was placed in the body of the nucleus the effects on firing rates were that of inhibition; twenty-one of thirty-three cells reduced their firing rates after a variable latency (15–50 msec) (Fig. 1) for 200–300 msec. In a few cases, when the cells exhibited spontaneous bursting, these burstings were synchronized with the stimulation to produce several peaks (Fig. 2). These, however, were not nearly as substantial as those produced by either fimbria or raphe stimulation (see below).

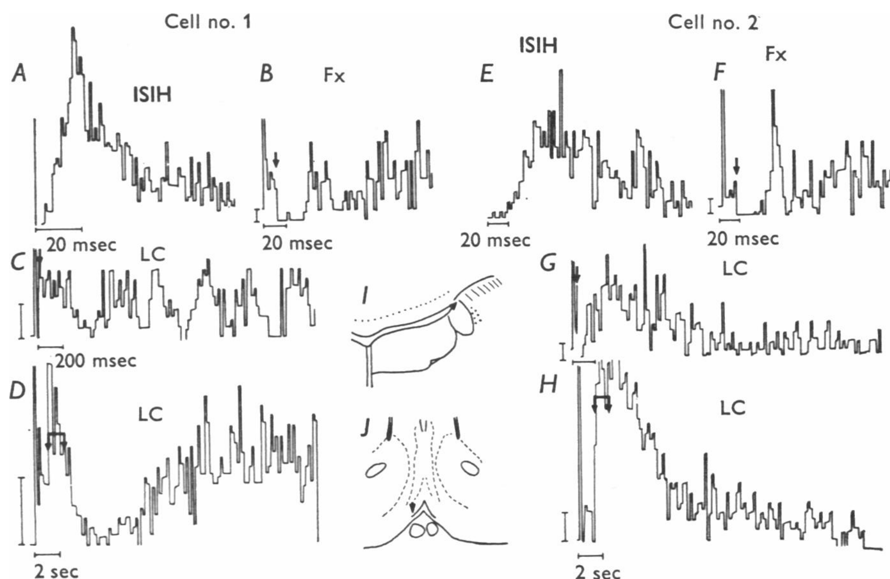

Fig. 2. Responses of two diagonal band neurones to LC fornix-fimbria (Fx) stimulation. Left-hand histograms are from one cell and right-hand histograms are from the other cell. *A*, *E*, interspike interval histograms (ISIH) of the two cells. Note the longer intervals (= slower firing rate) of cell no. 2 relative to cell no. 1. Note also in *A* a slight tendency to form a second peak, which characterizes a bursting cell. *B*, *F*, responses to Fx stimulation is characterized by a short delay, long (20–30 msec) duration of an inhibitory response. *C*, *G*, responses to single pulse stimulation of LC. Cell no. 1 responded by inhibition with a long latency and duration and the response was followed by repetitive bursting. Cell no. 2 responded by a monophasic excitatory response which was not accompanied by repetitive firing. *D*, *H*, responses of the two neurones to multiple shock stimulation of LC. Stimulation was applied at a rate of 10/sec for 1 sec. Cell no. 1 responded by long-lasting 5–6 sec slowing of spontaneous firing, cell no. 2 responded by excitation. Note in these two histograms the apparent increase in firing during stimulation which is actually due to inclusion of the stimulation artifacts in the record. *I*, placement of the stimulating electrode in the main body of n.LC (triangle). *J*, recording electrode tip placed in the nucleus of the diagonal band (arrow head).

Repetitive stimulation at a rate of 10–15 pulses/sec (Fig. 2) produced a long lasting (2–5 sec) reduction of spontaneous firing rates of these cells. Only three cells were excited by LC stimulation. These were slow firing, non-bursting cells. The excitation has a similar latency but appeared to have a shorter duration (100–200 msec) (Fig. 2) than the inhibitory responses. Nine more cells did not react to the stimulation. Similar results were obtained when the stimulating electrode was placed anterior to the LC, presumably in or near the dorsal bundle that originates in LC; seven of twenty-six cells were inhibited by the stimulation whereas three more were excited and thirteen were unaffected.

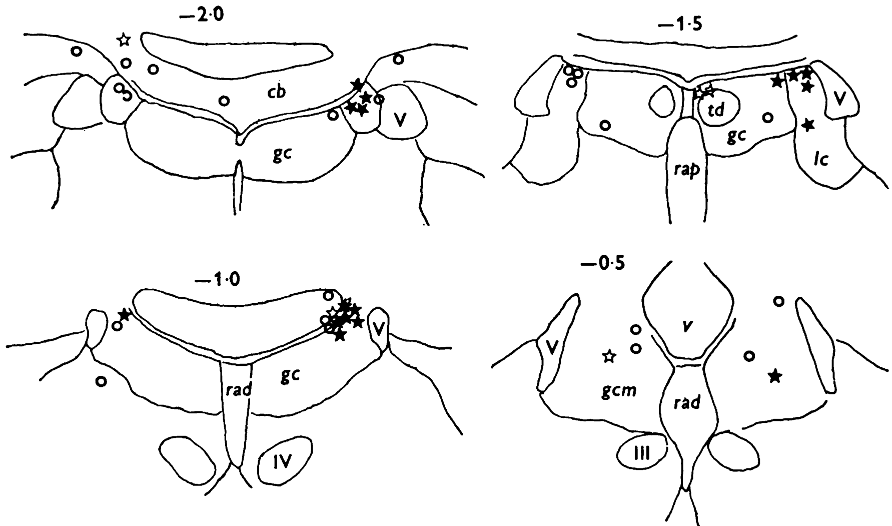

Fig. 3. Localization of the stimulating electrodes in the region of LC and the main effects produced by stimulation of these sites. The numerals above each schematic section represent the distance, in millimetres from the lambda suture. The right-hand side of each section contains all the electrodes placed in normal rats and on the left, from 6OHDA and reserpine-treated rats. Filled stars = inhibitory responses, open stars = excitatory responses, circles = no response. Abbreviations: *cb*, cerebellum; *gc*, central grey matter; *gcm*, mesencephalic central grey; *lc*, nucleus locus coeruleus; *rad*, nucleus raphe dorsalis; *rap*, nucleus raphe pontis; *td*, nucleus dorsal tegmentum; V, nucleus of the mesencephalic tract of the trigeminal complex; *v*, ventricle.

The distribution of responsive cells was quite different when the stimulating electrode was located in the adjacent cerebellum and mid-brain structures. Only three of twenty-two cells were inhibited by the stimulation, five cells were excited and five other cells had a short latency (3–5 msec) whereas nine other cells had an excitatory response that lasted for 20–40 msec.

Pharmacological manipulation of responses to LC stimulation

Four rats were treated with 6OHDA, eleven rats with reserpine and two more rats with both 6OHDA and PCPA. The activity of forty-five medial septal and diagonal band cells was recorded from these rats. Since the various treatments which reduce noradrenaline level in the brain caused similar effects they were grouped together. Among twenty-three cells,

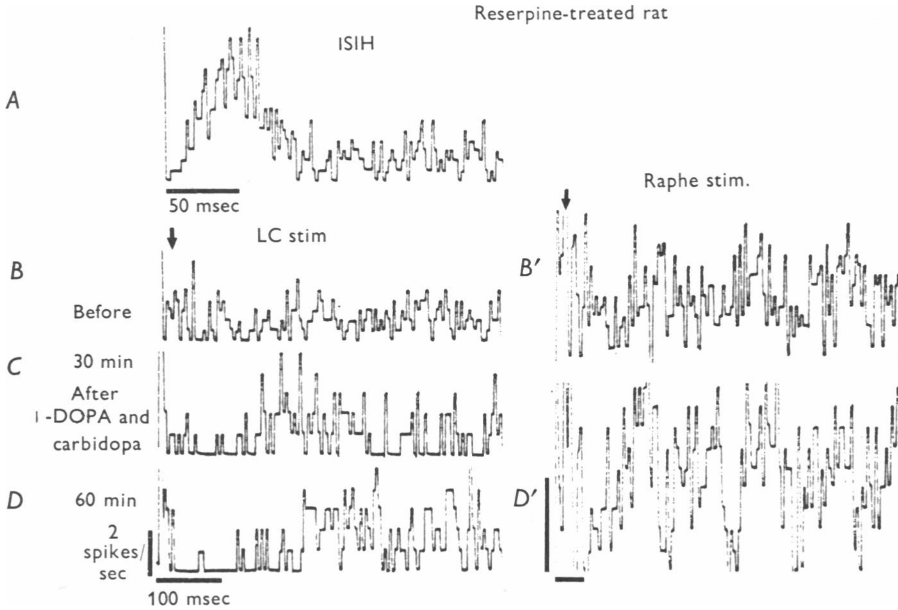

Fig. 4. Effects of reserpine and L-DOPA on cellular responses to brain stem stimulation. *A*, interspike interval histogram (ISIH) of a spontaneous medial septal bursting cell. *B*, 24 hr after reserpine treatment, a lack of cellular responses to LC stimulation is evident. Similarly, only a small response to raphe stimulation can be recorded. *C*, *D*, after parenteral injection of a noradrenaline precursor (L-DOPA) and the prevention by carbidopa of its peripheral catabolism, the typical inhibitory response to LC stimulation is created. A much smaller but clear augmentation of response to raphe stimulation can be seen, too, and that might be caused by noradrenaline, or dopamine acting as a 'false transmitter' in the serotonergic pathway. Note the difference in scales between the right and left-hand-side histograms.

in eight rats where the stimulating electrode was located in the LC, only two cells were inhibited by the stimulation. This inhibitory effect was much less pronounced than that observed in the normal rat and had a shorter time course. No long latency excitatory responses were found, four cells had a short latency excitatory response as seen in the normal rat, and a total of seventeen cells were not affected by the stimulation. Similarly,

Reserpine-treated rat

cells in rats where the stimulating electrode was located outside the LC did not react to the stimulation by an inhibitory response. One cell had a long latency excitatory response and six cells had a short latency excitatory response, characteristic in the normal rats to stimulation of cerebellum and adjacent mid-brain structures.

In an attempt to test if the lack of inhibitory responses in reserpinized rats was mediated by loss of catecholamines, L-DOPA, a catecholamine precursor was injected intraperitoneally together with a carbidopa which prevents the peripheral break-down of L-DOPA (Vickers, Stuart, Saari, Icing & Heuvel 1973) during the experiment in five rats. In three reserpine-treated rats an inhibitory response to LC stimulation became apparent some 15–30 min after the injection (Fig. 4). In two more rats L-DOPA injection was ineffective but the electrodes were found later to be outside LC.

A further test for the possible noradrenergic nature of the connexion between LC and the septum was done with the use of proprandol, a beta adrenergic antagonist. After recording a stable response to LC stimulation the drug was injected. All five cells tested stopped responding to the stimulation 5–20 min after the injection and a recovery was seen in four of these cells within 1–2 hr (Fig. 5).

Responses to stimulation in the raphe area

The activity of ninety-seven cells was recorded in forty-three rats (Fig. 6). Some of these rats also had stimulating electrodes placed in LC so that comparison between the effects of stimulating these two sites was possible. Altogether the responses to raphe stimulation were quite different from those recorded after LC stimulation. There were four main classes of responses which were produced by and large with nearly every stimulating site in the region of the raphe; there were long latency (20–50 msec) and long duration inhibitory or excitatory response, short latency (2–5 msec) inhibitory or excitatory responses which was accompanied by an evoked field potential. This evoked field potential was biphasic with an initial positivity followed by a negative going component. The averaged latency to the response onset was 2–3 msec.

Twelve of twenty-nine cells were inhibited with long latencies and durations (Fig. 1). Only one cell had a short latency inhibitory response, whereas four cells had short latency excitatory responses. Four more cells did not change their firing frequencies following the stimulation. When PCPA-treated rats were examined, of eight cells recorded, none had a long latency inhibitory response, one had a long latency excitatory and six more had short latency inhibitory responses. Stimulation of median raphe produced similar effects. In normal rats, eleven and ten of fifty-one cells displayed a long latency inhibitory and excitatory responses,

respectively. Fourteen and thirteen cells had short latency inhibitory and excitory responses, respectively. In PCPA or, alternately, reserpine-treated rats, only three and two of nineteen cells had long latency inhibitory

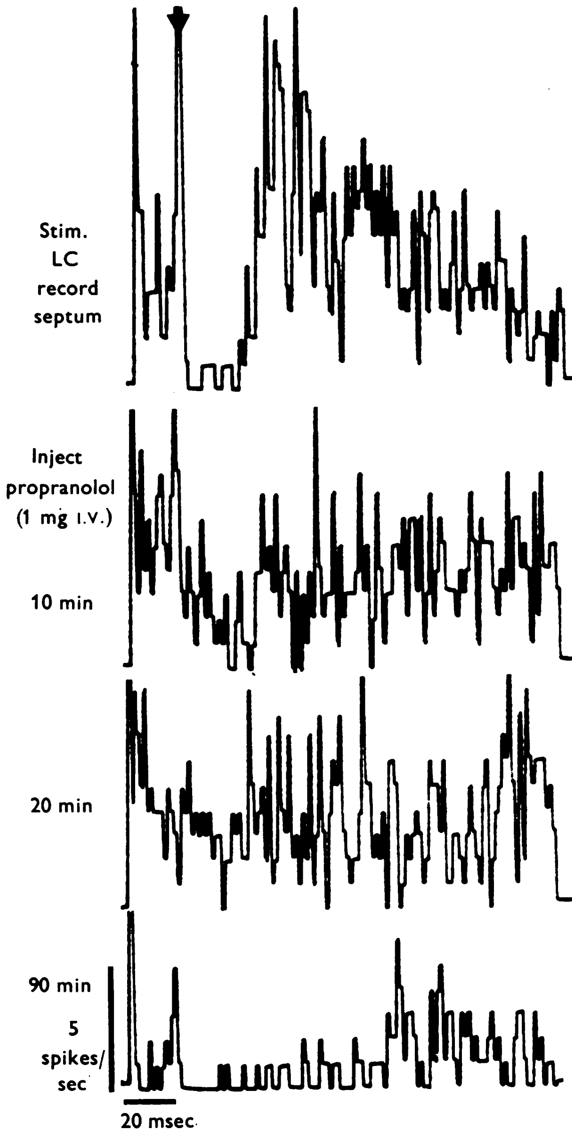

Fig. 5. Blockade of septal response to LC stimulation by propranolol. An inhibitory response to LC stimulation was first established, followed by the I.V. injection of the antagonist propranolol. Following the injection, the response to LC stimulation was blocked temporarily.

or excitatory responses, respectively. When the electrode was placed in the dorsal tegmental nuclei of gudden or in adjacent central grey substance, the dominant response was the short latency one that was accompanied by an evoked field potential. Of sixty cells recorded when stimulating these

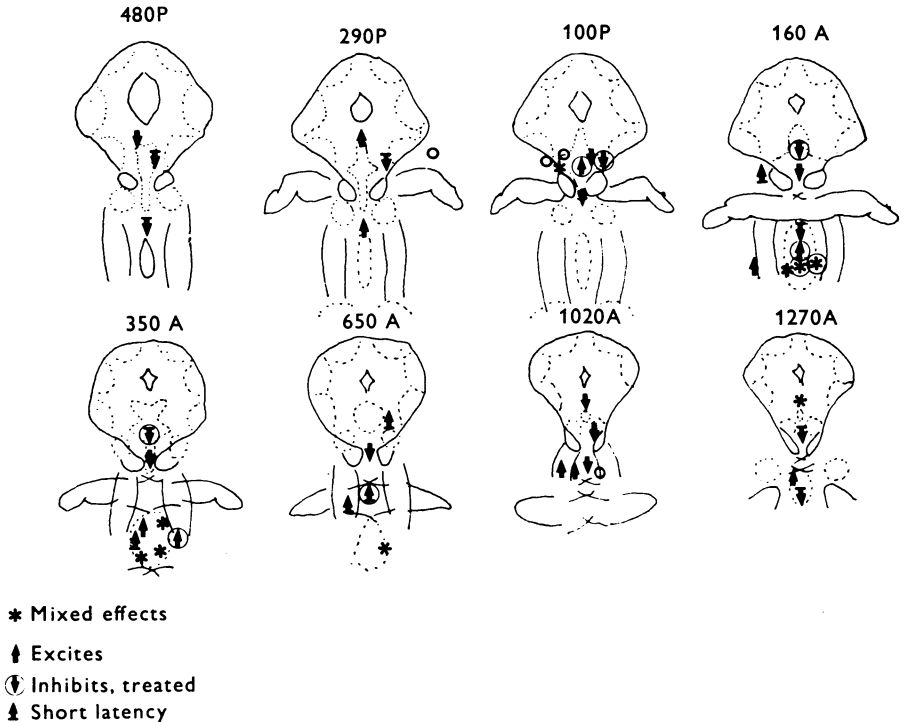

Fig. 6. Distribution of stimulation sites in the raphe area drawn on frontal schematic sections. Each point represents an electrode placement. The drawings are based in the atlas of the rat brain (Keonig & Klippel, 1963).

areas only seven cells had a long latency inhibitory response, five more had an excitatory response, ten and eleven cells had, respectively, short latency inhibitory and excitatory responses and the rest (twenty-seven) did not react to the stimulation.

With respect to long lasting effects of the stimulation, ten of the fast bursting cells appeared to be triggered by the stimulation to produce repetitive bursts regardless of their initial response, i.e. whether their initial short latency response was inhibitory or excitatory. Similarly, this repetitive bursting seemed to be independent of the presence of monoamines, as reserpine or PCPA did not abolish this response, since ten of the cells recorded in reserpine or PCPA-treated rats exhibited the triggered bursting pattern (Fig. 7). Since the responses of some septal bursting cells

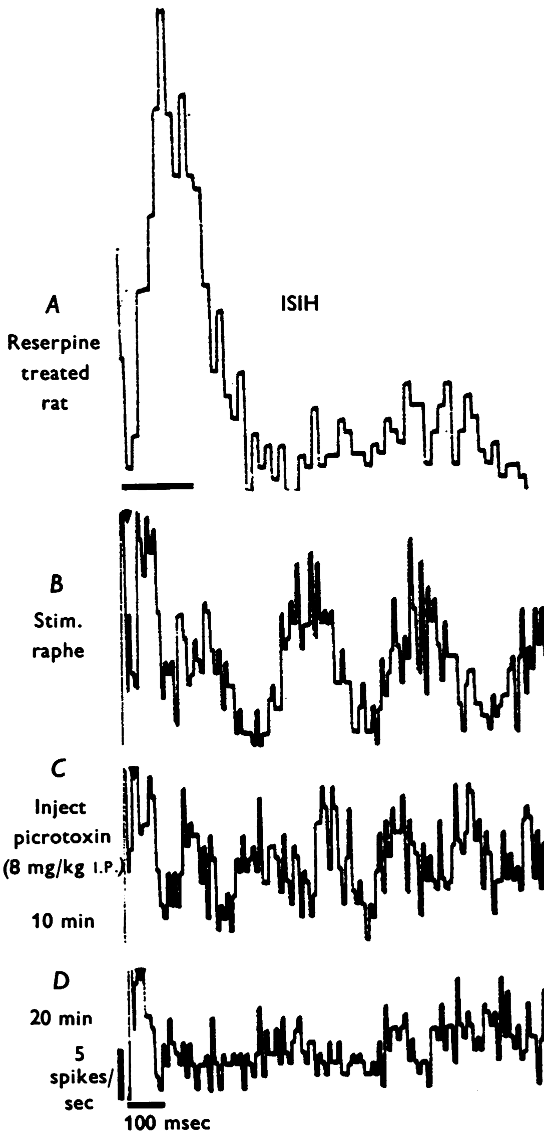

Fig. 7. Blockade by picrotoxin of rhythmic activity induced by raphe stimulation in a reserpine treated rat. *A*, interspike interval histogram (ISIH) of a spontaneously bursting cell in a reserpinized rat. *B*, post-stimulus time histogram averaging the responses of this cell to raphe stimulation, applied 20 msec after histogram onset (arrowhead). *C*, 10 min after injection of picrotoxin. *D*, 20 min after the injection. It appears that picrotoxin antagonized the rhythmic response to raphe stimulation.

to fimbria and raphe stimulation were similar, indicating the presence of a local generating mechanism presumably acting via a γ-aminobutyric acid (GABA) interneurone. The GABA-receptor blocker, picrotoxin, was injected to rats pre-treated with reserpine (Fig. 7). The repetitive response was abolished within 10 min and replaced by irregular high frequency firing rates.

Effects of fornix lesion and drug treatments on spontaneous firing rates of septal cells

Based on previous observations (Raisman, 1969; Moore, Björklund & Stenevi, 1971) a systematic test of spontaneous firing rates in the different experimental situations was carried out. The assumption was that depletion of monoamine inhibitory input to the septal cells by 6OHDA and/or PCPA increases spontaneous firing rates of septal cells whereas fornix lesion, which presumably causes hyperinnervation by the monoamine containing fibres will cause an excess of inhibitory input to the septum and hence decrease spontaneous firing rates of septal cells. Altogether, five groups were composed: cells from normal rats ($n = 17$); fornix lesioned rats ($n = 15$); and rats treated with 6OHDA ($n = 20$); PCPA ($n = 8$); and PCPA and 6OHDA ($n = 10$).

The results were compared by analysis of variance. The normal, PCPA and 6OHDA groups had similar mean interspike intervals (45, 46 and 53 msec, respectively) whereas the fornix lesioned group had a longer mean interspike interval (122 msec) and the combined PCPA and 6OHDA group had a shorter mean interspike interval (25·5 msec). It appears that in fornix-leasioned rats the spontaneous firing of medial septal cells is slower than normal and that only total amine depletion by a combination of 6OHDA and PCPA increases spontaneous firing of septal cells.

DISCUSSION

The results of the present experiments demonstrate the existence of a long latency inhibitory response in medial septal and diagonal band neurones to stimulation of the noradrenaline containing LG and suggest that this inhibitory response is mediated by noradrenaline. This suggestion is based on the following: there is a direct pathway between the LC and the medial septal nucleus (Segal & Landis, 1974; Lindvall & Björklund, 1974); there is noradrenaline in this region (Brownstein, Saavedra & Palkovits, 1974) and iontophonetic administration of noradrenaline reduces spontaneous firing of septal cells (Segal, 1974); and finally, the present data which demonstrate the existence of a reserpine and 6OHDA-sensitive inhibitory responses in the medial septal to LC stimulation. The long latency of these responses raises the possibility that a

multisynaptic pathway might be involved in the observed effects; nevertheless, it was shown recently (Nakamura & Iwama, 1975) that the conduction velocity of LC axons is slow (0·5–1·3 m/sec) and corresponds to the conduction of peripheral nonmyelinated c-type fibres, which would agree with the response latencies observed in the present experiment. Some excitatory responses were recorded mainly when stimulating structures adjacent to the LC. This might be originated in the cerebelloseptal connexion described by Paul, Heath & Ellison (1973) or from current spread to the central grey matter which also projects to the septal area.

The present experiments have also indicated a possible complex relationship between the raphe nuclei and the septal area; stimulation in the raphe area exerts potent effects towards cells in the medial septal nucleus. These effects can be divided into long latency responses which are sensitive to blockade of serotonergic transmission and short latency responses which are resistant to serotonergic antagonists. Since triggering of repetitive firing was similar to that produced by fimbria stimulation, it is assumed to originate in local circuits, probably involving interneurones or neurones of the lateral septal nuclei.

The dissociation between the short latency and long latency responses seen when serotonin is depleted indicate different origins of these two responses. An anatomical dissociation could be observed as well: when the stimulating electrode was placed in the raphe nuclei the responses were mixed; however, only the short latency response that was typically accompanied by an evoked field potential was found when stimulating the central grey matter and the dorsal tegmental nuclei caudal to the raphe area. It has been shown that the dorsal tegmental nuclei project rostally through the raphe area to the septal nuclei (Morest, 1961) and it appears likely that these fibres may have been stimulated when the electrodes were placed in the raphe area.

Physiologically, the serotonergic and noradrenergic innervations studied in various brain structures, i.e. the hippocampus (Segal & Bloom, 1974; Segal, 1975), the trigeminal nucleus (Sasa, Munekiyo, Ikeda & Takaori, 1974; Sasa, Munekiyo & Takaori, 1976) as well as the present, in the septum appear, to act similarly towards post-synaptic elements. Functionally, they appear to maintain quite different roles. Further studies where the effects of stimulation of the raphe and LC are tested in behaviourally relevant situations are needed before suggestions regarding functional specificity are offered.

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