Exp Brain Res (1991) 83:303–316

Experimental Brain Research

Midbrain stimulation inhibits the micturition, defecation and rhythmic straining reflexes elicited by activation of sacral vesical and rectal afferents in the dog

H. Fukuda and T. Koga

Department of Physiology, Kawasaki Medical School, Kurashiki 701-01, Japan

Received November 29, 1989 / Accepted August 20, 1990

Summary. Inhibition of the micturition, defecation and rhythmic straining reflexes by midbrain stimulation was compared with the inhibition of the jaw-opening reflex caused by tooth pulp stimulation in decerebrate dogs. All of the reflexes were inhibited by stimulation of the dorsal and ventral periaqueductal gray, dorsal raphe nucleus and central tegmental field with similar threshold intensities. After a hemisection of the spinal cord at the C2 segment, the midbrain stimulation still suppressed the micturition reflex as well as field potential changes which were evoked by stimulation of the pelvic nerve and recorded from the lateral funiculus just caudal to the hemisection, but did not influence the discharges of the vesical branch of the pelvic nerve which were elicited by stimulation of the lateral funiculus just rostral to the hemisection. The results suggest that stimulation of the neural elements in the 4 midbrain areas depresses the ascending activities from vesical and colorectal afferents of the pelvic nerve at the spinal level, and consequently inhibits the pelvic nerve reflexes. Systemic methysergide suppressed midbrain inhibition of the jaw-opening reflex, but did not affect the midbrain inhibition of the pelvic nerve reflexes. Systemic naloxone did not influence midbrain inhibition of the pelvic nerve reflexes or the jaw-opening reflex, but enhanced the micturition and rhythmic straining reflexes. Possible roles of the midbrain inhibition of the pelvic nerve reflexes are discussed.

Key words: Stimulation produced analgesia – Midbrain – Pelvic nerve – Defecation – Micturition – Dog

Introduction

Recently, sacral visceral afferents from the lower urinary tract, colon and anus have been shown to respond to a wide range of mechanical stimuli and intraluminal pressure (wide dynamic range property), and afferents from the uterus of rats exhibit polymodal responsiveness (Bahns et al. 1987; Berkley et al. 1987). Further, convergence of cutaneous nociceptive inputs and vesical or colonic ones onto sacral cord neurons, including spinothalamic tract cells, has been shown in monkeys (Milne et al. 1981), cats (Honda 1985) and rats (Ness and Gebhart 1987a, b). Moreover, the micturition reflex is enhanced by systemic naloxone (Roppolo et al. 1983), consequently inhibited by intrathecal application of opioid peptides (Hisamitsu and de Groat 1984), and impaired after systemic capsaicin treatment (Holzer and Lembeck 1984; Maggi et al. 1986). Thus, a single population of sacral visceral afferents encoding innocuous as well as noxious events seems to act as centripetal limbs of the reflexes from pelvic organs and also as the fibers mediating nociception, as emphasized in the intensity theory of visceral nociception by Jänig and Morrison (1986).

On the other hand, the micturition (Langworthy and Kolb 1933; Tang 1955) and rhythmic straining reflexes (Fukuda and Fukai 1986a, b, 1988; Fukuda, Fukai and Koga, unpublished results) induced by activation of sacral afferents in the pelvic nerve are enhanced after transection of the midbrain at the intercollicular level. The micturition reflex is also enhanced after destruction of the periaqueductal gray (PAG) (Barrington 1925) and the central tegmental field (CTF) just lateral to the PAG (Tang and Ruch 1956). Stimulation of the CTF inhibits vesical contractions (Gjone 1966; Kabat et al. 1936; Koyama et al. 1962) and colonic movements (Rostad 1973). The micturition reflex is also inhibited by stimulation of the raphe magnus nucleus which is known to receive afferents from the midbrain (McMahon and Spillane 1982; Morrison and Spillane 1986). Responses of sacral cord neurons to colorectal distention are also inhibited by stimulation of the raphe magnus and dorsal raphe nuclei (DR) (Gebhart and Ness 1986; Ness and Gebhart 1987a). Similarly, stimulation of the PAG, CTF, DR and the raphe magnus nucleus is well known to produce analgesia (stimulation produced analgesia, SPA) (Beson and Chaouch 1987).

Offprint requests to: H. Fukuda (address see above)

Thus, the midbrain structures involved in SPA may inhibit centripetal activities from the single population of pelvic nerve afferents at the sacral cord, and consequently suppress the reflexes and nociception of the pelvic organs. This hypothesis was examined in this work.

Material and methods

Thirty-seven dogs, each weighing 5–10 kg, were used in this study. Dogs were anesthetized with thiopental sodium (15 mg/kg, i.v.) and paralyzed with gallamine triethiodide (2 mg/kg, i.v.). They were maintained in a hyperventilated state by artificial ventilation through a tracheal cannula at rate of 10 to 20 strokes/min and a tidal volume of 150 to 250 ml. Under these conditions, inspiratory discharges of the phrenic nerve were suppressed and the rhythmic straining reflex was facilitated (Fukuda and Fukai 1988). All dogs were then decerebrated precollicularly under anesthesia deepened with an additional injection of thiopental sodium (15 mg/kg). Arterial blood pressure lowered by the deep anesthesia decreased hemorrhage and facilitated the decerebration procedure. After the decerebration, dogs were allowed to recover from the anesthesia, and no further anesthesia was applied.

In all dogs, all vesical and rectal branches of the pelvic nerves were bilaterally isolated, and the peripheral ends were cut. The hypogastric nerves were severed bilaterally rostral to the pelvic plexus. Thus, the bladder and rectum were denervated, with the exception of the rectal innervation by the lumbar colonic nerve. The left phrenic nerve and a nerve innervating the left rectus abdominis were exposed. Urethral and anal branches of the left pudendal nerve of 2 dogs, the nerve innervating the left digastricus of 12 dogs and the C1–C3 segments of the spinal cord of 6 dogs were exposed.

Dogs were then fixed on a stereotaxic head holder. All exposed nervous tissues were covered with liquid paraffin pools formed with the skin flaps. The vesico-vesical (micturition) reflex was elicited by stimulation (5 or 10 Hz, 0.5 ms, 10–15 V) of central cut-ends of vesical branches of the right pelvic nerve. The recto-rectal (defecation) reflex and rhythmic straining reflex were elicited by stimulation (10 or 20 Hz, 0.5 ms, 10–20 V) of central cut-ends of rectal branches of the right pelvic nerve. Intensities and frequencies of the stimulation were adjusted in each dog to produce a standard magnitude of reflex discharges. Frequency histograms (100 ms bins) of discharges in the left vesical, rectal, urethral and anal branches were recorded simultaneously with the histograms of the activities in the phrenic nerve and the nerve to the rectus abdominis. Bipolar platinum-wire hook electrodes were used for the stimulation and recording.

The tip (about 5 mm) of the cuspid tooth of the inferior maxilla was cut off to open the pulp canal in 12 dogs. Two lengths of platinum wire (50 μm in diameter) coated with cashew lacquer were inserted about 7 and 10 mm into the canal, respectively, so that the tips were about 3 mm apart. The pulp nerve was stimulated (0.5–1 Hz, 0.5 ms, 10–20 V) with these wires to elicit the tooth pulp-digastricus (jaw-opening) reflex. Compound action potentials were recorded from the nerve to the digastricus and averaged 10 or 30 times. Intensity of the pulp stimulation was adjusted in each dog to produce a standard amplitude of the compound action potential. End-tidal CO_2 concentration (in vol. %) and arterial blood pressure were monitored throughout the experiments.

Glass coated platinum wire electrodes (50 μm in tip diameter and about 100 μm in tip length) were used for stimulation of the midbrain and spinal cord, and for recording field potential changes from the left lateral funiculus.

To map the midbrain points from which the pelvic nerve reflexes were suppressed, the midbrain was monopolarly stimulated at each 1-mm intersection of four planar grids assumed to lie on transverse planes 0, 2, 4 and 6 mm rostral to the point where the dorsal intercollicular groove and the mid-line cross. During the systematic stimulation of 40–80 points on one of the transverse planes, 3 stimulated points were marked by lesions made by passing a direct current of 0.5 mA through the stimulating electrode for about 10 s.

After the experiment, the midbrain was fixed with 15% formalin solution, sectioned serially at 30 μm and stained by Nissl's method. The 3 marks and electrode tracks of the serial stimulation, which were usually distributed over 5–10 sections, were represented on a camera lucida sketch of one of the sections. Positions of all stimulated points were determined on the sketch. The dorsoventral distance was sometimes shorter than the horizontal distance between intersections of the reconstructed grids. This deformation may have arisen during the fixation and sectioning procedures. To compensate for the deformation, the stimulated points and the landmarks on the sketch were transferred to the corresponding points on a rectangular grid. In addition, the electrode tracks in individual dogs often differed from the standard coordinates, which were determined according to the positions of the dorsoventral mid-line and the most dorsal mark of the least deformed section. The differences seem to have been caused mainly by shifting of the brain from the original position during decerebration and by misses in determination of the point of origin at the intersection of the intercollicular groove and mid-line. To transfer the stimulated points in individual dogs to the sketch having the standard co-ordinates, the mid-line and landmarks of the standard sketch were superposed on a sketch of each dog, and the stimulated points were transcribed onto the standard sketch. We believe this transfer procedure the best, since wide homogeneous areas intervene betweeen landmarks in the midbrain sections. The effects of stimulation of the points transferred from the sketches of 2–6 dogs into each section (1 × 1 mm) of the standard co-ordinates were averaged. By this mapping experiment, the 4 midbrain areas (d-PAG, v-PAG, CTF and DR) in which stimulation inhibits the pelvic nerve reflexes were determined as described in the results.

After the mapping was accomplished, barreled electrodes consisting of 2–4 glass-coated platinum wire electrodes were used for successive stimulation of the 4 midbrain areas. The constituent electrodes and spacer(s) were bound with cotton thread, and the electrode tips were adjusted to the relative positions of the 4 midbrain areas from which the pelvic nerve reflexes were suppressed. Then the electrodes and spacer(s) were joined with resin. In the experiments, a barreled electrode was mounted on a manipulator, inserted into the midbrain in small steps of 0.2 to 0.5 mm to position each electrode tip at the point in the 4 midbrain areas in which monopolar stimulation yields maximum inhibition of the pelvic nerve reflexes.

Results

Midbrain areas in which stimulation inhibits the micturition, defecation and rhythmic straining reflexes

Effects of midbrain stimulation (50 μA, 5 ms, 10 Hz) on the micturition reflex were examined in 19 dogs at 1096 points on the 4 transverse planes 0, 2, 4 and 6 mm rostral to the intercollicular groove (Y = 0, 377 points in 6 dogs; Y = 2, 235 points in 4 dogs; Y = 4, 233 points in 4 dogs; Y = 6, 251 points in 5 dogs). Stimulation at many points inhibited discharges of the vesical branch in the micturition reflex elicited by stimulation of contralateral vesical branches (Fig. 1). The strength of the inhibition usually increased or decreased, or often the inhibition disappeared, when adjacent points were stimulated during penetration of the electrode in steps of 1 mm (Fig. 1C, D). However, stimulation of 3 points in the Y = 0 plane of one dog and 5 points in the Y = 4 plane of 3 dogs only exhibited after-inhibition, in which discharges of the vesical branch did not change during the stimulating period, but briefly decreased just

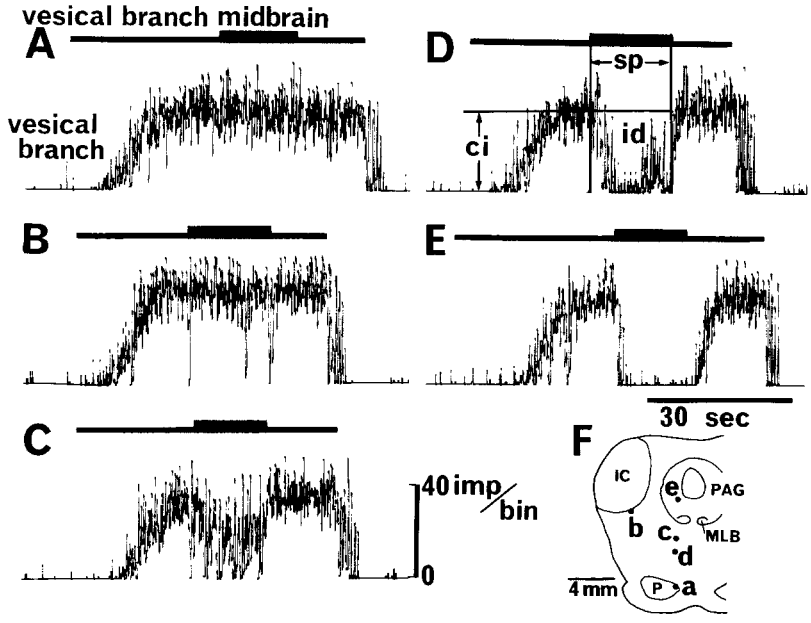

Fig. 1A–F. Inhibition of the micturition reflex by midbrain stimulation. Traces show frequency histograms (100 ms bins) of centrifugal discharges of a vesical branch of the left pelvic nerve. During the periods indicated by the horizontal line, central cut-ends of the contralateral vesical branches were stimulated. Increases in the discharges correspond to the vesico-vesical reflex (micturition reflex). During the periods indicated by thickened parts of the horizontal lines in **A–E**, the midbrain points indicated in **F** with corresponding small letters were stimulated with pulses of 10 Hz, 5 ms and 50 μA while vesical branches were stimulated. This explanation applies to the following figures. **D** id, degree of inhibition of the micturition reflex; ci, control intensity of the reflex; sp, period of midbrain stimulation. Meanings of abbreviations in **F** are given in the legend to Fig. 2

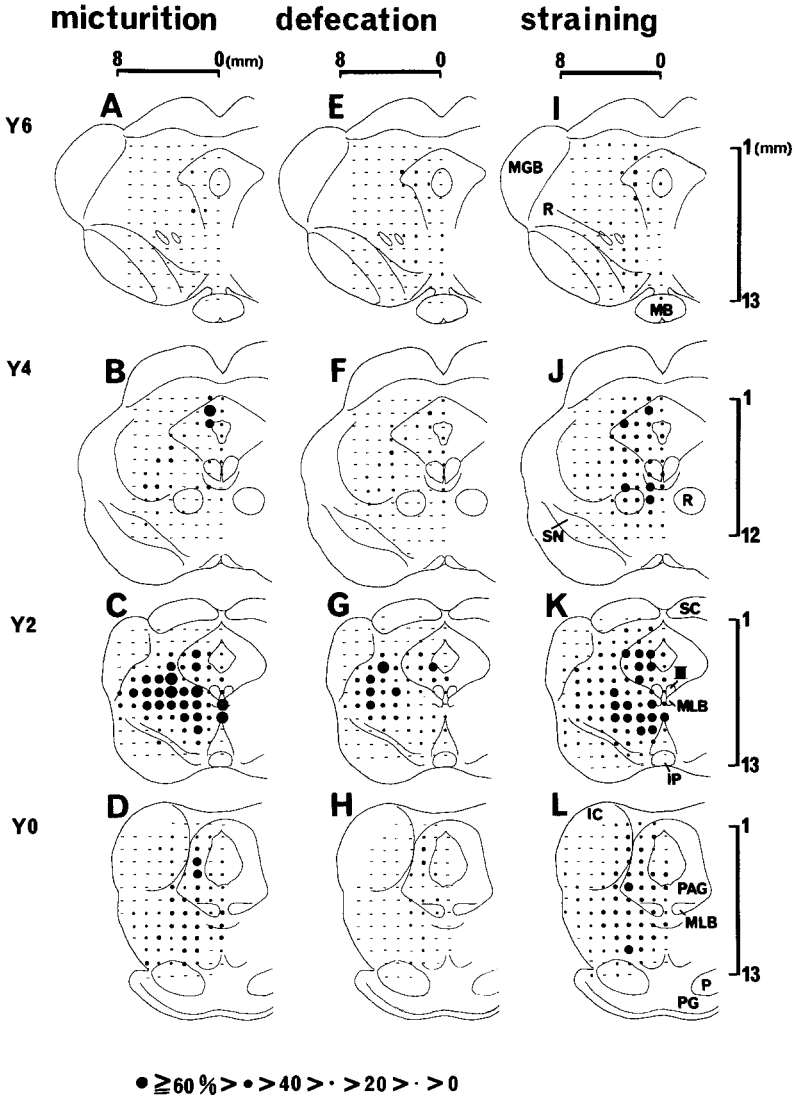

Fig. 2A–L. Midbrain inhibitory areas of the micturition (**A–D**), defecation (**E–H**) and rhythmic straining (**I–L**) reflexes. The areas are shown on sketches of standard sections of the midbrain 0 mm (Y0), 2 mm (Y2), 4 mm (Y4) and 6 mm (Y6) rostral to the intercollicular groove. Filled circles represent averaged percent inhibitions of the pelvic nerve reflexes as shown at the bottom of this figure. Ineffective points are indicated by (−). IC, inferior colliculus. IP, interpeduncular nucleus. MB, mamillary body. III, oculomotor nucleus. MGB, medial geniculate body. MLB, medial longitudinal bundle. P, pyramidal tract. PAG, periaqueductal gray. PG, pontine gray. R, red nucleus. SC, superior colliculus. SN, substantia nigra. These abbreviations apply to the following figures

after the end of the stimulation. All the 8 points were located in the PAG.

The degree of inhibition of the micturition reflex was expressed as the mean percent reduction (id) of vesical branch discharges in the midbrain stimulation period (sp, 18 s) with respect to the mean activity (ci) in the pre-stimulation period (6 s) (100% × id/ci, Fig. 1). The percentage inhibition caused by stimulation of corresponding midbrain points in 2–6 dogs were averaged (see methods). The averaged percentages were represented by filled circles having corresponding diameters (Fig. 2A–D).

Effects of stimulation on discharges of the rectal branch (defecation reflex) were examined at 875 points in 16 dogs (Y = 0, 182 points in 3 dogs; Y = 2, 210 points in 4 dogs; Y = 4, 232 points in 4 dogs; Y = 6, 251 points in 5 dogs). Midbrain stimulation at many points inhibited the discharges (Fig. 4). The inhibitory effects are summarized in Fig. 2E–H similarly as the effects on the micturition reflex. After-inhibition was also observed with PAG stimulation (at 21 points on the Y = 2 planes of 3 dogs and 7 points on the Y = 4 planes of 2 dogs).

The effects of midbrain stimulation on rhythmic straining elicited by stimulation of rectal branches were examined at 1123 points in 20 dogs (Y = 0, 396 points in 7 dogs; Y = 2, 243 points in 4 dogs; Y = 4, 233 points in 4 dogs; Y = 6, 251 points in 5 dogs). The stimulation also inhibited rhythmic straining, which is represented by rhythmic and synchronous increases in the discharges of both the phrenic nerve and the nerve to the rectus abdominis (Fig. 3). While rhythmic straining was inhibited by midbrain stimulation, the phrenic nerve usually exhibited augmented inspiratory activities which could be distinguished from its straining activities by the lack of concomitant increases in discharges of the abdominal muscle nerve or by concomitant inspiratory pauses in discharges of the muscle nerve (Figs. 4, 5, 9, 10). To evaluate the midbrain inhibition of the rhythmic straining reflex, we measured the 3 periods of rhythmic straining, i.e., the period just before midbrain stimulation (a), the longest period observed during midbrain stimulation (c) and a period after recovery from after-inhibition or after-excitation (b) (Fig. 3D). The periods were converted to the frequencies of a′ = 1/a, b′ = 1/b and c′ = 1/c. Then, percentage of the midbrain inhibition was calculated in accordance with 100% × [1 − c′/{(a′ + b′)/2}]. The inhibition percentages were summed similarly as for the inhibition of the micturition reflex (Fig. 2I–L).

The results summarized in Fig. 2 show that the micturition, defecation and rhythmic straining reflexes are inhibited by stimulation of the same 4 areas corresponding to the ventral part of the periaqueductal gray (v-PAG), the central tegmental field (CTF) ventrolaterally adjacent to the v-PAG and the dorsal raphe nucleus (DR) at a level 2 mm rostral to the intercollicular groove, and the dorsal part of the PAG (d-PAG) at the level 4 mm rostral to the groove.

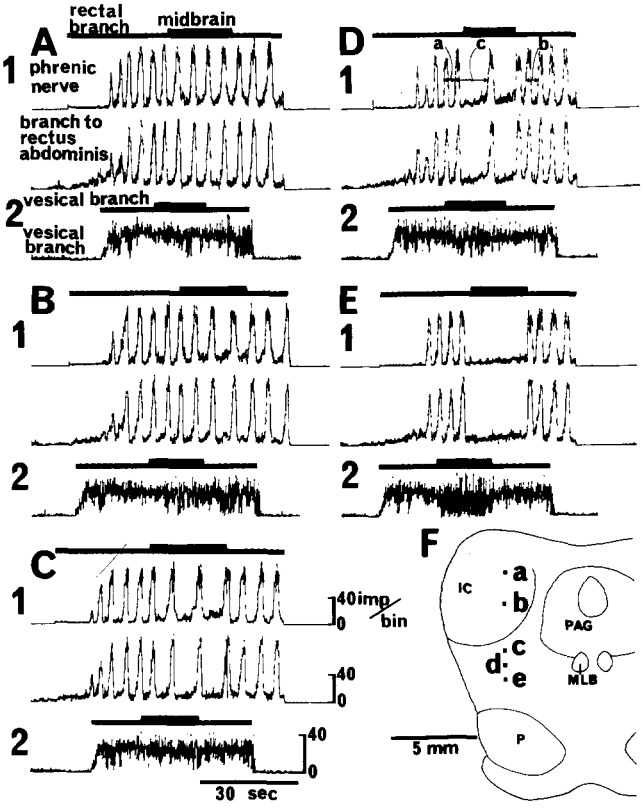

Fig. 3A–F. Midbrain inhibition of the rhythmic straining reflex. **A1–E1** Upper trace: centrifugal discharges of the left phrenic nerve. Lower trace: discharges of a branch of the lumbar spinal nerve which innervates the rectus abdominis. Horizontal lines indicate stimulation of rectal branches. Rhythmical and synchronous increases in discharges of both nerves represent rhythmic straining. Thickened parts of horizontal lines show midbrain stimulation (10 Hz, 5 ms, 50 μA) at the points indicated in **F** with corresponding small letters. **D** a, control interval of rhythmic straining before midbrain stimulation; c, longest interval during the stimulation; b, control interval after the stimulation. **A2–E2** Inhibition of the micturition reflex by stimulation of the same points as in **A1–E1**

Effects of midbrain stimulation on spontaneous discharges of the vesical branch, rectal branch, phrenic nerve and nerve to the rectus abdominis

After stimulation of the points in the d-PAG, v-PAG, DR and CTF were confirmed to inhibit the micturition, defecation and rhythmic straining reflexes, effects of stimulation of the same points with the same pulses on spontaneous discharges of the vesical branch, rectal branch, phrenic nerve and nerve to the rectus abdominis were observed in 13 dogs (Table 1). In some of our preparations of decerebrated dogs, pelvic vesical branches exhibited spontaneous dischargers (Figs. 1, 3, 5, 7–10), but the frequencies were very low (Table 1). Contrary to the reflex discharges of these nerves, their spontaneous discharges were not inhibited by the stimuli, but rather enhanced in some cases. Midbrain stimulation usually resulted in enhancement of inspiratory discharges of the phrenic nerve. The enhancement was accompanied by a decrease in spontaneous discharges of the nerve to the rectus abdominis in some cases (one point in the PAG of 3 dogs and in the CTF of 2 dogs). All discharges induced in these

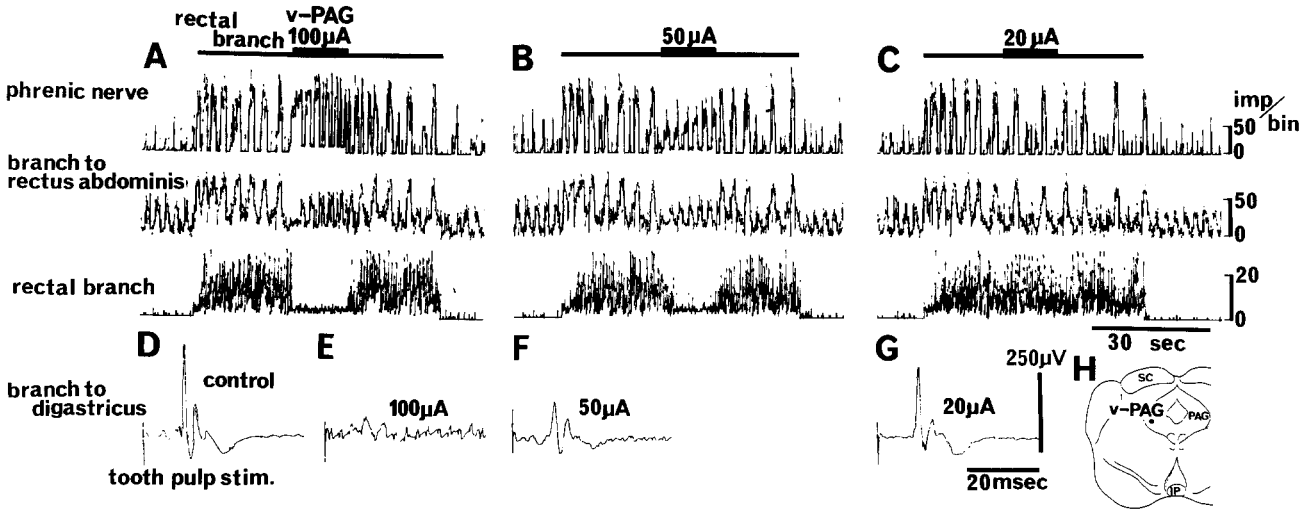

Fig. 4A–H. Intensity of midbrain stimulation required to inhibit the rhythmic straining, defecation and jaw-opening reflexes. **A–C** The point shown in **H** was stimulated with pulses of indicated intensities, 40 Hz and 0.5 ms during stimulation of right rectal branches. **D** Compound action potentials of a digastricus branch of the inferior alveolar nerve were elicited by single pulse stimulation of the pulp nerve of the left cuspid tooth of the inferior maxilla. The action potentials were averaged 30 times. **E–G** Compound action potentials of the digastricus branch were averaged similarly as in **D**, while the v-PAG was stimulated with the same pulses as in **A–C**

nerves by the midbrain stimulation usually did not last longer than the stimulation period and was much lower in frequency than the reflex discharges of these nerves (Table 1).

Thresholds and latencies in the inhibition of the pelvic nerve reflexes by midbrain stimulation

The intensity of midbrain stimulation required for inhibition of the pelvic nerve reflexes was examined in 4 dogs. In the dog shown in Fig. 4, the defecation and straining reflexes elicited by stimulation of the rectal branches were obviously inhibited by 100 μA (40 Hz, 0.5 ms) and 50 μA stimulation of the v-PAG (A, B), but inhibition by 20 μA stimulation was not so obvious (C). Consequently, 20 μA seems to be the threshold intensity for the inhibition of both reflexes. In the other three dogs, similar threshold intensities (20–30 μA, 0.5 ms, 40 Hz) were confirmed for inhibition of the micturition, defecation and rhythmic straining reflexes by v-PAG stimulation.

However, threshold intensities for the inhibition of individual reflexes differed from each other in some cases. The case shown in Fig. 5 was performed in the early stage of this work where the midbrain was stimulated with pulses of 5 ms duration. The micturition reflex elicited by stimulation (10 V, 10 Hz, 0.5 ms) of the vesical branches and rhythmic straining caused by stimulation (10 V, 10 Hz, 0.5 ms) of the rectal branches were inhibited by stimulation (10 Hz, 100 μA, 5 ms) of the CTF, but the defecation reflex elicited simultaneously with rhythmic straining was not effected by stimulation of the CTF (Fig. 5A, B). However, the defecation reflex caused by stimulation at 5 Hz was inhibited by the same CTF stimulation (C). In another experiment shown in Fig. 3, stimulation (10 Hz, 50 μA, 5 ms) of a point (Fig. 3F, c) in the CTF obviously inhibited rhythmic straining, but did not inhibit the micturition reflex (C, 1 and 2). Thus, the degree of inhibition was affected not only by intensity of the midbrain stimulation but also by the magnitude of the reflex activity.

Latencies (150–300 ms) of midbrain inhibitions of the micturition reflex were examined in 3 dogs. The latencies were measured on the averaged post-stimulus frequency histograms which were obtained as follows: discharges of the vesical branch in the reflex were inhibited by train-pulse stimulation (100 Hz, 2 ms, 50 or 100 μA, 4–10 pulses) of the CTF, d-PAG and v-PAG, and the post-stimulus frequency histograms (bins of 5 ms) were averaged 20 times.

The site in the reflex arcs at which midbrain stimulation inhibits the pelvic nerve reflexes

Three different experiments were performed to examine whether the midbrain inhibition of the pelvic nerve reflexes is executed in the spinal cord or in the brain stem.

In the first experiment, the effects of midbrain stimulation on activities of urethral and anal branches of the pudendal nerve in the micturition and defecation reflexes were examined in 2 dogs. No change in discharges of the urethral and anal branches appeared during inhibition of the defecation reflex by CTF, v-PAG and DR stimulation (Fig. 6A). However, when the micturition reflex was inhibited by the midbrain stimulation, the anal and urethral branches exhibited transient and long lasting discharges, respectively (C). Similar effects of stimulation of the 3 midbrain areas were confirmed in the other dog. The result indicates that the midbrain stimulation inhibits or disfacilitates the vesical parasympathetic neurons and reciprocally excites or disinhibits the sphincter motor

Table 1. Effects of midbrain stimulation on spontaneous discharge of the vesical branch, rectal branch, phrenic nerve and nerve to the rectus abdominis. ↑, enhancement. →, no effect. ↓, inhibition. T, total. Dog numbers are shown. Spont. dis., rates of spontaneous discharge (imp./bin; mean ±S.D.). Changed dis., rates changed by midbrain stimulation

Nerve	Vesical br.				Rectal br.				Phrenic n.				n. to rectus abd.			
Effects	↑	→	↓	T	↑	→	↓	T	↑	→	↓	T	↑	→	↓	T
v-PAG	2	10	0	12	3	9	0	12	7	5	0	12	1	9	2	12
d-PAG	2	1	0	3	0	1	0	1	3	0	0	3	2	2	1	5
DR	2	3	0	5	3	2	0	5	2	3	0	5	2	3	0	5
CTF	4	9	0	13	3	10	0	13	10	3	0	13	0	11	2	13
T	10	23	0	33	9	22	0	31	22	11	0	33	5	25	5	35
Spont. dis.	1.2±2.0				3.1±1.9				0.5±1.2				14.3±11.6		11.9±10.3	
Changed dis.	6.0±5.8				7.9±3.0				7.0±6.9				41.6±41.8		1.7± 0.9	

neurons. On the other hand, descending activities from the pontine micturition reflex center are known to exert converse effects on both the parasympathetic and sphincter neurons (Okada and Yamane 1974). Thus, the result may suggest that the midbrain stimulation decreases the descending activities from the pontine micturition reflex center, but does not directly inhibit the parasympathetic neurons. As a result, disfacilitation of the parasympathetic neurons and disinhibition of the sphincter motor neurons seem to be simultaneously induced.

In the second experiment, a 4-barreled electrode was initially inserted into the midbrain (Fig. 7K) and moved in 0.2 to 0.5 mm steps to seek the optimum points in the d-PAG, v-PAG, CTF and DR. At the optimum point, monopolar stimulation with each constituent electrode yielded nearly maximum inhibition of discharges of the vesical branch in the micturition reflex, which was elicited by stimulation of the contralateral vesical branches (Fig. 7A). Then, centrifugal discharges of the vesical branch were evoked by train-pulse stimulation of the left lateral funiculus at the C2 segment, and the post-stimulus frequency histograms (5 ms of bins) were averaged 30 times (Fig. 7C-1). The evoked discharges of the vesical branch were averaged again while one of the 4 midbrain points was stimulated with the same stimulus used to inhibiting the micturition reflex. The evoked discharges were not influenced by stimulation of the CTF (D-1), v-PAG (E-1), d-PAG (F-1) or DR (G-1).

The left half of the C2 segment was cut at the level caudal to the stimulating electrode (Fig. 7K). After the hemisection, discharges of the vesical branch in the micturition reflex decreased, but were still inhibited by midbrain stimulation (B). Train-pulse stimulation of the lateral funiculus evoked discharges of the vesical branch even after the hemisection, but the discharges decreased slightly (C-2). Stimulation of the 4 midbrain points did not affect the evoked discharges (D-2, E-2, F-2, G-2). Similar results were obtained in another dog.

This result suggests that the midbrain inhibition of the micturition reflex acts mostly at sites other than the pontine micturition reflex center (Barrington 1925; Okada and Yamane 1974) and the descending pathway including the spinal synaptic structures relaying the descending tract fibers to the parasympathetic preganglionic neurons.

In the third experiment, discharges of vesical and rectal branches in the micturition and defecation reflexes were first confirmed to be inhibited by v-PAG and CTF stimulation (Fig. 8A, B). Then effects of stimulation of the same sites in both areas on field potential changes in the C2 lateral funiculus due to stimulation of the pelvic nerve were examined (C,E). The field potential changes disappeared in the record averaged during stimulation of the two sites. Field potential changes were noted even after a hemisection of the left half of the C2 segment at a level rostral to the recording site (D). Midbrain stimulation at the two sites also almost completely inhibited the field potential changes after the hemisection. Similar results were obtained in 3 other dogs. In 2 of the 3 dogs, the CTF and v-PAG were stimulated on both sides with a 4-barreled electrode, and similar inhibition of the field

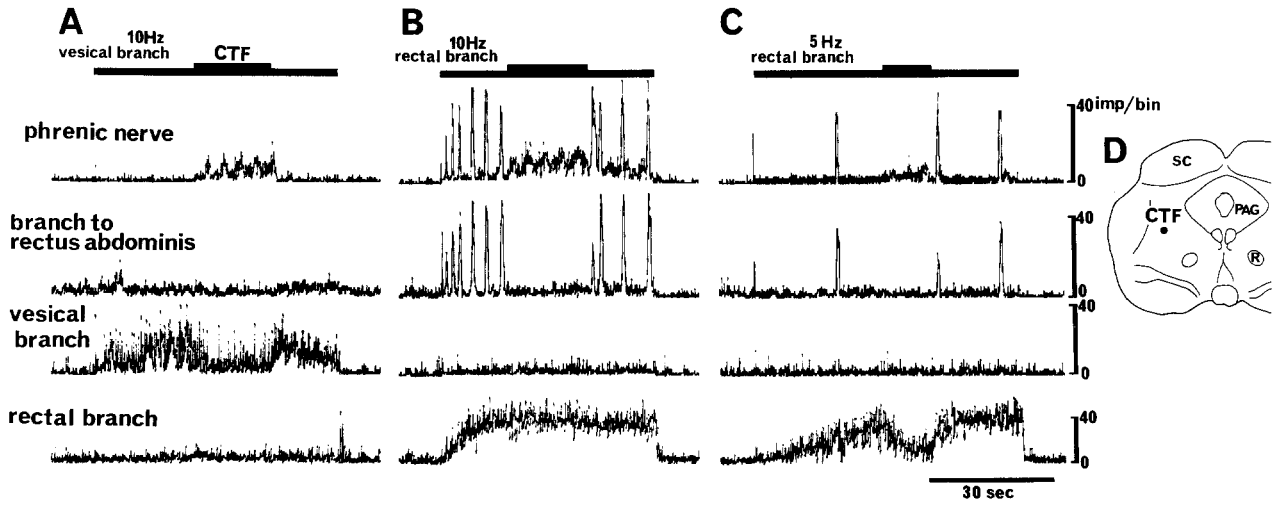

Fig. 5A–D. Effects of stimulation (10 Hz, 5 ms, 100 μA) of a point in the CTF (**D**) on the micturition (**A**), defecation and rhythmic straining (**B**, **C**) reflexes. **A**–**C** Central cut-ends of the indicated branches were stimulated with pulses of indicated frequencies, 0.5 ms and 10 V

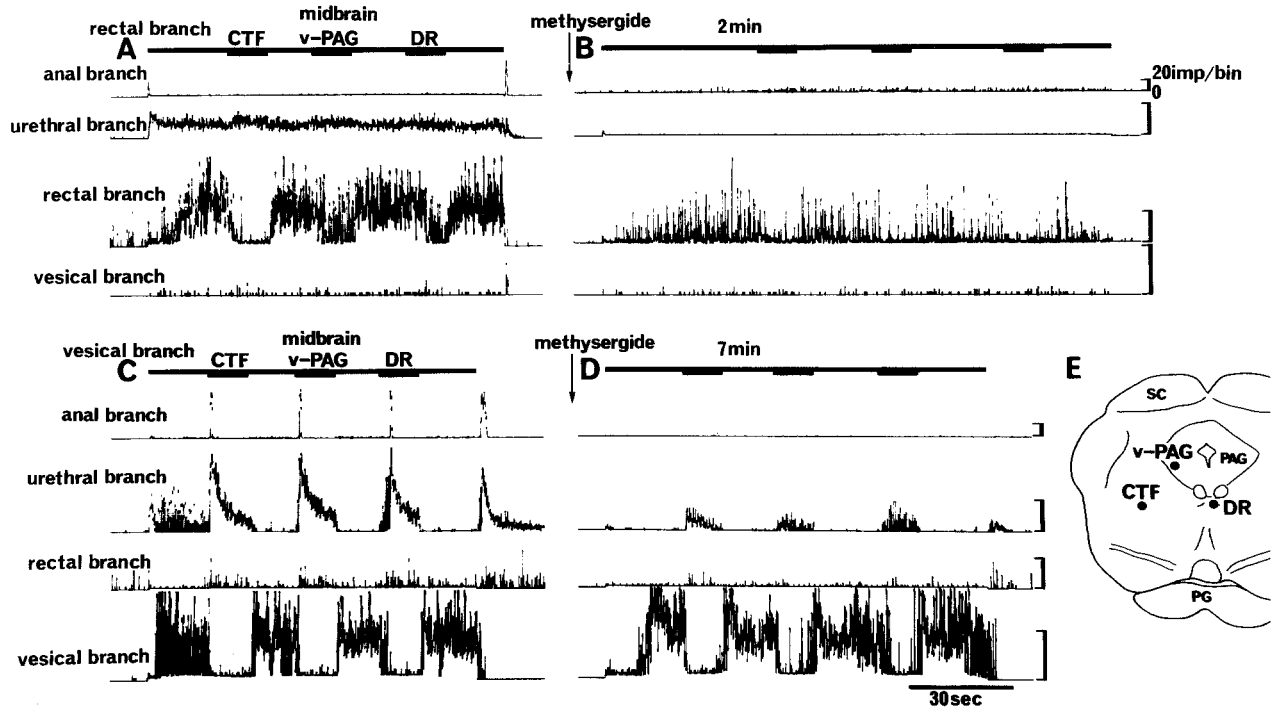

Fig. 6A–E. Activities of urethral and anal branches of the pudendal nerve during midbrain inhibition of the micturition (**C, D**) and defecation (**A, B**) reflexes and effects of methysergide on these activities (**B, D**). **A, B** Effects of stimulation of rectal branches. **C, D** Effects of stimulation of vesical branches. **A, C** Controls. Midbrain points indicated by v-PAG, CTF and DR in **E** were stimulated (40 Hz, 0.5 ms, 100 μA). **B, D** Traces recorded 2 and 7 min after injection (i.v.) of methysergide (3 mg/kg). The midbrain points were stimulated in the same order as in **A, C**

potential changes was confirmed by stimulation of either side of the CTF and v-PAG.

It may be concluded from this result that stimulation of the v-PAG and CTF interrupts ascending activities from pelvic afferent fibers at a spinal relay station. As the result, the pelvic nerve reflexes seem to be suppressed.

Comparison of midbrain inhibition of the pelvic nerve reflexes with stimulation produced analgesia (SPA)

Stimulation of the d-PAG, v-PAG, CTF and DR which inhibited the micturition, defecation and rhythmic straining reflexes also suppressed the jaw-opening reflex elicited

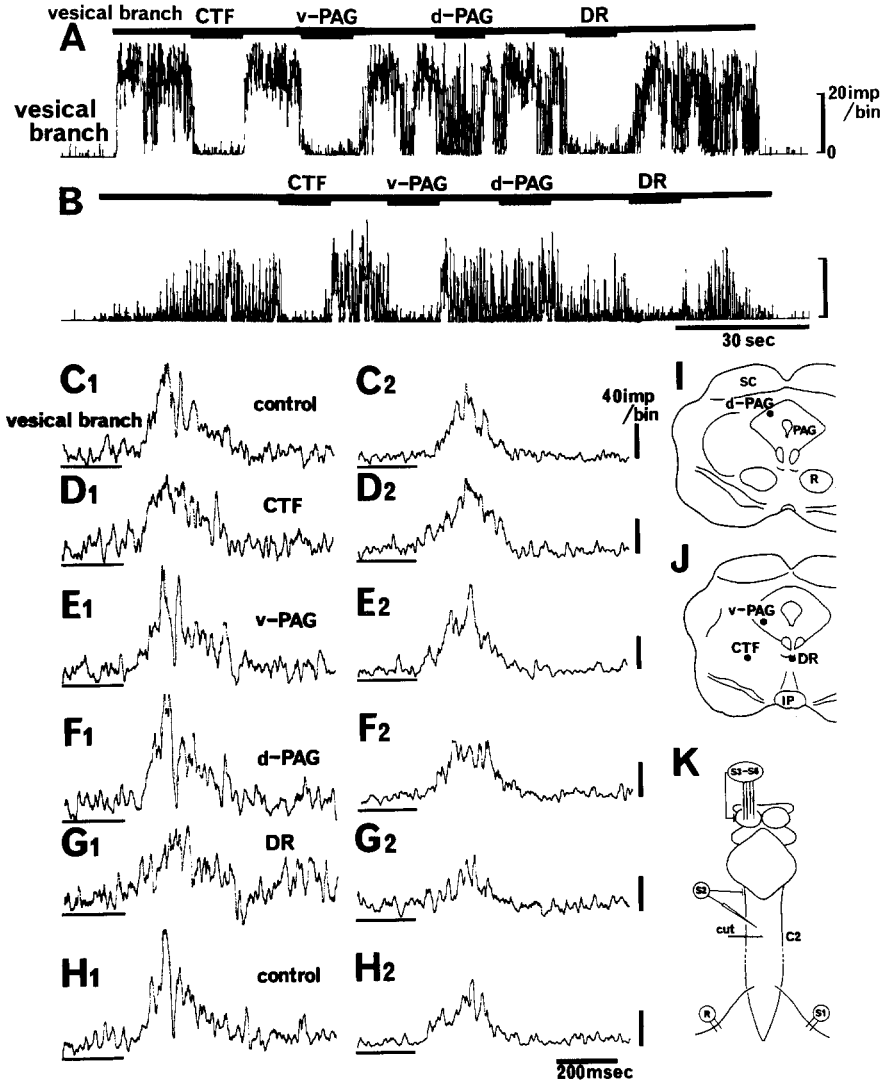

Fig. 7A–K. Effects of midbrain stimulation on discharges induced in a vesical branch by stimulation of the lateral funiculus at the C2 segment of the spinal cord. Arrangement of electrodes is shown in **K**. **A, B** Discharges of a left vesical branch during the micturition reflex elicited by stimulation (S1) of right vesical branches and their inhibition by midbrain stimulation (S3–S6; 40 Hz, 0.5 ms, 100 μA) at the points indicated in **I, J**. **A** Control. **B** A trace recorded 84 min after a hemisection of the C2 segment as indicated in **K**. **C1–H1, C2–H2** Discharges provoked in the vesical branch by train-pulse stimulation (S2; 100 Hz, 0.5 ms, 200 μA, 20 pulses and 1 Hz in repeating frequency) of the lateral funiculus at the point indicated in **K**. The discharges were averaged 30 times. **C1–H1** Traces recorded before the hemisection. **C2–H2** Traces recorded 5–60 min after the hemisection. **C1, C2, H1, H2** Control. **D1–G1, D2–G2** The discharges averaged during stimulation of indicated midbrain points with the same stimulus as in **A, B**. Horizontal lines under the initial part of each trace in **C–H** indicate the periods during which the lateral funiculus was stimulated

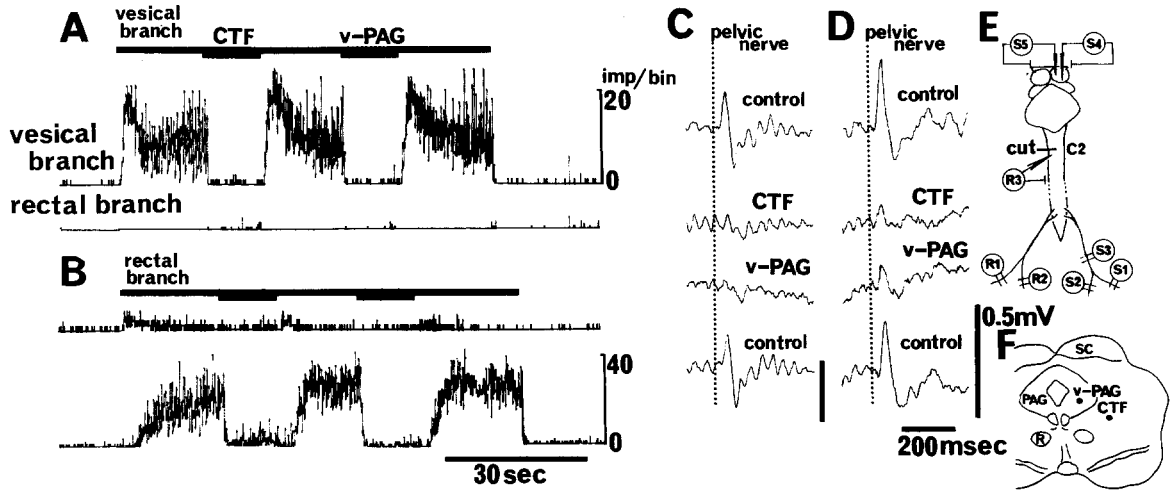

Fig. 8A–F. Effects of midbrain stimulation on field potential changes provoked in the lateral funiculus of C2 segment by stimulation of the stem of the pelvic nerve. Arrangement of electrodes is shown in **E**. **A, B** Effects of stimulation of vesical (S1) and rectal (S2) branches and their inhibition by stimulation (40 Hz, 0.5 ms, 100 μA) of the midbrain points (S4, S5) indicated in **F**. Both traces were recorded before hemisection of the spinal cord at the level just rostral to the electrode (R3 in **E**). **C, D** Field potential changes recorded from the lateral funiculus of the C2 segment with R3 after single pulse stimulation (S3; 0.5 Hz, 0.5 ms, 20 V) of the stem of the pelvic nerve. The potential changes were averaged 30 times before (**C**) and after (**D**) the hemisection. Top and bottom traces are controls. The middle 2 traces are of the potential changes averaged during stimulation of the indicated midbrain points with the same pulses as in **A, B**

Table 2. Effects of methysergide (2–3 mg/kg) and naloxone (2–3 mg/kg) on the micturition, defecation, rhythmic straining and jaw-opening reflexes, and on midbrain inhibition of the reflexes. Dog numbers in parentheses and mean ± S.D. are shown

A Effects of methysergide on firing rates of the vesical and rectal branches respectively in the micturition and defecation reflexes, frequencies of rhythmic straining, amplitudes of compound action potentials of the nerve to the digastricus in the jaw-opening reflex and latencies of the reflexes. Changes in the rates, frequencies and amplitudes are shown as: those after drug/those before drug × 100%. *, $p<5\%$. **, $p<1\%$

Reflex	Micturition			Defecation			Straining			Jaw-opening		
	cont.	no.	effect	cont.	no.	effect	cont.	no.	effect	cont.	no.	effect
Rate, freq. and amp. (%)	100	(16)	92.1 ± 29.8	100	(8)	58.6 ± 30.6**	100	(12)	104.1 ± 31.6	100	(11)	60.7 ± 26.3**
Latency (s)	3.1 ± 2.6	(16)	17.4 ± 8.6**	5.0 ± 4.1	(8)	8.2 ± 6.6**	5.6 ± 1.9	(12)	6.3 ± 4.4			
B Effects of naloxone on the reflexes												
Rate, freq. and amp.	100	(12)	121.3 ± 20.8**	100	(6)	53.3 ± 32.4*	100	(11)	127.0 ± 27.2**	100	(10)	96.3 ± 13.5
Latency (s)	9.1 ± 8.2	(12)	4.0 ± 3.4**	4.7 ± 4.9	(7)	9.2 ± 13.8*	6.7 ± 4.0	(11)	4.4 ± 1.9			
C Effects of methysergide on midbrain inhibition of the reflexes. Percentage reductions by midbrain stimulation observed before and after the drug in the rate, freq. and amp. are shown as: (1-reduced ones/control ones) × 100%												
v-PAG	73.2 ± 11.5	(10)	73.3 ± 7.7	59.5 ± 16.4	(8)	61.6 ± 17.4	78.7 ± 3.7	(6)	78.8 ± 4.1	72.9 ± 21.2	(5)	21.0 ± 33.7*
d-PAG	57.2 ± 17.6	(9)	54.7 ± 20.6				80.6 ± 2.7	(5)	77.4 ± 2.5	62.3 ± 32.0	(4)	32.4 ± 23.0*
DR	67.6 ± 8.0	(8)	73.8 ± 10.7	54.2 ± 8.7	(5)	60.0 ± 9.8	77.7 ± 6.4	(6)	76.5 ± 7.7	60.9 ± 14.4	(5)	22.3 ± 11.8*
CTF	72.1 ± 5.5	(10)	57.9 ± 9.8	65.0 ± 13.4	(8)	62.6 ± 15.7	80.2 ± 2.7	(6)	75.8 ± 5.2	78.3 ± 19.8	(5)	33.5 ± 46.5*
D Effects of naloxone on midbrain inhibition of the reflexes												
v-PAG	68.6 ± 15.0	(5)	62.0 ± 17.8	50.7 ± 35.2	(3)	52.7 ± 19.7	69.6 ± 11.7	(6)	76.8 ± 7.3	65.6 ± 26.4	(5)	53.4 ± 20.3
d-PAG	69.0 ± 9.0	(6)	65.2 ± 8.4				82.7 ± 2.3	(3)	85.3 ± 1.5	25.7 ± 26.9	(3)	65.6 ± 18.0
DR	64.5 ± 25.5	(6)	64.3 ± 20.3				78.7 ± 4.9	(3)	78.7 ± 6.7	48.3 ± 39.1	(3)	64.8 ± 17.9
CTF	72.8 ± 15.5	(5)	72.4 ± 9.8				73.8 ± 13.0	(5)	80.6 ± 3.2	44.4 ± 23.5	(3)	43.7 ± 37.4

by tooth pulp stimulation (Figs. 4, 9–10). Similar threshold intensities of 20–30 μA for inhibition of the pelvic nerve reflexes and the jaw-opening reflex by v-PAG stimulation were confirmed in 4 dogs (Fig. 4).

Effects of methysergide (2 or 3 mg/kg, i.v.) and naloxone (2 or 3 mg/kg, i.v.) on the reflexes and their midbrain inhibition were examined in 20 dogs (Table 2). The intensities of the reflexes and the degree of their midbrain inhibition were determined similarly as shown in Figs. 1 and 3. Then, effects of the drugs were evaluated by comparison of the means of the intensities and degrees of inhibition obtained in two control trials performed before the injection of the drug with the means obtained in two test trials carried out from 5 to 10 min and from 20 to 30 min, respectively, after the injection.

Methysergide significantly decreased the frequency of rectal branch discharges in the defecation reflex, reduced the amplitude of compound action potentials of the nerve to the digastricus in the jaw-opening reflex, and extended delays in starts of reflex discharges of the vesical and rectal branches after stimulation of the contralateral homonymous branches (Fig. 9, Table 2A). Furthermore, the drug almost completely inhibited discharges of urethral and anal branches of the pudendal nerve which occurred while the micturition reflex was inhibited by midbrain stimulation (Fig. 6). However, the intensity of the micturition reflex and frequency of rhythmic straining were not influenced by the drug (Fig. 9, Table 2A).

Midbrain inhibition of the micturition, defecation and rhythmic straining reflexes was not affected by methysergide (Fig. 9B, D), but the inhibition of the jaw-opening reflex was significantly decreased (Fig. 9F, Table 2C). The effects of methysergide on the midbrain inhibition did not depend on which midbrain structure was stimulated. All effects of methysergide disappeared 1.5–2 h after the injection.

Naloxone significantly enhanced the micturition (Fig. 10D–F) and rhythmic straining (A–C) reflexes and suppressed the defecation reflex (not shown), but did not influence the jaw-opening reflex (G–J; Table 2B). In many dogs, small discharges of the vesical branch were elicited by stimulation of the contralateral rectal branches during the initial 5–30 s of the stimulating period (Fig. 10A), but thereafter the discharges disappeared and discharges of the rectal branch appeared (not shown in A, see Fig. 8B). The discharges of the vesical branch were also enhanced by naloxone (Fig. 10B, C). Stimulation of vesical branches at a frequency of less than 10 Hz usually did not elicit rhythmic

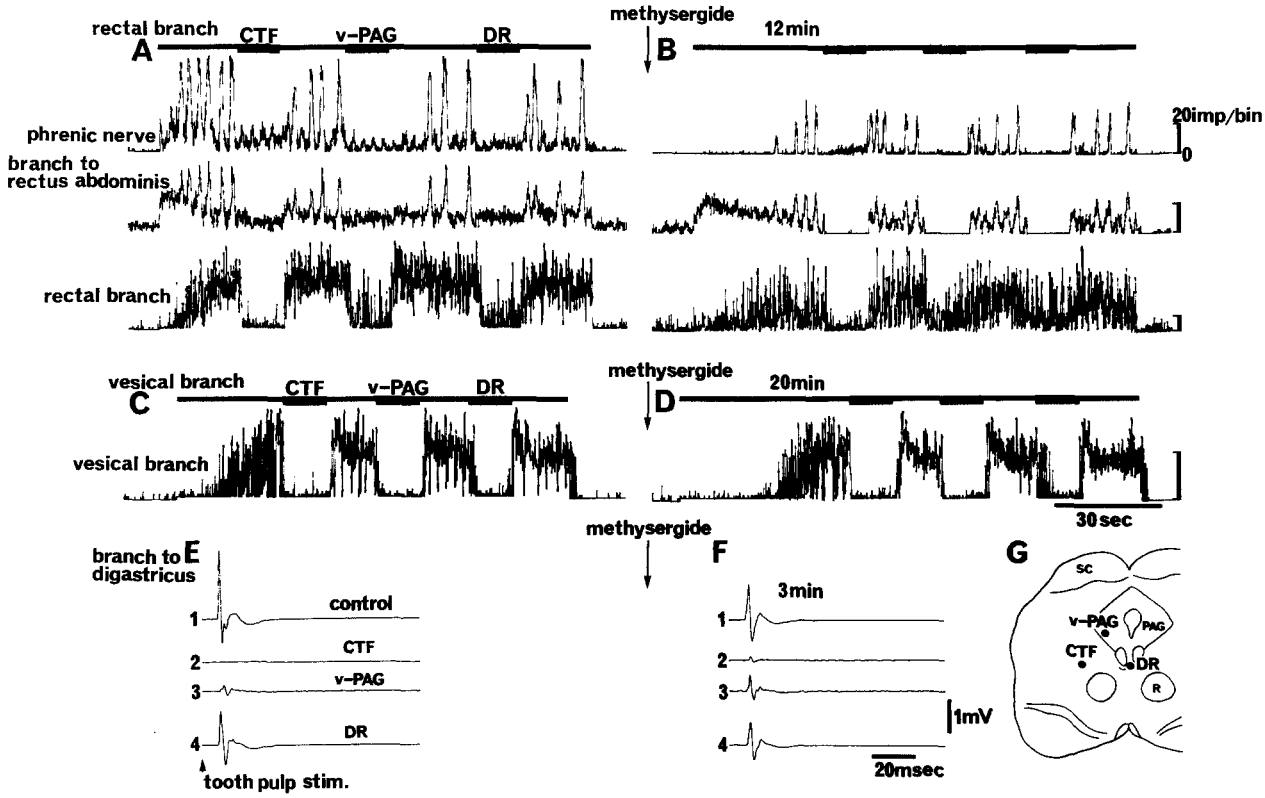

Fig. 9A–G. Effects of methysergide on midbrain inhibition of the micturition, defecation, rhythmic straining and jaw-opening reflexes. **A, B** Effects of stimulation of rectal branches and their inhibition by midbrain stimulation (40 Hz, 0.5 ms, 150 μA) at the points indicated in **G**. Traces were recorded before (**A**) and 12 min after (**B**) injection of methysergide (2 mg/kg, i.v.). **C, D** Effects of stimulation of vesical branches and their inhibition by midbrain stimulation at the same points with the same pulses as in **A, B**. Traces in **D** were recorded 20 min after the injection of methysergide. **E, F** Compound action potentials provoked in a digastricus branch of the inferior alveolar nerve by stimulation (1 Hz, 0.5 ms, 30 V) of the left cuspid tooth pulp. The potentials were averaged 10 times. 1: control. 2–4: the potentials averaged during midbrain stimulation at the same points with the same pulses as in **A–D**. **F** Traces recorded 3–10 min after the injection of methysergide

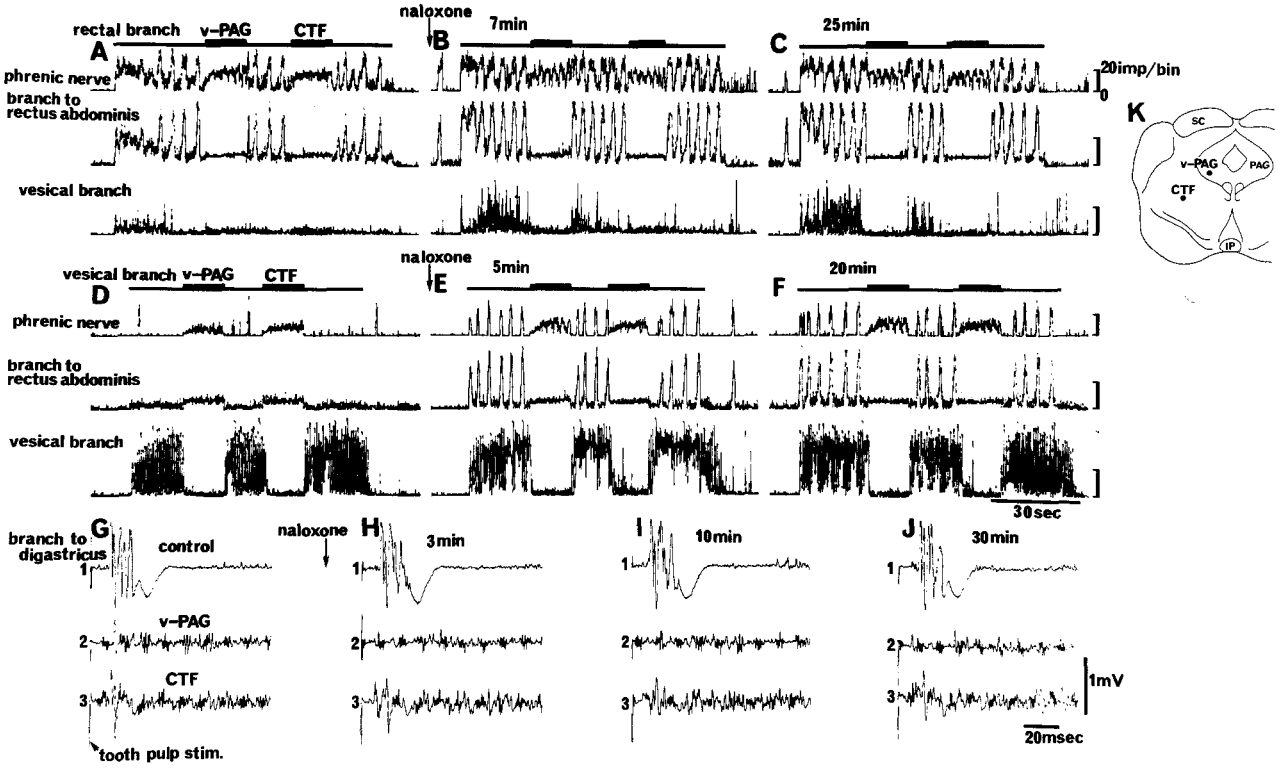

Fig. 10A–K. Effects of naloxone on midbrain inhibition of the micturition, rhythmic straining and jaw-opening reflexes. **A–C** Effects of stimulation of rectal branches and their inhibition by stimulation (40 Hz, 0.5 ms, 75 μA) of the midbrain points indicated in **K. D–F** Effects of stimulation of vesical branches and their inhibition by stimulation of the same midbrain points with the same pulses as in **A–C. G–J** Compound action potentials evoked in a digastricus branch of the inferior alveolar nerve by stimulation (1 Hz, 0.5 ms, 30V) of the left cuspid tooth pulp. 1: controls. 2, 3: their inhibition by midbrain stimulation at the same points with the same pulses as in **A–F. A, D, G** Traces recorded before injection of naloxone (2 mg/kg, i.v.). **B, C, E, F, H–J** Traces recorded various times after the injection of naloxone

straining (D), but it did after administration of naloxone (E, F).

Naloxone did not influence midbrain inhibition of the micturition, defecation, rhythmic straining or jaw-opening reflexes (Fig. 10, Table 2D). Effects of naloxone on midbrain inhibition of the defecation reflex could not be examined in many cases, since naloxone usually produced almost complete inhibition of the reflex.

Discussion

The results of the present work show that stimulation of the v-PAG, d-PAG, CTF and DR in the midbrain inhibits the micturition, defecation and rhythmic straining reflexes. Since inhibition produced by stimulation of one point often was not produced by stimulation of an adjacent point while advancing the electrode in steps of 1 mm, the effective radius of the stimulation (50 μA, 5 ms, 10 Hz) was probably less than 1 mm in this mapping experiment. In the later experiments, the reflexes were inhibited as shown in Fig. 7 by successive monopolar stimulation of the 4 midbrain areas with a 4-barreled electrode whose constituent electrode tips were previously fixed in the relative positions of the 4 inhibitory areas in accordance with the maps presented in Fig. 2. Thus, the maps in Fig. 2 appear to show the correct positions and extent of the 4 midbrain inhibitory areas. Effects of the secondary reflexes caused by centripetal impulses from the contracted effector organs would not be expected to be involved in the inhibition, since the dogs were paralyzed and vesical and rectal branches of the pelvic and hypogastric nerves were completely severed.

The inhibitory area in the CTF seems to correspond to the area where destruction facilitates the micturition reflex (Tang and Ruch 1956) and consequently where stimulation inhibits vesical contraction (Gjone 1966; Kabat et al. 1936; Koyama et al. 1962) and colorectal movements (Rostad 1973). DR stimulation causing inhibition of the pelvic nerve reflexes is consistent with the report that DR stimulation inhibits discharges of sacral cord neurons induced by colorectal distention in rats (Gebhart and Ness 1986). The inhibition by v- and d-PAG stimulation may be consistent with inhibition of the micturition reflex due to stimulation of the raphe magnus nucleus (McMahon and Spillane 1982), since the nucleus is known to receive afferents from the PAG (Besson and Chaouch 1987). Thus, it may be concluded that stimulation of the v-PAG, d-PAG, CTF and DR inhibits the micturition, defecation and rhythmic straining reflexes.

Despite a hemisection of the spinal cord at the C2 segment, stimulation of the midbrain suppressed the micturition reflex and field potential changes induced in the lateral funiculus just caudal to the hemisection by stimulation of the whole pelvic nerve. However, stimulation of the midbrain did not influence the discharges provoked in the vesical branch of the pelvic nerve by stimulation of the lateral funiculus at a site just rostral to the hemisection (Figs. 7 and 8). The results indicate that stimulation of the midbrain interrupts ascending impulses from pelvic nerve afferents at the spinal level, thereby inhibiting the pelvic nerve reflexes. Consequently, the results may correspond with the observation that responses of the sacral cord neurons to distention of the rectum and/or bladder are inhibited by stimulation of the nucleus raphe magnus in cats (Lumb 1986; McMahon et al. 1982) and by stimulation of the DR and nucleus raphe magnus in rats (Ness and Gebhart 1987a).

However, stimulation of the PAG has been shown to enhance vesical contraction (Gjone 1966) and colorectal movements (Rostad 1973) in cats. Similarly, spontaneous discharges of vesical and rectal branches were enhanced sometimes in the present work by midbrain stimulation, which was confirmed to inhibit both the micturition and defecation reflexes (Table 1). Consequently, neural elements enhancing and suppressing vesical and colorectal movements may coexist in the midbrain areas and work in different manners in different situations of animals.

Comparison of the midbrain inhibition of the pelvic nerve reflexes with SPA

The areas in the d-PAG, v-PAG, DR and CTF which inhibit the pelvic nerve reflexes correspond to areas in which stimulation has been shown to produce analgesia (SPA) (Dostrovsky et al. 1982; Fardin et al. 1984; Fields and Heinricher 1985; Oliveras et al. 1974; Oliveras et al. 1979) (see also rev. by Besson and Chaouch 1987). The jaw-opening reflex elicited by stimulation of the tooth pulp, which is known to be innervated by nociceptive fibers alone (see rev. by Mason et al. 1985), is also inhibited by stimulation of SPA areas in the midbrain (Dostrovsky et al. 1982). In the present study, compound action potentials of the nerve to the digastricus in response to tooth pulp stimulation (jaw-opening reflex) were inhibited by d-PAG, v-PAG, CTF and DR stimulation, which was confirmed to suppress the micturition, defecation and rhythmic straining reflexes. Moreover, comparable threshold intensities (20–30 μA) were observed in the inhibition of the pelvic nerve reflexes and jaw-opening reflex by stimulation of the v-PAG of some dogs. Similarly, McMahon and Spillane (1982) demonstrated that the micturition reflex is inhibited by stimulation of the raphe magnus nucleus which is well known to exert SPA. Thus, all the SPA areas examined are confirmed to suppress the pelvic nerve reflexes, although the SPA neural elements in these SPA areas seem to work in different ways as mentioned in the last section of this discussion. Consequently, a common neuronal mechanism is reasonably supposed to underlie the phenomenon that activation of the many SPA areas causes a common effect, i.e., simultaneous suppression of nociception and the pelvic nerve reflexes.

On the other hand, Jänig and Morrison (1986) offered the intensity theory of visceral nociception which postulates that both noxious and innocuous events in the visceral domain are encoded by the intensity of the discharges of the same population of visceral afferents. If pelvic nerve afferents consist of the same kind of afferent fibers as emphasized by the intensity theory, inhibition of the pelvic nerve reflexes by the SPA neural elements in the many SPA areas seems very reasonable, since stimulation of the SPA elements should suppress ascending activities from the same kind of pelvic nerve afferents which encode both noxious and innocuous events, and consequently would inhibit nociception of the pelvic organs as well as the pelvic nerve reflexes. However, this assumption must be confirmed with further studies, since this study indicated that midbrain inhibition of the jaw-opening reflex is mediated at least partially by serotonin which is not involved in midbrain inhibition of the pelvic nerve reflexes.

SPA is thought to be mediated by endogenous opioid peptides (Adamus 1976; Fields and Anderson 1978; Hosobuchi et al. 1977; Tanaka and Toda 1982), serotonin (Carstens et al. 1981; Yezierski et al. 1982) and/or other substances (see rev. of Besson and Chaouch 1987; Duggan 1985; Fields and Heinricher 1985). We found that methysergide partially but significantly decreased the midbrain inhibition of the jaw-opening reflex, while neither it nor naloxone influenced midbrain inhibition of the micturition, defecation and rhythmic straining reflexes. These results indicate that the SPA caused by midbrain stimulation of dogs is mediated at least in part by serotonergic descending pathways. In contrasts midbrain inhibition of the pelvic nerve reflexes is mediated by transmitter(s) other than serotonin and the opioids antagonized by naloxone as shown in some studies of SPA (see rev. of Besson and Chaouch 1987; Duggan 1985; Fields and Heinricher 1985).

However, application of naloxone enhanced the micturition and rhythmic straining reflexes, but in contrast, suppressed the defecation reflex in this study. The enhancement of the micturition reflex by naloxone has been shown in cats (Roppolo et al. 1983). Moreover, intrathecally and intracerebroventricularly applied opioid peptides were reported to inhibit the micturition reflex (Hisamitsu and de Groat 1984). These observations indicate that the rhythmic straining and micturition reflexes are under inhibitory control exerted by some structures in the neuraxis lower than the midbrain and mediated by endogenous opioids. The suppression of the defecation reflex by naloxone seems to be caused at least partially by the enhancement of the micturition reflex, since reciprocal inhibitory connections exist between both the reflex arcs (Floyd et al. 1982; Fukuda et al. 1983; de Groat et al. 1982).

Possible roles of the midbrain inhibition of the pelvic nerve reflexes

Electrical stimulation of the midbrain reticular formation and also natural stimulation that produces arousal and

behavioral alertness are well known to exert stereotyped variations in somato-vegetative functions, such as EEG arousal, acceleration of cardiac and respiratory rhythms, facilitation of monosynaptic reflexes and inhibition of the jaw-opening reflex and other polysynaptic reflexes induced by noxious stimulation (Hugelin 1972; Hugelin and Cohen 1963; Willer and Albe-Fessard 1980). The reticular activating area in the caudal midbrain corresponds with the portion (CTF) in the midbrain tegmentum where stimulation inhibited the pelvic nerve reflexes and the jaw-opening reflex in this work. Thus, we speculate that the CTF inhibits micturition and defecation while the animal is alert to prepare body for subsequent motion.

Stimulation of the PAG elicits piloerection, vocalization and integrated flight and attack in cats, monkeys and rats (Bandler 1982; Hunsperger 1956; Nakao et al. 1968; Fardin et al. 1984). Production of lesions in the PAG abolishes the defensive reactions of cats (Hunsperger 1956) and rats (Edwards and Adams 1974; Liebman et al. 1970). In the present work, stimulation of the PAG inhibited the pelvic nerve reflexes. Consequently, it may be supposed that PAG acts to suppress micturition and defecation during defensive reactions.

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