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Excitation of certain posterolateral hypothalamic units by cyclopropane and ether

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Summary

1. Extracellular activity was recorded from single units in the posterolateral hypothalamus in nineteen cats before, during, and after the administration of the inhalation anaesthetics cyclopropane, diethyl ether and halothane.

2. Unit discharge was significantly increased by 25–50% cyclopropane in eighteen of the forty-four cells tested with this anaesthetic, and in seven of fourteen cells tested with diethyl ether. This excitatory effect was associated with cortical EEG suppression.

3. The remaining cells tested were depressed by cyclopropane or ether, and this also occurred during halothane administration.

4. Excitation of certain cells in the posterolateral hypothalamus is discussed in relation to the increased preganglionic sympathetic activity evoked by cyclopropane and ether.

Introduction

Increased sympathetic activity, inferred from raised plasma catecholamine concentrations in man (Price, Linde, Jones, Black & Price, 1959) has been demonstrated by direct recording of preganglionic impulse discharge in rabbits and cats during the administration of cyclopropane or diethyl ether (Millar & Biscoe, 1965 ; Price, Warden, Cooperman & Millar, 1969). It was possible, in these studies, to attribute sympathetic excitation by lower concentrations of cyclopropane to pharmacological suppression of afferent baroceptor pathways (Biscoe & Millar, 1966), but this explanation could not account for the increased preganglionic discharge measured when high cyclopropane concentrations were given to cats in which all the baroceptor nerves had previously been divided. The possibility existed, therefore, that cyclopropane, or other agents with similar effects (for example, diethyl ether), could exert direct excitant actions in areas of the central nervous system concerned with efferent sympathetic control.

It is well known that electrical stimulation of the posterolateral hypothalamic area increases peripheral sympathetic activity (Pitts, Larrabee & Bronk, 1941), and causes a cardiovascular pressor response (Manning & Peiss, 1960), similar to that evoked by hypoxia or hypercapnia (Cross & Silver, 1963). We have, therefore, sought an

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answer to the question whether certain general anaesthetics might increase the discharge rate of single neurones in the posterolateral hypothalamus.

Methods

Experiments were carried out on cats of both sexes weighing 2·5–4·5 kg. Anaesthesia was induced using a halothane/oxygen mixture administered through a face mask. Cannulae were inserted into one femoral artery and one femoral vein, and into the trachea. Warm chloralose solution (40 mg/kg) was then injected intravenously and the halothane administration was discontinued. Mechanical ventilation was started using a Palmer respiration pump, end-tidal CO_2 concentration being monitored in the range 3·5–5·0% by means of a Beckman infrared CO_2 analyser sampling from the trachea. Gallamine triethiodide (4 mg/kg) was given intravenously at intervals of about 45 minutes.

The animal's head was placed in a Baltimore stereotaxic instrument. After reflecting the skin on the scalp, two holes were drilled in the frontal bone on each side of the mid-line to allow insertion of microelectrodes into the hypothalamus. The dura was excised from the brain surface and the holes were sealed with warm bone wax. A stainless steel EEG electrode was inserted through a separate small hole into the frontal cortex.

Tungsten and stainless steel microelectrodes with tip sizes of 0·5–3·0 μm were prepared by electropolishing, and were mounted in the micro-manipulator of the

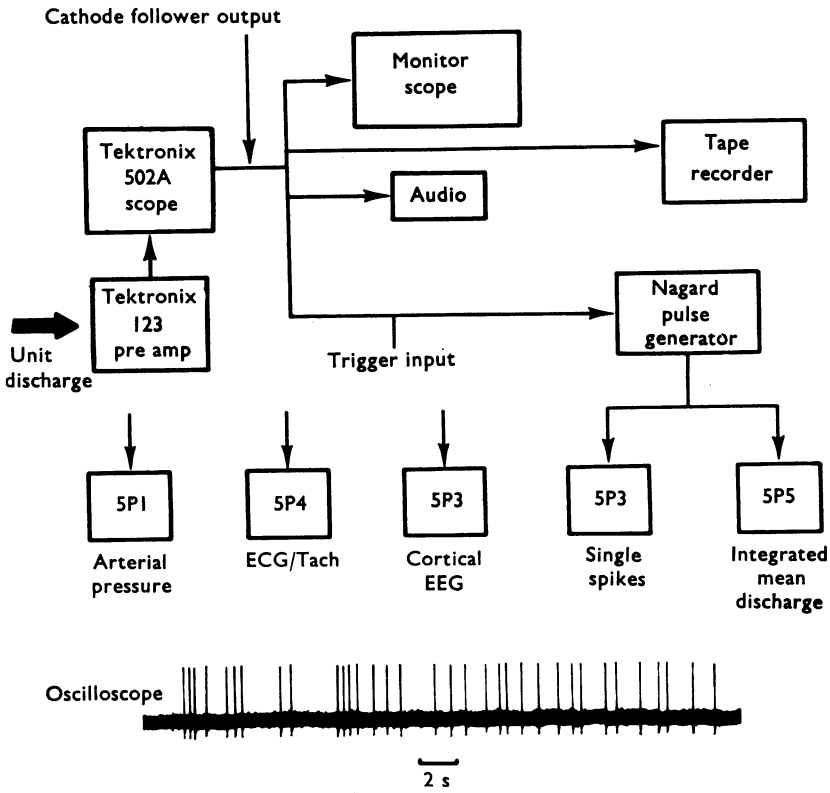

FIG. 1. Scheme of apparatus used for recording the discharge of single cells in the posterolateral hypothalamus. A film strip from the oscilloscope is shown below.

stereotaxic instrument and placed in the diencephalon using stereotaxic Horsley-Clarke coordinates. The lateral hypothalamic area is situated 20–25 mm below the brain surface, 2–3·5 mm lateral to the midline, and 10·5–12·0 mm anterior to the interaural plane. The atlas used was by Jasper & Ajmone-Marsan (1954).

Action potentials from single units were fed to a Tektronix 123 preamplifier and thence to a Tektronix 502A oscilloscope. The cathode follower output from this was fed in parallel to a large monitor screen (Airmec Ltd., Model 383), to an audio unit and to the trigger input of a Nagard pulse generator. The output from the pulse generator was fed in parallel to an EEG preamplifier (Grass 5P3) for recording individual action potentials, and to an integrator preamplifier (Grass 5P5) for recording units that were too fast to record satisfactorily as individual spikes. The outputs from these preamplifiers drove pens on a Model 5 Grass Polygraph.

The EEG electrode was connected to a Grass 5P1 preamplifier, and subcutaneous needle electrodes in right fore and left hind limb (E.C.G. Lead 2) were used to drive a 5P4 ECG/tachograph preamplifier. Arterial pressure (1 mmHg≡1.333 mbar) was recorded via the femoral cannula using a Statham P23AC transducer connected to a Grass 5P1 preamplifier. A schematic diagram of the apparatus used, and an oscilloscope trace illustrating the discharge of a single hypothalamic unit are shown in Fig. 1.

Oxygen and cyclopropane were delivered from a Boyle's apparatus and halothane from a calibrated Fluotec (Cyprane Ltd.). Ether was vaporized by passing a 2 l. oxygen flow across 100 ml liquid contained in a Boyle ether bottle. The outflow from the Palmer pump was discharged through an outside window in order to minimize explosion risks.

At the end of an experiment the animal was killed with intravenous sodium pentobarbitone. The electrodes were left in their final site or in a position which had given valuable recordings. A small lesion was made by passing a direct current of 3–5 μA for 10 s through the electrode. The carotid arteries were isolated and 20 ml of 10% formal saline was injected into each vessel. The jugular veins were cut to allow escape of blood and perfusion fluid. If stainless steel electrodes were used potassium ferrocyanide was added to the perfusion fluid to produce a Prussian Blue spot at the lesion site. After perfusion the animal was left in the head holder for a few hours with the electrodes *in situ*. These were then removed, and the brain was taken out of the skull and placed in formal saline to complete the fixation process. It was then trimmed and arranged on a freezing microtome so that the sections were cut in the plane of the electrode track. Serial sections of the experimental area were cut, mounted and stained with cresyl violet, and the electrode tracks and positions of cells were subsequently identified.

Results

Cyclopropane

This anaesthetic was studied most frequently, for two reasons: first, its pharmacological effects include preganglionic sympathetic excitation (Price *et al.*, 1969), which might be related to effects exerted on hypothalamic neurones; second, its rapid uptake and elimination shortened the necessary period over which optimal recording conditions had to be maintained. The effects of 25 or 50% cyclopropane were studied on a total of forty-five cells in the posterolateral hypothalamus in sixteen cats.

Cyclopropane increased the discharge rate in eighteen cells (that is, 40%); the data are given in Table 1. Comparison of the firing rate during cyclopropane administration with the average of the before and after control levels shows that there was a mean increase of thirteen impulses/s (S.E. $\pm 1{\cdot}71$, $P<0{\cdot}001$). Table 1 refers to the effects of a single administration of the inhalation anaesthetic on individual cells; however, these excitatory effects were reproduced on a second administration in two cells (N2, S2 of Table 1), and three occasions in another two cells (C1 and E2). The increased discharge was also demonstrated on more than one hypothalamic cell in four of the eleven experiments.

Excitation by cyclopropane was usually pronounced; the single exception (G3 of Table 1) is included because the effects of cyclopropane may have occurred in association with a declining level of spontaneous activity, shown by the slower discharge rate after recovery.

Measurements during recovery from cyclopropane were always sought at times corresponding to within 2 min of the duration of its administration, and this was possible in twelve of the eighteen tests; in the remainder, a delayed recovery, or a deterioration in the recording conditions, were responsible for differences between the periods on and off cyclopropane shown in Table 1. The mean of the before and after cyclopropane control measurements showed clearly that the increased hypothalamic discharge rates could not be explained on the grounds of a slow 'spontaneous' rise in activity of the cells.

Figure 2 illustrates the increased firing rate of a single posterolateral hypothalamic cell during three consecutive administrations of cyclopropane; recovery occurred satisfactorily after the first and second tests, the cell being lost after the final administration. Mean arterial pressure increased during the first exposure, and showed small reductions subsequently.

TABLE 1. *Responses from eighteen single cells in the posterolateral hypothalamus, in eleven cats showing an increased discharge level during cyclopropane administration*

Experiment and cell number	Cell position (mm)			Duration of administration (min)	Concentration %	Discharge rate		Recovery	
	Ant.	Lat.	Depth			Control	Cyclopropane	Discharge rate	Time (min)
B 3	11·5	3·0	22·8	10	25	3·9	8·0	1·2	12
C 1	11·5	3·5	20·4	18	25–50	9·5	35	10	11
D 1	11·5	3·5	22·5	12	50	7/min	9·5	2·3	4
2			23·2	3	50	17	35	22	5
3			24·6	3	50	18/min	7·5	1·2	4
8			22·0	7	50	16	33	15	8
E 2	11·5	3·5	22·8	11	50	6·3	14	8	11
G 1	11·5	3·0	22·0	12	50	12	23	19	12
3	11·5	3·5	23·0	11	50	4·2	4·5	24/min	7
N 2	10·5	2·0	22·1	6	50	2·0	18	1·8	10
3	12·0	3·0	21·4	6	50	6·8	23	12	4
7	10·5	2·0	21·7	11	50	10	22	12	11
O 1	11·5	3·5	22·2	6	50	19	41	22	8
P 3	12·0	3·5	23·8	9	50	7·5	32	7·2	14
Q 3	10·5	2·5	21·5	13	50	5·5	31	6·8	13
R 2	10·5	2·5	23·1	13	50	11	20	9·2	13
S 2	11·5	3·3	22·6	7	50	4·2	9·8	5·0	12
3	11·5	3·3	23·6	5	50	24	43	12	7

Except for the '/min' figures, the discharge rates refer to impulses/second. The anterior and lateral coordinates and the depth of each cell are shown. All cells were within the lateral hypothalamic area; B 3, D 2 and D 3 bordered on the perifornical area.

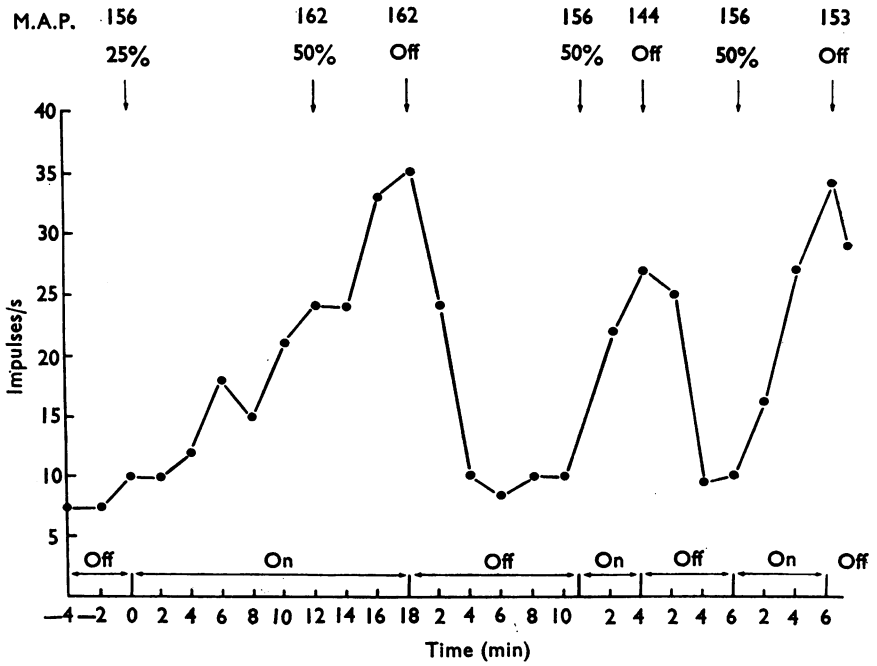

FIG. 2. Excitatory effects on a single posterolateral hypothalamic cell during three consecutive administrations of cyclopropane, with intervals for recovery. Sequence: 25% cyclopropane for 12 min followed by 50% cyclopropane for a further 6 min; recovery for 11 min; 50% cyclopropane for 4 min; recovery for 6 min; 50% cyclopropane for 6 minutes. The upper figures (M.A.P.) refer to mean arterial pressure (mmHg).

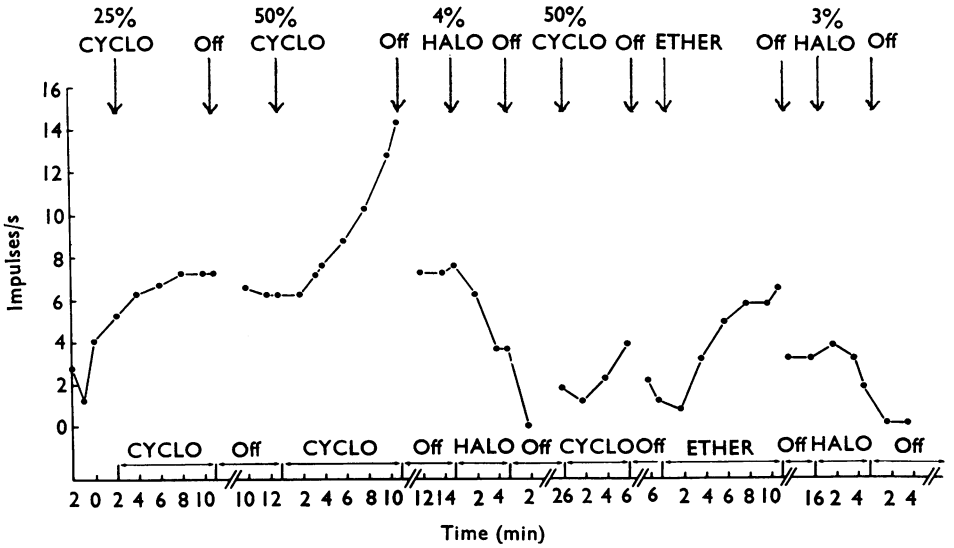

FIG. 3. Effects of the three inhalation anaesthetics on a single cell in the posterolateral hypothalamus. Sequence: 25% cyclopropane for 11 min: excitation; recovery for 13 min; 50% cyclopropane for 11 min: excitation; recovery for 15 min; 4% halothane for 5 min: depression; recovery for 26 minutes; 50% cyclopropane for 6 min; excitation; recovery for 7 min; ether for 11 min; excitation; recovery for 16 min; 3% halothane for 5 min; depression.

Figure 3 shows the data obtained from the study of a single cell over a period of about 2 h during which satisfactory recording conditions were maintained and all three inhalation anaesthetics were given; on three separate occasions cyclopropane increased the discharge rate.

A decreased discharge rate occurred during cyclopropane administration in twenty-six cells in the posterolateral hypothalamus (that is, 58%) of thirteen cats (Table 2); in ten instances the activity was abolished. The mean fall in firing rate (related to the average of the before and after control values) was by five impulses/s (S.E. $\pm 1{\cdot}31$, $P<0{\cdot}001$). There was no evidence that early inhibition of activity was followed by excitation, so that administration of cyclopropane was usually stopped whenever the discharge rate was depressed; the period of administration averaged 5 min (Table 2), and the mean recovery time was 6 minutes. In fifteen of the twenty-six tests (58%) the discharge rate did not recover to near the preadministration level, which was exceeded in only three instances after recovery from cyclopropane. This contrasts with the excitation effects listed in Table 1, after which only three cells (17%) failed to recover to near the initial control, and the discharge rate recovered to above the preadministration rate in eleven tests (61%).

One cell (B3 in Tables 1 and 2) showed initial excitation when 50% cyclopropane was given, but the discharge rate later fell to zero; a second administration of 25% cyclopropane increased the activity. These responses are included in the data presented since they raise the possibility that excitatory effects may be concentration dependent, in the case of a few hypothalamic cells.

TABLE 2. *Data from twenty-six single cells in the posterolateral hypothalamus, in fifteen cats, showing depression or inhibition of the discharge during cyclopropane administration*

Experiment and cell number	Cell position (mm)			Duration of administration (min)	Concentration %	Discharge rate		Recovery	
	Ant.	Lat.	Depth			Control	Cyclopropane	Discharge rate	Time (min)
A 1	11·5	3·0	24·0	11	50	9·5	0	7/min	11
2	11·5	3·0	24·5	11	50	19/min	1/min	2/min	7
B 1	11·5	4·0	20·4	6	50	16	13	30	3
3	11·5	3·0	22·8	12	50	2·8	0	7·5	12
D 4	11·5	3·5	24·7	4	50	9·0	3	14	5
D 6			25·1	3	50	14/min	0	7/min	3
D 7			22·0	4	50	3·4	2·0	2·4	6
F 1	11·5	3·5	22·8	5	50	16	20/min	4·3	7
2			22·9	6	25	21	16/min	19	6
G 2	12·0	3·5	22·5	4	50	9/min	1/min	2/min	5
4	11·5	3·5	24·1	4	50	4/min	1/min	13/min	4
J 2	11·5	3·0	24·5	7	25	40/min	0	6/min	5
L 1	11·5	2·5	24.0	4	50	15	8/min	13/min	6
M 1	12·5	3·0	20·5	3	50	10	1	3·5	5
N 1	10·5	2·0	22·0	6	50	12/min	0	5/min	3
4	12·5	3·0	20·5	3	50	2·7	0	3/min	4
5	12·0	3·0	20·0	3	50	3·5	11/min	11/min	3
6	12·0	3·0	21·9	3	50	3·5	22/min	3·5	8
P 1	12·0	3·5	22·4	4	50	11/min	0	9/min	6
2	12·0	3·5	23·0	9	50	6·8	8/min	2·2	8
Q 1	12·0	2·5	23·1	4	50	17	0	3/min	6
2	10·5	2·5	21·4	5	50	4·2	15/min	37/min	5
R 1	10·5	2·5	22·3	6	50	2·8	0	2·2	10
3	12·5	3·5	22·5	4	50	29	12/min	22	4
4	12·5	3·5	23·4	6	50	20	7/min	17	6
S 1	10·5	2·5	22·2	4	50	25/min	0	12/min	9

Except for the '/min' figures, the discharge rates refer to impulses/second. The anterior and lateral coordinates and the depth of each cell are shown. All cells were within the lateral hypothalamic area; B 3, D 4, D 6 and J 2 bordered on the perifornical area.

Changes shown by two other cells have been excluded from the Tables; in one case, effects on the discharge rate associated with cyclopropane were not reproduced on a second administration; the other cell showed apparent excitation on two repeated occasions, but the discharge rate continued to rise immediately after discontinuing cyclopropane.

Diethyl ether

In seven of fourteen cells tested, ether administration for an average of 7 min increased the discharge rate, with satisfactory evidence of recovery after a similar mean time interval (Table 3). The average increase (derived from the mean of the before and after control rates) was by 2·8 impulses/s (S.E. $\pm$0·83, $P<0·05$).

In the remaining seven cells tested (50%), ether reduced the firing rate, the duration of administration and recovery averaging 7 minutes. Due to the wide range of control rates, the mean reduction of 4·6 impulses/s (S.E. $\pm$1·96, $P<0·1$) was not statistically significant. Expressed in percentage form, the reductions averaged 81·7% (S.E. $\pm$4·83, $<0·001$).

There were aberrant responses in three cells. One of these showed a reduced discharge rate after 8 min of ether, although there was no change during a subsequent administration lasting 12 minutes. The activity of another cell was also reduced after 4 min of ether, after which there was an increased rate up to 11 minutes. A third cell, data from which are excluded, showed excitation in response to ether but during a second test the discharge fell to zero and the cell was lost.

Excitatory effects of ether on a posterolateral hypothalamic cell are illustrated in Fig. 3. This cell (the only one to be tested with both cyclopropane and ether) also showed an increased discharge on three separate administrations of cyclopropane.

There was no evidence to suggest that the excitatory response to cyclopropane or ether was related to the discharge rate of the cell before their administration (in the presence of chloralose alone). The average firing rate for cells which showed excitation and depression by cyclopropane were, respectively, 8·9 and 7·5 impulses/second. Also, the corresponding control levels for cells which were excited and depressed by diethyl ether were 5·6 and 7·8 impulses/s respectively.

TABLE 3. *Increased activity in six posterolateral hypothalamic cells, in four cats, during diethyl ether administration*

Experiment and cell number	Cell position (mm)			Duration of administration (min)	Discharge rate		Recovery	
	Ant.	Lat.	Depth		Control	Ether	Discharge rate	Time (min)
E 2	11·5	3·5	22·8	11	1·2	6·5	3·2	16
H 5	12·0	3·5	22·5	4	28	33	23	4
6	12·0	3·5	23·8	4	2·5	5·5	2·5	3
I 1	11·5	3·0	20·7	11	0·5	2·0	1·2	3
4	11·5	3·0	22·8	11	1·2	2·6	16/min	8
K 1	11·5	3·0	21·5	7	14/min	2·8	1·8	9
2	11·5	3·0	21·5	11	17/min	2·0	22/min	14

Except for the '/min' figures, the discharge rates refer to impulses/second. The anterior and lateral coordinates and the depth of each cell are shown. All cells were within the lateral hypothalamic area.

Halothane

In eight cats, ten single hypothalamic cells were studied during halothane administration for an average period of about 6 minutes. Depression or complete inhibition of activity occurred in all tests. Because of the wide range of control values (obtained from the mean of the before and after levels), the considerable fall in firing rate caused by halothane, averaging 11·6 impulses/s, was nevertheless not statistically significant (S.E. ±8·0, $P<0·2$). Expressed as a percentage, the reductions averaged 62·5% (S.E. ±13·0, $P<0·01$). Although the recovery times (average 9 min) commonly exceeded the period of administration, the discharge rate frequently failed to regain the prehalothane level.

Depressant effects occurring in two separate administrations of halothane are shown in Fig. 3; this cell showed an increased discharge when cyclopropane was given on three occasions and during one test with ether.

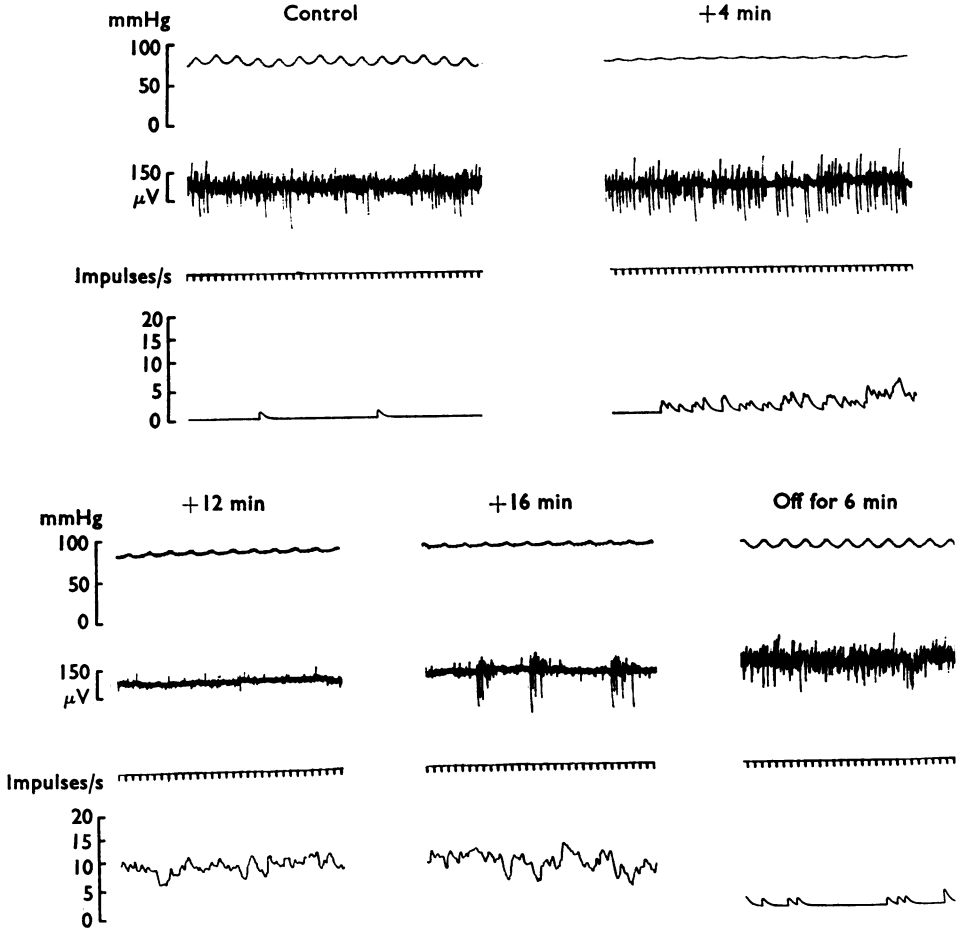

FIG. 4. Excitatory effects of cyclopropane on a single posterolateral hypothalamic unit. The records refer to control conditions, to 4, 12 and 16 min of 50% cyclopropane, and to recovery for 6 minutes. Each section shows, from above down: mean arterial pressure (mmHg), cortical electroencephalogram, 1 s time marks and hypothalamic unit discharge (impulses/s).

Cortical electroencephalogram (ECoG)

In the cat anaesthetized with chloralose alone, bursts of activity in single hypothalamic cells often coincided with increased high voltage activity on the ECoG. During administration of the inhalation anaesthetics the changes in the ECoG were as expected, progressing toward complete suppression. It is important to emphasize, therefore, as illustrated after 12 min of cyclopropane in Fig. 4, that when single hypothalamic units increased their discharge rate during cyclopropane or ether administration, this occurred in conjunction with pronounced depression or complete suppression of the ECoG.

Figure 4 shows that ECoG depression became marked after about 4 min of 50% cyclopropane. In this experiment, there was a late recurrence of bursts of surface activity after 16 min of cyclopropane; it is uncertain whether this is a frequent phenomenon, since few administrations could be extended for this length of time. Cortical depression by cyclopropane is also illustrated in Fig. 6; in this instance there was a reduced hypothalamic discharge.

Changes in arterial pressure

Figure 5 shows that arterial hypertension, produced by 2 μg adrenaline chloride injected intravenously in one experiment, caused no detectable change in the discharge rate of a single hypothalamic neurone, during steady state conditions and in the absence of an inhalation anaesthetic.

As expected from much previous work (Miller & Biscoe, 1965), arterial pressure was often unchanged or slightly raised by cyclopropane, while there was consistent hypotension with halothane (Millar, Warden, Cooperman & Price, 1970) and to a lesser degree with ether.

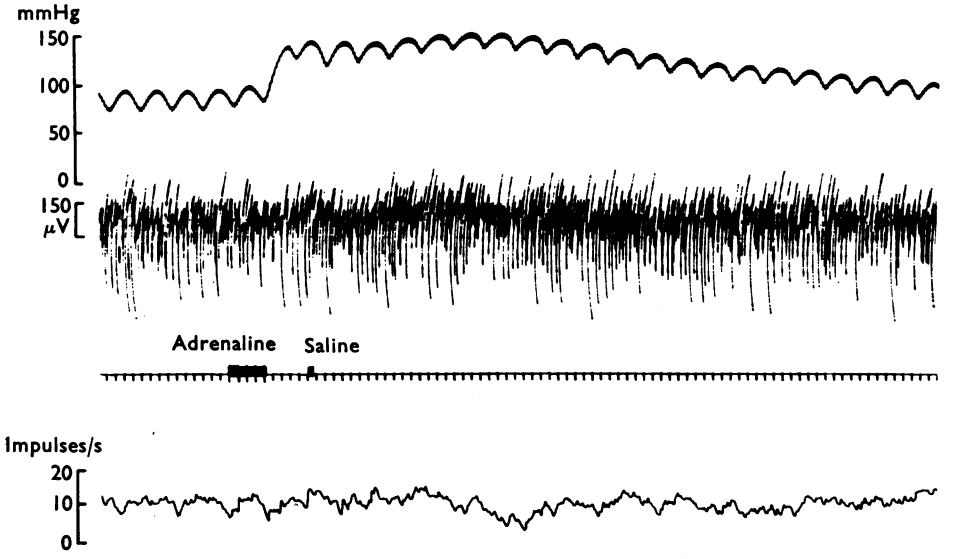

FIG. 5. From above down: mean arterial pressure (mmHg), cortical encephalogram, 1 s time marks and the discharge rate of a single posterolateral hypothalamic cell (impulses/s). Adrenaline chloride, 2 μg, followed by saline, was injected intravenously as indicated.

Responses to pain

In seventy-four of the total of 135 posterolateral hypothalamic cells from which recordings were started, attempts were made to demonstrate a change in the discharge level in response to pain, cold (ethyl chloride spray), or touch. Firm squeezing of a limb evoked an increase in the discharge level of twenty-six cells (35%), depression of activity in nine cells (12%), and no change in the remaining thirty-nine cells (53%). Records were obtained during inhalation anaesthesia from fifty of these seventy-four cells. Ten of the thirteen cells which showed an increased pain

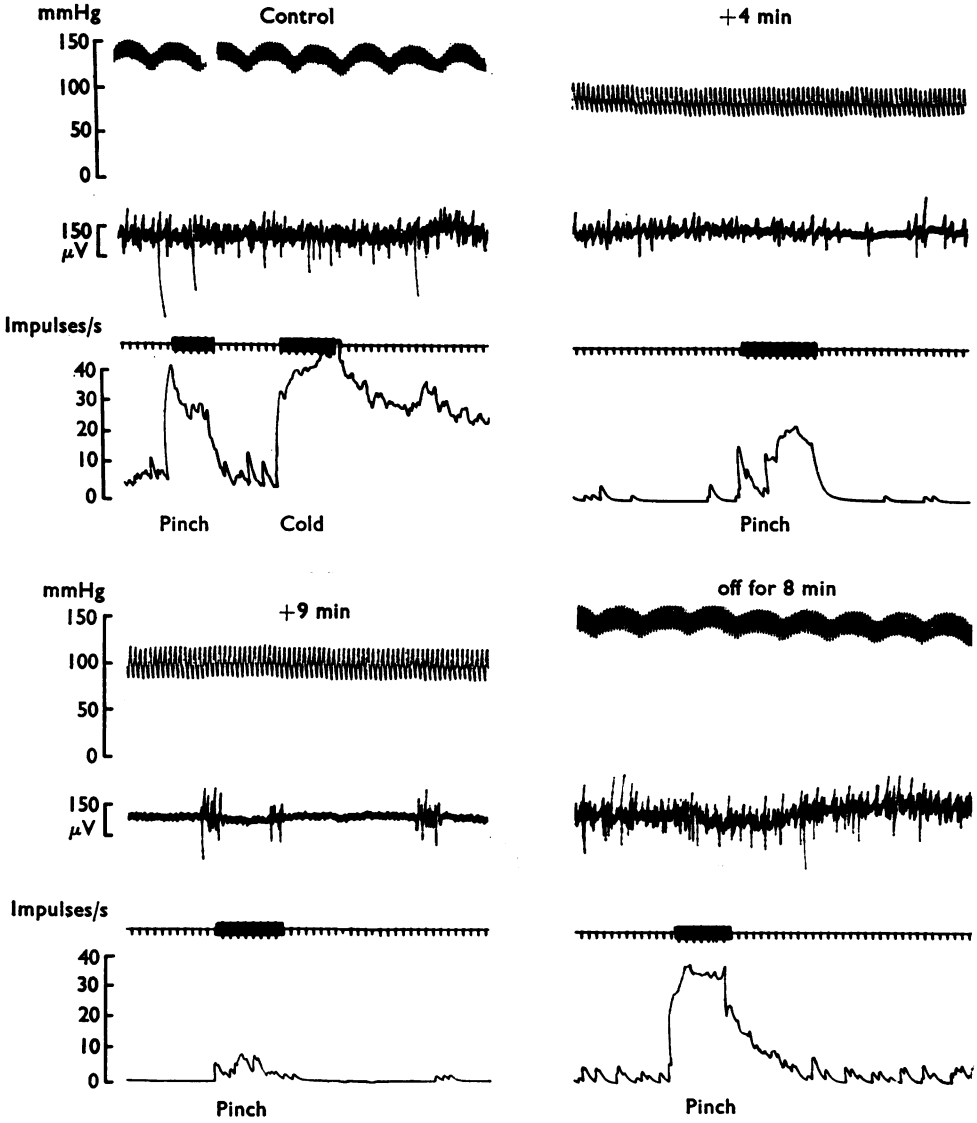

FIG. 6. Responses of a single posterolateral hypothalamic unit to pain or cold stimuli applied to one limb before, during, and after administration of cyclopropane. The records refer to control conditions, to 4 and 9 min of 50% cyclopropane, and to recovery for 8 minutes. Each section shows, from above down: arterial pressure (mmHg), cortical encephalogram, 1 s time marks, and hypothalamic unit discharge (impulses/s). Stimuli were applied as shown by the horizontal bars on the time mark traces.

response were depressed by cyclopropane or ether; in five instances where pain reduced the activity, so did cyclopropane or ether; the remaining thirty-two cells which failed to show any response to painful stimuli included twelve which were excited and twenty which were depressed by cyclopropane or ether. Thus, no correlation was apparent between the effects of cyclopropane or ether and the responses to pain before their administration, while halothane was depressant to all cells.

When an increased discharge occurred in response to a tactile stimulus (before the administration of an inhalation anaesthetic), the effect diminished progressively when cyclopropane or ether was given. This is illustrated in Fig. 6, where it is notable that although the pain response becomes greatly damped, it is still evident after as long as 9 min of 50% cyclopropane administration. In another experiment in which the discharge rate was virtually unchanged (in the absence of painful stimuli) after 11 min of ether anaesthesia, there was a similarly declining although persistent response to squeezing of a limb.

Discussion

The characteristics of the hypothalamic neurones studied in these experiments were generally similar to those previously described in rabbits anaesthetized with urethane (Cross & Silver, 1963). However, fewer hypothalamic units were detected in the course of an electrode track, which may support previous observations (Stuart, Porter, Adey & Kamikawa, 1964) that small doses of chloralose or pentobarbitone given to cats drastically reduced the number and firing rate of spontaneously active hypothalamic units, which were also unresponsive to afferent stimulation of peripheral nerves.

There was usually a reduction in the amplitude of the extracellularly recorded hypothalamic action potentials when the inhalation anaesthetics were given. This diminution in spike height seemed to be a direct action of the anaesthetics. It was clearly distinguishable from cell death which was associated with a rapid burst of action potentials and a decline in signal-to-noise ratio over a few seconds. In many instances the fall in spike amplitude was progressive as the inhalation anaesthetic was given, with subsequent recovery. Brain movement caused by alterations in arterial pressure may have influenced spike height and firing rate, but we found no evidence to indicate this. In the absence of the general anaesthetics, the pronounced rise in arterial pressure evoked by intravenous adrenaline in one experiment did not affect the discharge of a hypothalamic unit. This test was not repeated during cyclopropane or halothane administration because of the likelihood of precipitating ventricular arrhythmias or fibrillation.

There was no apparent correlation between an excitant effect caused by painful stimulus and by, say, cyclopropane, for a given hypothalamic unit; nor was there any association between the firing rate before administration of the inhalation agent and the response produced. Also, cells showing excitatory or inhibitory responses to cyclopropane or ether were randomly distributed in the lateral hypothalamic area.

The main interest of the results described is the demonstration that excitatory effects can be produced by certain anaesthetics within the central nervous system. In accord with their well known effects on the cortical electroencephalogram, a depressant action of all potent anaesthetic agents on other central nervous cells

would be expected. But this was the case in only about half the number of hypothalamic neurones studied with cyclopropane and ether. In the remainder, increased activity occurred and was associated with suppression of the cortical electroencephalogram; thus, there appeared to be dissociation between these two areas of central nervous function. This may accord with previous studies of EEG activity in superficial and deep structures during inhalation anaesthesia (Domino & Ueki, 1959) and the effect should also be related to earlier experiments in which diethyl ether caused excitation of some reticular units (Rossi & Zirondoli, 1955; Schlag & Brand, 1958). A further consideration is that following removal of the cerebral cortex, the cat may show a 'sham rage' reaction accompanied by rises in arterial pressure; this response is mediated by diencephalic structures, and can be induced by excitation of systemic chemoreceptors (Bizzi, Libretti, Malliani & Zanchetti, 1961). Although entirely speculative at present, a possible relation might therefore exist between cortical inhibition, hypothalamic excitation, and increased chemoreceptor activity (Biscoe & Millar, 1968) during cyclopropane and ether anaesthesia. The finding that ether administration depleted the noradrenaline content of the hypothalamus is also of possible relevance (Vogt, 1954).

The importance of the posterolateral hypothalamus in cardiovascular control (Smith, Jabbur, Rushmer & Lasher, 1960; Uvnas, 1960; Keller, 1960) and the excitant effects of cyclopropane and ether on sympathetic activity which have been reported (Millar & Biscoe, 1965), raise the question whether stimulation of certain hypothalamic areas by these anaesthetic agents could play a part in the excitatory circulatory picture presented, or whether the hypothalamic effects may be duplicated in areas such as the medulla or spinal cord (Price *et al.*, 1969; Millar *et al.*, 1970) which are more directly concerned with circulatory control. Previous studies (Millar & Biscoe, 1965; Price *et al.*, 1969) showed that the action of cyclopropane on preganglionic activity was exerted following decerebration, although no quantitative comparison with intact animals was attempted. The effects of cyclopropane and ether on hypothalamic neurones are very unlikely, therefore, to play a crucial role in the cardiovascular responses. There is no evidence from our study to show that any particular cell group responds in an individual way, and the results are at present merely descriptive. Thus, while an apparent excitatory effect on hypothalamic neurones could be attributable to a direct action on the cell, it might also result from a change in the excitatory or inhibitory influences normally acting on the unit, or more indirectly from non-specific effects on central nervous activity in nearby areas.

It has been argued elsewhere (Millar, Warden, Cooperman & Price, 1969) that while halothane depresses preganglionic sympathetic discharge in the cat under steady state conditions, this effect is not directly responsible for the arterial hypotension. In these experiments we have found that halothane consistently depresses single unit discharge in the posterolateral hypothalamus, and that this can occur in cells whose discharge is increased by cyclopropane and ether. Other experiments have revealed a depressant action of halothane on sympathetic neurones at spinal cord level (Millar *et al.*, 1969), while effects in the medulla remain to be investigated.

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