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ACTIVITY OF SINGLE NEURONES IN THE HYPOTHALAMIC FEEDING CENTRES: EFFECT OF GASTRIC DISTENSION

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SUMMARY

1. Unit activity from neurones of hypothalamic 'feeding' and 'satiety' centres, and from adjacent hypothalmic regions, was recorded by means of steel micro-electrodes inserted by a stereotaxic method, under Dial anaesthesia.

2. The spike frequency of these neurones was observed during inflation of the stomach with intragastrically placed balloons, and during electrical stimulation of the gastric branches of the vagus. As control measures, distension of the peritoneal cavity and stimulation of a sensory nerve were also carried out. These tests were repeated after severing the gastric vagal branches.

3. In fasted animals the frequency of spontaneous discharge was slower in the units of the satiety centre as compared with those of the feeding centre. The spike frequency of neurones in these two hypothalamic regions maintained an inverse relationship in all experimental situations.

4. Distension of the stomach and stimulation of the gastric vagal branches increased the spike frequency of satiety neurones, decreased the spike frequency of feeding neurones, and did not produce any change in spike frequency of adjacent hypothalamic neurones. A few units in the lateral mammillary region also changed their spike frequency on gastric distension. These responses were abolished after severing the gastric nerves.

5. The results suggest that distension of the stomach brings about satiation through vagal afferents activating the hypothalamic satiety mechanism.

6. The role of this in the nervous regulation of food intake is discussed.

INTRODUCTION

The role of the central nervous system in regulating food intake is now well recognized. Following the observations by Hetherington & Ranson (1940) that obesity occurs in animals with bilateral lesions in the ventromedial nuclei of the hypothalamus, and that this results from the production of hyperphagia (Brobeck, Tepperman & Long, 1943; Kennedy, 1950), later studies by Anand & Brobeck (1951*a*, *b*), and Anand, Dua & Shoenberg (1955) produced evidence that there are two opposing mechanisms in the hypothalamus regulating food intake, namely a mechanism in the lateral hypothalamus which initiates feeding, and one in the medial hypothalamus which brings about satiation. Further studies by Anand and colleagues; (Anand, 1961; Anand, Dua & Chhina, 1958, 1961; Delgado & Anand, 1953) have confirmed these observations, and have demonstrated the existence of integrative cerebral influences.

Various suggestions have been put forward to explain the activation of these hypothalamic centres both in satiety after food had been eaten, and in hunger after the food eaten has been disposed off by conversion to heat, work, or stored energy. It is believed that the changes introduced in the body as a result of feeding behaviour, supply information to the nervous centres which regulate feeding by two mechanisms (Anand, 1962, 1963). Firstly, certain changes occurring in the *milieu interieur*, as a result of feeding, act as 'signals' to these centres, and an extensive search is being made to discover such changes. Suggestive experimental evidence points towards the level of glucose utilization in the body being an important signal (Anand, Dua & Singh, 1961; Anand, Chhina, Sharma, Dua & Singh, 1964). As considerable delay is involved before precise information can be supplied through this channel, a second mechanism must also exist, routed via the afferent nerves coming from the alimentary tract.

Although Cannon & Washburn's (1912) and Carlson's (1916) original hypothesis, basing hunger sensation entirely on gastric hunger contractions, was refuted by the experimental and clinical observations that feeding persists after removal of stomach or its denervation, Grossman (1955, 1960) and Janowitz & Grossman (1949, 1951) suggested on the basis of a number of experimental observations that satiety after a meal is brought about by gastric distension. In agreement with this Sharma, Anand Dua & Singh (1961) found that the electroencephalographically recorded activity of the hypothalamic satiety centres changes selectively with distension of an intragastrically placed balloon.

Thus presumptive evidence exists for the presence of neurones in these hypothalamic centres which respond to gastric distension. This encouraged us to investigate whether any differences in firing frequency could be

detected in neurones of the satiety and feeding centres as a result of changes of intragastric pressure and stimulation of gastric nerves.

METHODS

A total of sixty-seven cats of either sex, weighing from 2·5 to 4 kg, was used for this study. They were generally starved for 15–20 hr before they were anaesthetized with Dial (Ciba), 0·5 ml./kg body wt. administered intraperitoneally.

Operative procedures

(*a*) *Gastric distension.* The abdomen of the animal was opened by a mid-line incision and the abdominal oesophagus and stomach exposed. A rubber balloon, tied at the end of a thin polyethylene tube was passed through the mouth and oesophagus, and guided into the middle of the gastric cavity. Another similar balloon was placed in the peritoneal cavity between the stomach and the diaphragm and its tube fixed to the xiphisternum. The outer ends of the tubes were connected to syringes and mercury manometers, for altering and registering the pressures in the balloons. Before closing the abdomen, the pressures required to just inflate the stomach and peritoneal cavity were noted.

(*b*) *Stimulation of gastric afferents.* After exposing the abdominal oesophagus, the vagal trunks were recognized and their gastric branches carefully dissected out. A pair of silver electrodes, insulated throughout except at their tips, were hooked around all the branches of a single nerve trunk. Small pieces of cotton-wool soaked in liquid paraffin were wrapped around these electrodes to minimize the spread of stimulating current. The insulated portions of the wires were fixed to the xiphisternum. Similar stimulating electrodes were also applied to the dissected femoral nerve.

(*c*) *Division of the gastric branches of the vagi.* Loops of thread were passed around all the gastric branches of the vagi. Where stimulating electrodes were applied to some gastric vagal branches, care was taken that the loop of thread was central to the stimulating electrodes. By pulling on these loops the nerves could be severed.

After these procedures (*a*, *b*, *c*) the tube of the peritoneally placed balloon, the wire leads to the stimulating electrodes, and the loose ends of the thread loops around the nerves were all brought out through the wound when the abdominal opening was sutured.

(*d*) *Recording unit activity.* The head of the animal was fixed in a Johnson stereotaxic apparatus, the skull exposed on its dorsal surface and tiny burr holes made in it. Steel microelectrodes, with their tips etched to 1–2 μ and the shafts insulated with polystyrene, were guided stereotaxically into hypothalamic areas for recording extracellular unit activity. The activity picked up by these was fed into a Grass preamplifier through a cathode-follower input probe, and displayed on a Dumont oscilloscope. Photographs were made with a Grass camera. The unit activity was recorded in different animals from neurones in different hypothalmic regions including the satiety and feeding centres.

In some animals electrodes were also implanted on the cortical surface, and connected to a Grass e.e.g. machine, for simultaneous monitoring of cortical activity.

Experimental procedures

After catching a unit from the hypothalamic region, its activity was observed and occasionally photographed for about an hour, and if its activity remained stable during this period it was then exposed to the experimental procedures detailed below. These stable units were generally bigger. The activity of the smaller units from these regions did not remain stable for long periods and so these could not be tested with the experimental procedures. In some cats it was possible to test the responses of only one unit to the various experimental procedures, while in others it was possible to study more than one unit. A total number of 131 units from different hypothalamic regions was thus studied.

(*a*) Eighty-four units were tested with distension of the stomach, by injecting air into the intragastric balloon. A pressure in the balloon of about 15 mm Hg was gradually applied in the first instance and maintained for 5–10 min. This was then raised further to about 30 mm Hg pressure, but distension beyond 35 mm Hg pressure was not carried out. The pressure in the balloon was then lowered to atmospheric. Spike activity during all these manoeuvres was photographed for analysis. After waiting for 10–15 min the pressure in the intraperitoneally placed balloon was then similarly raised and lowered, to act as a control.

This was followed by severing of the gastric branches of the vagus by pulling on the thread loops, after which inflation of the balloons was repeated.

(*b*) Twenty other hypothalamic units in other animals were exposed to stimulation of the gastric vagal branches, and the spike activity photographed before, during and after stimulation. Stimulation was carried out with square-wave pulses of 0·5 msec duration at frequencies of 20, 30, or 40/sec and intensities varying from 4 to 6 V. Such stimuli were applied for not more than 1 sec at a time, and their effects on hypothalmic spike activity watched for a few minutes afterwards. As a control experiment in all these animals such stimuli were also applied to the femoral nerve on one side.

This was followed by severing of the gastric branches of the vagus by pulling on the thread loops, and the stimulation of the peripheral portion of the cut gastric branches repeated.

(*c*) Twenty-seven units from various hypothalamic regions were first exposed to gastric distension, followed by stimulation of the gastric vagal branches; and these manoeuvres were repeated after severing the gastric branches.

Disposal of animals and locating micro-electrodes

At the end of an experiment a small deposit of iron was made at the site of the unit recorded by passing a direct current of 3 mA for 30 sec through the micro-electrode. The brain was then perfused through the carotid artery; firstly with a freshly made 1–2% solution of potassium ferrocyanide (to give the Prussian blue reaction with the iron deposit) and later with 10% formalin. The brain was removed, serially sectioned and examined. The marker lesion was large enough to be detected by naked eye.

The abdomen was also explored to see that the gastric vagal branches had been properly severed.

RESULTS

General characteristics

Spikes recorded from all the hypothalamic regions showed similar characteristics and were indistinguishable from each other. The spontaneous spike activity of hypothalamic neurones was generally low, the firing rates varying from about 1 in 10 sec to 10/sec. Only a few units had a spontaneous firing rate as high as 20–30/sec, while some others fired at a rate of about 1/min or even less. The amplitude of these extracellular spikes varied greatly, but it was generally between 0·2 and 5 mV.

All the animals (except one) were starved for a number of hours, and it was observed that in this hunger state the frequency of spontaneous discharge was much slower in units of the satiety centre as compared with those of the feeding centre. The frequency of discharge of satiety neurones generally varied from 1 in 15 sec to 6/sec, whereas the unit activity of neurones in the feeding centre (and of some other hypothalamic neurones) had

TABLE 1. Changes in the frequency of spike activity of hypothalamic neurones tested with gastric distension and stimulation of gastric branches of vagi

Hypothalamic region	No. of units exposed to *gastric* distension	No. of units showing *increased* frequency	No. of units showing *decreased* frequency	No. of units showing *no change* in frequency	No. of units exposed to *stimulation* of gastric branches	No. of units showing *increased* frequency	No. of units showing *decreased* frequency	No. of units showing *no change* in frequency	* No. of units out of these exposed both to gastric distension and to stimulation of gastric branches
Satiety centre (ventromedial)	17*	16*	—	1	11*	9*	—	2	4
Feeding centre (lateral)	16*	—	15*	1	12*	—	11*	1	6
Mamillary area	14*	3	2	9*	7*	—	—	7*	5
Posterior hypothalamus	22*	—	—	22*	6*	—	—	6*	5
Anterior hypothalamus	17*	—	—	17*	6*	—	—	6*	4
Supraoptic area	16*	—	—	16*	5*	—	—	5*	3
Preoptic area	9	—	—	9	—	—	—	—	—

Note. Only bigger units whose activity remained stable for a number of hours have been included in this Table.

a frequency varying from 1/sec to 30/sec. Within the satiety area (ventromedial nucleus) itself neurones which were medially situated had a much slower frequency of discharge (about 1 in 15–30 sec) than neurones which were situated more laterally in the same nucleus. The units studied from the medial region of the ventromedial nucleus often remained silent for several seconds followed by one or two spikes, and these were the neurones which gave the largest response to distension of stomach. Keeping the

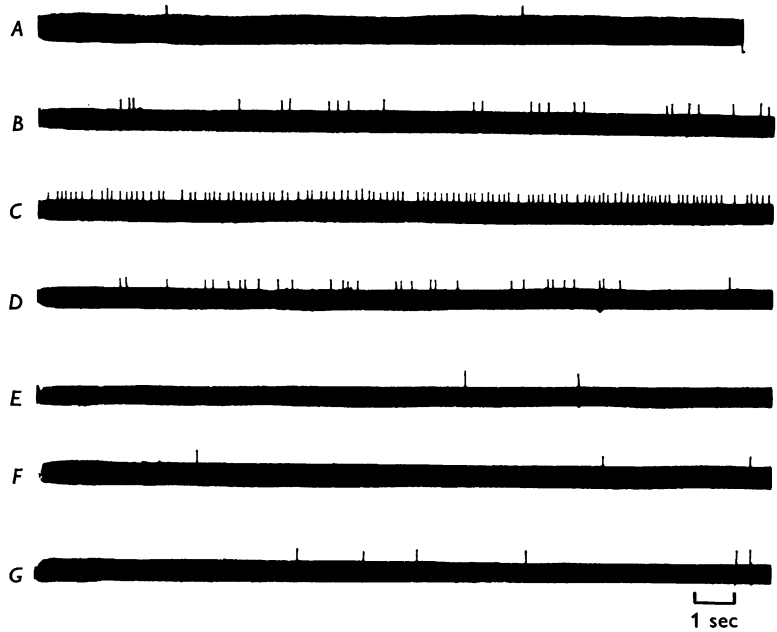

Fig. 1. Spontaneous unit activity recorded from a neurone in the satiety centre of a starving cat. (*A*) control; (*B*) immediately after raising the intragastric pressure to 15 mm Hg; (*C*) immediately after raising the intragastric pressure to 30 mm Hg; (*D*) 5 min after raising the intragastric pressure to 30 mm Hg; (*E*) after deflation of the intragastric balloon; (*F*) after raising the pressure in the intraperitoneal balloon to 30 mm Hg; and (*G*) on raising the pressure in the intragastric balloon after severing the gastric vagal branches. The unit activity increased with increase of intragastric pressure. (Spikes retouched.)

stomach slightly distended often helped to reveal the presence of these medial units. Satiety neurones in the fed cat, however, had a higher frequency discharge of 9–13/sec.

Effects of distension of stomach

(*a*) *Satiety centre.* Seventeen units recorded from the satiety centre were tested with distension of both intragastric and intraperitoneal balloons. Sixteen of these (Table 1) responded with a variable increase in their

spike frequency on distension of the intragastric balloon, while distension of the intraperitoneal balloon did not produce any apparent change (Fig. 1). One unit, however, did not respond to this manoeuvre. The increase in unit activity occurred within a second of inflation of the intragastric balloon and was maintained as long as this inflation was kept up (Fig. 2).

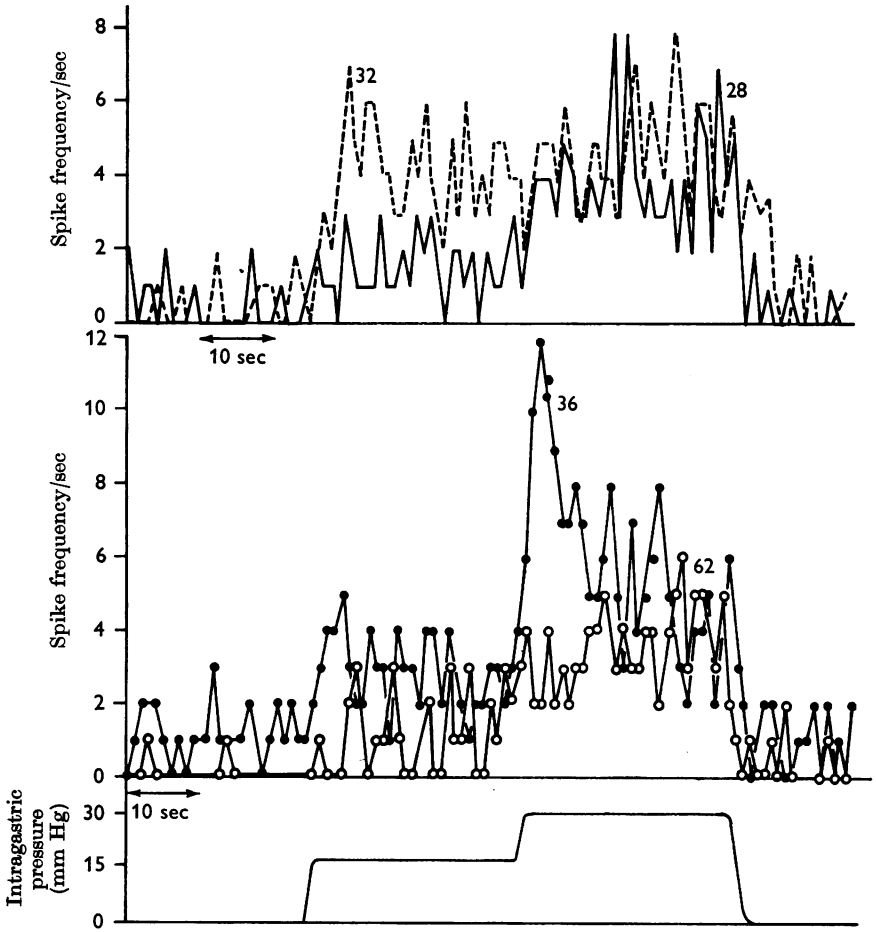

Fig. 2. Spike frequency of four units from the satiety centre of different cats correlated with changes of pressure in the intragastric balloon. The roughly linear relationship between the spike frequency and the intragastric pressure is demonstrated. One of these units (number 36) showed some adaptation after exposure to 30 mm Hg intragastric pressure.

The spike frequency of most of these units showed a roughly linear relationship with the level of intragastric pressure and maintained their discharge rate with very little adaptation as long as gastric distension was continued (Fig. 2). This was most true of the units from the medial part of

this region, which had a low spontaneous firing rate. A few units, however, especially those placed somewhat laterally in this area, showed some adaptation of their frequency of discharge on sustained gastric distension (Fig. 1*D*; Fig. 2 unit number 36). Also, some of these lateral units did not show any further increase in their frequency when intragastric pressure was raised from 15 to 30 mm Hg (Fig. 2 unit number 32).

The activity of all these units from the satiety area returned to the levels found before distension within 30 sec of lowering the pressure in the intragastric balloon to atmospheric.

Intragastric inflation was repeated after severing the gastric branches of the vagi by pulling on the thread (see Methods), and now this procedure did not produce any apparent change in the spike frequency of satiety neurones (Fig. 1), except in one experiment in which a slight increase in frequency was observed. On post-mortem examination of this animal it was seen that all the gastric vagal branches had not been severed.

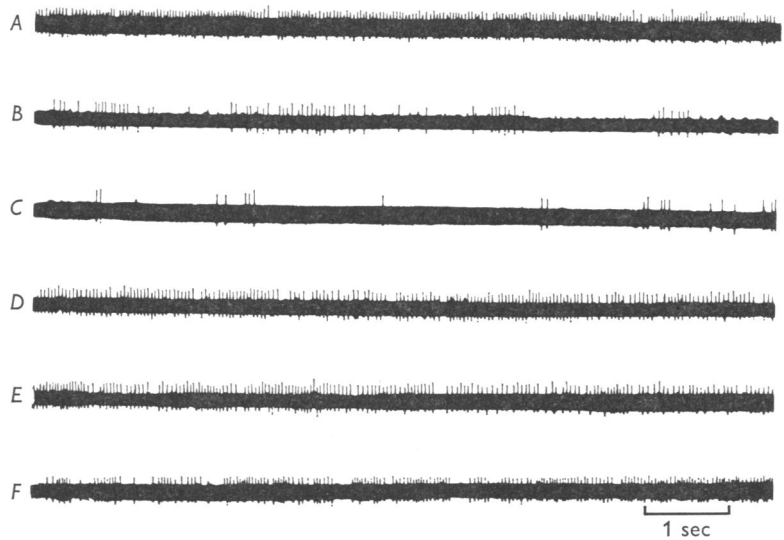

Fig. 3. Spontaneous unit activity recorded from a neurone in the feeding centre of a starving cat. (*A*) control; (*B*) immediately after raising the intragastric pressure to 15 mm Hg; (*C*) immediately after raising the intragastric pressure to 30 mm Hg; (*D*) after deflation of the intragastric balloon; (*E*) after raising the pressure in the intraperitoneal balloon to 30 mm Hg; and (*F*) on raising the pressure in the intragastric balloon after severing the gastric vagal branches. The unit activity decreased with increase of intragastric pressure. (Spikes retouched.)

(*b*) *Feeding centre.* Sixteen units picked up from the feeding centre slowed their discharge during distension of the intragastric balloon (Table 1), while no such change was observed on inflation of the intraperitoneal balloon (Fig. 3). The reduction in spike activity varied in different units,

ranging from some slowing to complete inhibition of firing in certain cases (Fig. 4), and this was maintained as long as distension of the stomach was kept up.

The activity of all these units returned to the levels found before distension immediately on lowering the intragastric pressure.

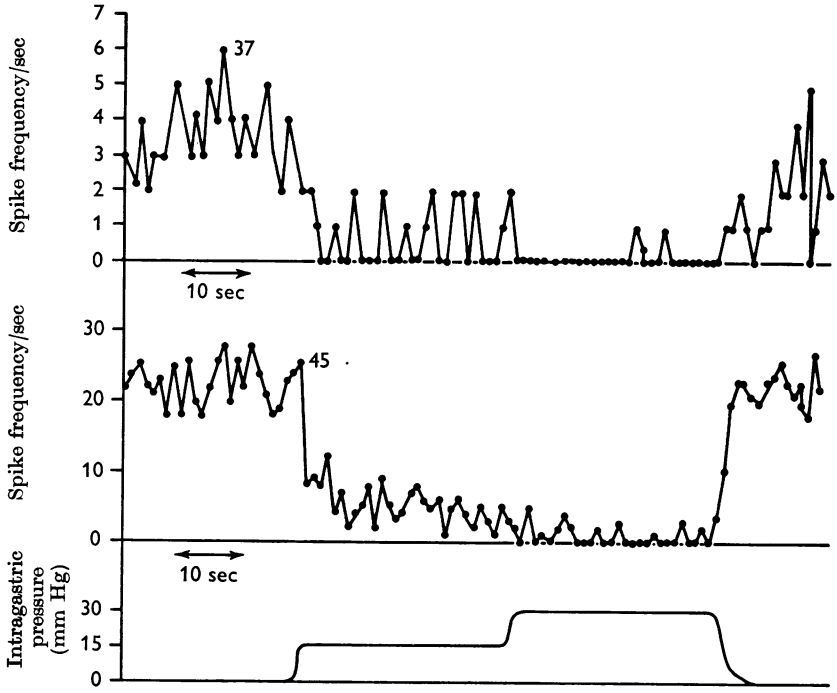

Fig. 4. Spike frequency of two units from the feeding centre of different cats, correlated with changes of pressure in the intragastric balloon.

Intragastric distension was repeated after severing the vagal gastric branches, and this now did not produce any reduction in spike frequency (Fig. 3).

(*c*) *Other hypothalamic regions.* Table 1 summarizes the results on a number of units from other hypothalamic regions which were studied under similar conditions. Out of seventy-eight such units tested with gastric distension, only three units from the lateral mamillary region registered an increase, and two other units from the same area showed a decrease, in their frequency discharge. The remaining seventy-three units from various hypothalamic regions did not respond either to intragastric or to intra-peritoneal distension.

Effects of stimulation of gastric vagal branches

(*a*) *Satiety centre.* Eleven units in the satiety centre were tested with stimulation of gastric vagal branches. The spike frequency of nine of these units showed a variable increase for some time after the stimulation was over (Fig. 5). The increase in spike frequency was related to the fre-

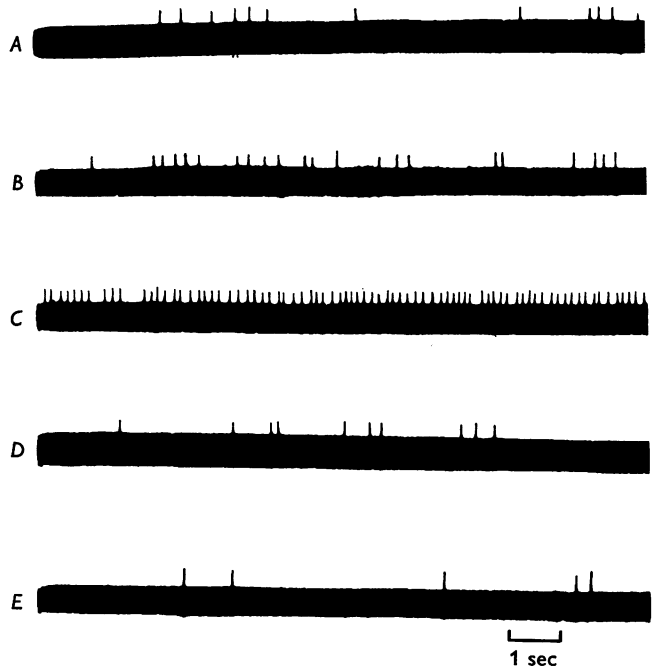

Fig. 5. Unit activity recorded from a neurone in the satiety centre. (*A*) Control; (*B*) immediately after 1 sec stimulation of gastric vagal branches with stimulus pulses of 0·5 msec duration, 20/sec frequency and 6 V intensity; (*C*) immediately after stimulation of gastric branches with stimulus pulses of 0·5 msec duration, 40/sec frequency and 6 V intensity; (*D*) immediately after stimulation of the femoral nerve with similar parameters; and (*E*) on stimulation of the peripheral portion of the cut gastric vagal nerves. The unit activity increased in response to stimulation of gastric vagal branches. (Spikes retouched.)

quency of stimulation and its intensity, a more marked increase in spike frequency being produced either by increasing the pulse frequency (Fig. 5*B*, *C*) or the voltage of the pulses.

Stimulation of the femoral nerve did not produce any such change in the spike frequency of satiety neurones (Fig. 5).

After severing the gastric branches, stimulation of the peripheral portion of the cut nerves (see Methods) did not produce any change in spike frequency of satiety neurones.

(*b*) *Feeding centre.* Twelve units from the feeding centre were similarly tested with stimulation of the gastric vagal branches and eleven of these showed a decrease in their firing rate (Fig. 6). This decrease also was related to the frequency and intensity of stimulation.

Similar stimulation of the femoral nerve did not produce any change in activity in the feeding centre.

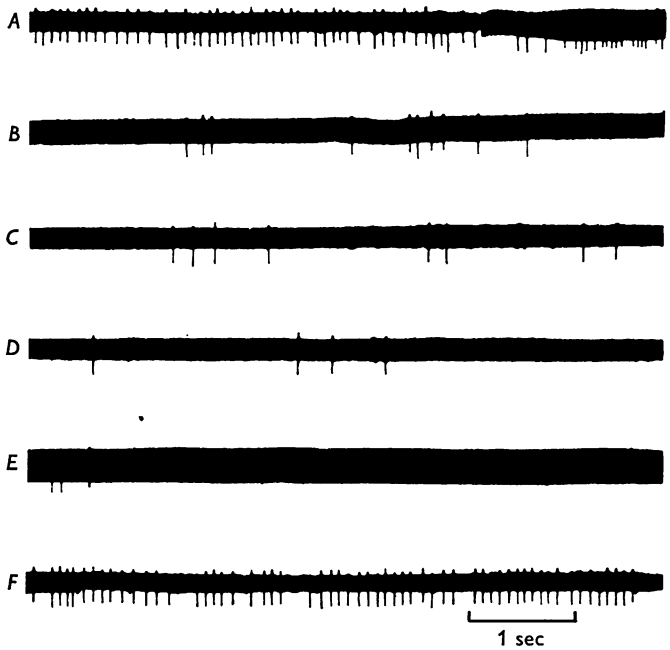

Fig. 6. Unit activity recorded from a neurone in the feeding centre. (*A*) Control; (*B*) immediately after 1 sec stimulation of gastric vagal branches with the stimulus pulses of 0·5 msec duration, 20/sec frequency and 4 V intensity; (*C*) immediately after stimulation of gastric branches with stimulus pulses of 0·5 msec duration, 20/sec frequency and 6 V intensity; (*D*) immediately after stimulation of gastric branches with stimulus pulses of 0·5 msec duration, 30/sec frequency and 6 V intensity; (*E*) immediately after stimulation of gastric branches with stimulus pulses of 0·5 msec duration, 40/sec frequency and 6 V intensity; and (*F*) on repeating the stimulation of the peripheral portion of the cut gastric vagal nerves. The unit activity decreased in response to stimulation of gastric vagal branches.

Again, stimulation of the peripheral portion of the severed gastric branches did not result in any change in the firing rate of feeding neurones (Fig. 6*F*).

(*C*) *Other hypothalamic regions.* Twenty-four units from various other hypothalamic regions (Table 1) were also exposed to stimulation of gastric vagal branches and none of them responded by any change in its spike frequency.

Effects of distension of stomach and stimulation of gastric vagal branches on the same neurone

Four units from the satiety centre which responded to distension of the stomach by increasing their spike frequency were then tested with stimulation of gastric vagal branches, and showed a similar increase in their spike frequency. After severing the gastric branches repetition of both these manoeuvres did not produce any change in unit activity.

Similarly, six units from the feeding centre which responded to distension of the stomach by decreasing their spike frequency were then exposed to stimulation of gastric vagal branches, and showed a similar decrease in their activity. Severing the gastric vagal branches abolished the response to gastric distension as well as to stimulation of gastric nerves.

Electrocorticographic activity and blood pressure

In fourteen animals electrocorticograms were taken on an e.e.g. machine, and, except for 'arousal' responses, these did not show any change during the experimental procedures. Similarly, in five animals electrocardiograms, blood pressure and respiration were recorded, and these did not show any significant changes even when the intragastric pressure was raised to 30 mm Hg. These records were taken to rule out any indirect effects of these on the specific responses observed in this study.

DISCUSSION

Previous studies (Anand, 1961; Anand & Brobeck, 1951*b*; Anand *et al.* 1955; Delgado & Anand, 1953) had provided an anatomical basis for the suggestion that central mechanisms in the hypothalamus regulate food intake, the lateral feeding mechanism providing the basic urge to eat, and the medial satiety mechanism inhibiting it. Brobeck (1955) has summarized the suggested changes in the body which may 'signal' these centres.

The facts which stand out from the present study are that individual neurones in hypothalamic 'satiety' and 'feeding' centres exhibit spontaneous activity, and that this activity is changed in response to distension of the stomach and stimulation of the gastric vagal branches. Cross & Green (1959) had shown spontaneously discharging hypothalamic units responding to changes of osmotic pressure. Changes shown by the satiety and feeding neurones were not exhibited by neurones which were explored under similar experimental conditions in the adjacent hypothalamic areas, except for a few units in the lateral mamillary region which responded to gastric inflation. Similarly, distension of the peritoneal cavity in the vicinity of the stomach and stimulation of other sensory nerves in the body did not change the activity of the hypothalamic centres, thus demon-

strating the specific role of afferents coming from the stomach. Our results show that these afferents run in the vagi, and the responding mamillary units may be on their route.

The role of gastric distension in bringing about inhibition of further eating and drinking has been demonstrated previously by various workers (Adolf, 1950; Holmes & Montgomery, 1960; Share, Martyniuk & Grossman, 1952; Towbin, 1949). The present study strongly suggests that this inhibition of eating is brought about by activation of the satiety centre through gastric afferents. Paintal (1954) had shown that the discharge of vagal afferent fibres from the stomach is linear to the intragastric volume, and we have found a roughly linear relationship between the frequency of discharge of neurones in the satiety centre and the intragastric pressure. The comparatively short latency (about 1 sec) between the beginning of gastric distension and the production of changes in spike frequency rules out the possibility of some chemical agent being the mediator for activating the satiety centre. This is further corroborated by the fact that the spike activity returns to predistension level immediately on lowering the intragastric pressure. The detectable latency between gastric inflation and the activation of satiety neurones is possibly due to the low conduction velocity of gastric afferents as shown by Iggo (1958).

The changes in the activity of satiety and feeding centre neurones were inversely related. It is worth noting that in the fasted animal the rate of spontaneous activity recorded from feeding-centre neurones was generally much higher than the rate of spontaneous activity of satiety-centre neurones. This emphasizes that in hunger state the feeding centre is more active, and when on taking a meal satiety neurones are activated, the activity of feeding neurones is decreased. It is not clear whether decrease in the activity of feeding centre neurones as a result of gastric distension is a direct effect of the gastric afferents projecting on to the feeding centre, or whether the feeding neurones are indirectly 'inhibited' as a result of increased activity of satiety neurones. Experimental evidence has been provided previously (Anand & Brobeck, 1951*b*) for the inhibition of the feeding centre by the activation of the satiety centre, possibly through lateral projections.

The present study also does not rule out the 'metering' of the hypothalamic satiety and feeding centres when the food passes through the oropharyngeal regions (Janowitz & Grossman, 1949), or when the gastric contents move on further into the intestinal canal. There is also suggestive evidence for the presence of chemoreceptors, responding to some products of digestion, in the experiments of Sharma & Nasset (1962).

Sharma *et al.* (1961) had demonstrated that gastric hunger contractions are produced only when the stomach is empty and the satiety centre is not

activated by increased glucose utilization. On the other hand, activation of the satiety centre inhibits gastric contractions of an empty stomach. It may, therefore, be surmised that when food enters the stomach and inflates it, this brings out satiation by activation of the satiety centre (and inhibition of the feeding centre). This state of satiation is later on maintained as a result of changes produced in the internal environment (glucose utilization, as shown by Anand *et al.* 1964). When this activation of the satiety centre passes off after some hours, inhibition of the feeding centre is removed, leading to the subjective feeling of hunger. Simultaneously, the empty stomach now produces 'hunger' contractions which provide an objective feeling of hunger.

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