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THE VASOMOTOR RESPONSES DUE TO ELECTRICAL STIMULATION OF THE SINUS AND VAGUS NERVES OF THE CAT AND THEIR MODIFICATION BY LARGE DOSES OF SODIUM PENTOBARBITAL (NEMBUTAL)

By W. W. DOUGLAS, I. R. INNES and H. W. KOSTERLITZ

From the Physiology Department, University of Aberdeen

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It is generally accepted that electrical stimulation of the central ends of the buffer nerves, that is the carotid sinus and aortic nerves, causes a fall in arterial blood pressure. Since chemosensory pressor fibres are present in both nerves, it should be possible to obtain pressor responses by electrical stimulation if conditions are made favourable for a preponderance of the pressor element. This is readily done in both nerves by abolishing the barosensory depressor response by means of large doses of sodium pentobarbital (nembutal), and in the carotid sinus nerve by so varying the strength of the stimulus as to activate more effectively the chemosensory component than the barosensory. Similarly, the depressor response obtained by administering strong electrical stimuli to the central ends of the vagi can be converted to a pressor one by overdosage with nembutal.

The more important of these findings have already been presented at meetings of the Physiological Society (Douglas, Innes & Kosterlitz, 1948, 1949).

METHODS

Cats were anaesthetized with nembutal (40–50 mg./kg., intraperitoneally) or urethane (25% (w/v) solution, 1–1·5 g./kg., intraperitoneally).

In order to minimize the effects on the arterial blood pressure of changes in blood gas tensions and intrathoracic pressure following stimulation or inhibition of the respiratory centre, an open pneumothorax was applied in most experiments. In a few early experiments the pneumothorax was effected by intubation by means of a rubber tube through the diaphragm. In most experiments, however, a bilateral open pneumothorax was applied by resection of a rib to produce an opening in each side of the chest, measuring about 1·5 cm. in diameter. To ensure a pulmonary ventilation similar to that prior to the pneumothorax, the lungs were inflated through a tracheal cannula by means of an 'Ideal' pump so that in normally anaesthetized animals respiratory movements of the chest were not suppressed but were just present. These respiratory movements were, of course, quite independent of the rhythmic inflations of the lung produced by the pump and could in no way interfere with pulmonary ventilation which was maintained at a constant rate throughout the experiment. Tracings of the spontaneous respiratory movements were obtained by means of a

stethograph and tambour, and gave a good record of excitation or inhibition of the respiratory centre after stimulation of the buffer nerves and of depression of the centre after large doses of nembutal. This procedure was not possible in some animals, in which, obviously due to the anaesthetic, the respiratory centre was found to be too depressed before the application of the pneumothorax. In these animals spontaneous respiratory movements were absent when the artificial ventilation of the lungs was kept at a level adequate to prevent cyanosis.

The arterial blood pressure was recorded, with heparin as anticoagulant, in a femoral artery or in the left carotid artery, when the left sinus nerve was divided.

The aortic nerve was identified as a small nerve leaving the vagus and joining the superior laryngeal nerve, and the sinus nerve was readily found after ligature and section of the external carotid artery and dissection of the glossopharyngeal nerve which was cut about 1 cm. distally to the entry of the sinus nerve. Great care was taken to free the sinus nerve from surrounding tissue in order to prevent spreading of the stimulating current. For stimulation, the sinus nerve was placed on shielded silver—silver chloride electrodes embedded in Perspex. No signs of spreading of current were ever observed. Stimuli 8–10 times greater than the strongest used in the experiments described in this paper were required to produce such spreading. With such, and even stronger stimuli, ligation of the sinus nerve centrally to the stimulating electrodes abolished all effects on the vasomotor and respiratory centres, showing that current spread, even if it occurred, was not responsible for the observed phenomena. In almost all experiments both vagi and the left sinus nerve were cut while the right sinus nerve was left intact. Thus, the central ends of the vagus and aortic nerves were stimulated, while the right sinus nerve was usually stimulated intact. This was done to preserve the delicate nerve for the whole duration of the experiment which sometimes lasted several hours. In a small number of experiments the right sinus nerve was stimulated before and after section of the nerve close to the carotid sinus. No significant difference was observed.

Cold block was applied to the sinus nerve by placing the nerve on a U-shaped fine copper tube through which brine at about -8 to $-10°$ C. was allowed to flow. The nerve in contact with the U-tube was frozen in a very short time. It was thawed by stopping the flow of brine and irrigating the nerve with warm Ringer-Locke solution.

Decerebration was carried out in the usual way. In experiments where the medulla was sectioned, the cerebellum was first removed. Sections of the medulla were made with a single sweep of a decerebrator. As each slice of the medulla was removed, it was transfixed with a needle and the individual slices were built up on the needle to reproduce the whole. The responses to electrical stimulation of the buffer nerves were tested after each section.

Three stimulators were used for electrical stimulation: (1) The stimulator designed by Whitfield (1946), consisting essentially of condenser discharges through a neon tube. The duration of the exponentially declining pulse is approximately 0·3 msec. and its physiological efficacy corresponds to a rectangular pulse of approximately 0·03 msec. duration. (2) A thyratron stimulator of conventional design, the exponentially declining pulse lasting between 0·4 and 3·5 msec. corresponding to rectangular pulses lasting between approximately 0·04 and 0·35 msec. (3) The Ritchie-B.N.I. (Walter & Ritchie, 1945) 'square wave' stimulator, with rectangular pulses lasting between 0·02 and 10 msec. By a minor modification it was possible to obtain frequencies additional to those provided in the instrument. The frequency, pulse duration and voltage (base-peak) of the stimuli were confirmed by continuous monitoring by means of a cathode-ray oscilloscope. Bipolar platinum electrodes were used for stimulation of the vagi and shielded bipolar silver-silver chloride electrodes for the sinus and aortic nerves.

Since in the experiments to be described, the voltage and the duration of the stimulating pulses vary, it will be impossible to define the stimuli in terms of strength (voltage) alone. For this reason, the stimuli will be characterized by the product voltage × duration (Vt).

The results presented in this paper are based on experiments on over eighty cats.

RESULTS

Changes in arterial blood pressure and respiration on electrical stimulation of the sinus nerves in nembutalized and urethanized cats

On stimulation of the right sinus nerve, with both vagi and the left sinus nerve cut, pressor or depressor responses were obtained in more than forty cats, depending on the *Vt* (voltage × pulse duration) of the stimuli. In many animals anaesthetized with nembutal or urethane, three different responses were obtained, viz. a depressor response with stimuli of low *Vt*, a pressor response with stimuli of slightly higher *Vt*, and again a depressor response with stimuli of considerably higher *Vt*. The first response was present in about half the cats, the second in all animals and the third in most animals. As was to be expected, relatively high voltages were required when very short pulses were used, while with longer pulses the voltages were considerably lower. For example, with a rectangular pulse lasting 0·02 msec., 3 V. caused a depressor response, 8 and 10 V. pressor responses, and 30 V. again a depressor response (Fig. 1). In another cat, with rectangular pulses lasting 0·1 msec., 0·5 and 1 V. gave pressor responses, 2 V. a poorly maintained rise of blood pressure followed by an after-fall, 3 V. a biphasic response consisting of a rise followed by a transient fall, 4 V. a fall of blood pressure after a considerable lag and 5 V. a marked depressor response (Fig. 2). If, for a given voltage and pulse duration, the response was pressor, increasing the *Vt* by prolonging the pulse duration also led to a depressor response. These results were in no way influenced by the type of stimulator used.

No quantitative comparisons could be made between the products of voltage and pulse duration required to obtain similar responses in different animals, and, even in the same animal, this was rarely possible if some time had elapsed between the tests. The experimental conditions, particularly the depth of anaesthesia and the resistance of the nerve, could not be kept sufficiently constant to permit a quantitative evaluation of simultaneous variations in voltage and pulse duration. There is, however, no doubt about the validity of the qualitative findings: increasing the *Vt* of the stimulus, either by increasing the voltage or the pulse duration, will almost always convert a pressor response to a depressor unless, as will be shown later, too much nembutal has been given.

The depressor response elicited by stimuli of low *Vt* was readily obtained only with weak pulses of very short duration. The range over which it was present was remarkably narrow, any slight increase in the voltage evoking a pressor effect. The fall in blood pressure was always slight, much smaller than that observed in the depressor responses with stimuli of high *Vt*. It is also to be noted that the pressor responses were obtained over a wide range and that, with stimuli of increasing *Vt*, there were responses intermediate between pressor and depressor (Fig. 2).

When spontaneous respiratory movements were present, stimulation of the sinus nerve with stimuli of medium and high *Vt* always caused an increase of these movements, whether the vasomotor response was pressor or depressor (Fig. 2). The maximum respiratory activity was achieved before the pressor

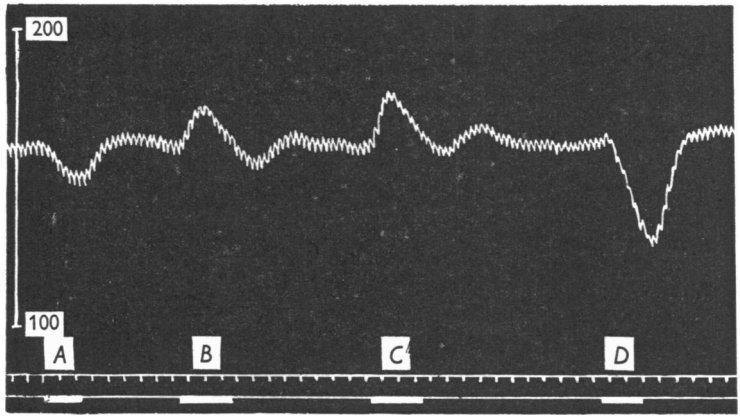

Fig. 1. Cat. Urethane, 1·5 g./kg. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left carotid artery in mm. Hg. Time 5 sec. Stimulation of right sinus nerve, 0·02 msec., square wave, 70 cyc./sec. *A*, 3 V.; *B*, 8 V.; *C*, 10 V.; *D*, 30 V.

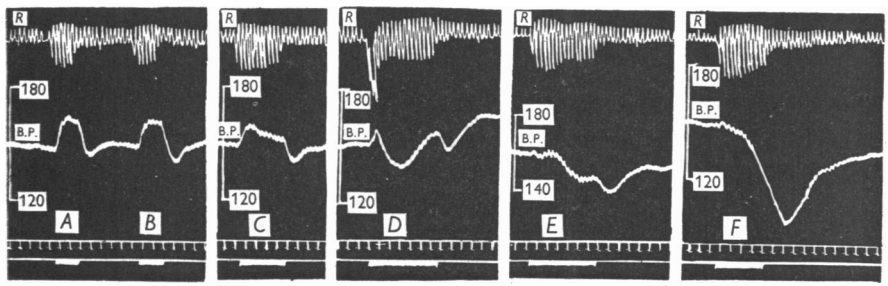

Fig. 2. Cat. Nembutal, 40 mg./kg. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. *R*, respiratory movements, inspiration downwards. B.P. in left carotid artery in mm. Hg. Time 5 sec. Stimulation of right sinus nerve, 0·1 msec., square wave, 70 cyc./sec. *A–F*: consecutive stimuli over a period of 8 min. *A*, 0·5 V.; *B*, 1 V.; *C*, 2 V.; *D*, 3 V.; *E*, 4 V.; *F*, 5 V.

response became purely depressor. On the other hand, stimuli of low *Vt* giving a depressor response did not influence the respiratory centre. When spontaneous respiratory movements were absent, respiratory movements often reappeared on stimulation of the sinus nerve with stimuli of medium or high *Vt*.

The effects of changes in frequency of the stimulus have not been examined systematically; it has been found, however, that changes in frequency caused a 'reversal' of the response only when the stimulus was of such a *Vt* that the

response was on the borderline between pressor and depressor. For instance, square wave stimuli of 0·02 msec. duration and 7 V. gave pressor responses at frequencies between 1·5 and 300 cyc./sec. When the voltage was raised to 30 V., frequencies below 20 cyc./sec. resulted in pressor, and frequencies over 70 cyc./sec. in depressor responses.

The fact that the choice of the anaesthetic, nembutal or urethane, had no influence on the results obtained in cats given the normal dose of anaesthetic is of some importance, since, as will be shown later, overdosage with urethane, unlike nembutal, does not convert depressor into pressor responses.

The effect of overdosage of nembutal on the response to electrical stimulation of the sinus, vagus and aortic nerves, and the action of picrotoxin

The sinus nerve. It was shown that electrical stimulation of the sinus nerve with a strong stimulus of short duration led to a marked depressor response in the cat given the normal anaesthetic dose of about 40–50 mg./kg. nembutal. It will be suggested in the discussion that such a stimulus activates three types of fibres, viz. large barosensory, small chemosensory and small barosensory fibres, the net result being a fall in blood pressure. If, however, the animals had received a second dose of nembutal of half the amount required for the initial anaesthesia, then strong stimuli of the type just described did not result in a fall of blood pressure, but led to pressor responses (Fig. 3). These reached a maximum in about 45 min. after the additional dose of anaesthetic and lasted for an hour or more without decrement. During this period the blood-pressure level was lower than before the administration of the second dose of nembutal. Sometimes, before the pressor response was fully developed, pressor responses with an after-fall (Fig. 4*B*) or biphasic responses (Fig. 4*C*), were observed. Once the pressor responses were fully developed, no variation in voltage or pulse duration was able to elicit depressor responses. The pressor responses were remarkably uniform with no variations in the heart rate. A further administration of nembutal eventually led to a disappearance of all vasomotor responses to sinus nerve stimulation.

The response of the respiratory centre to sinus nerve stimulation in the over-nembutalized animal persisted in twenty-one out of thirty-four cats. The response, however, was smaller than that found before the second dose of nembutal (Fig. 5).

When the animals were allowed to recover in the course of a few hours from the effects of the overdosage, still remaining fully anaesthetized, the pressor response slowly diminished and, eventually, the response to sinus nerve stimulation was again depressor as in the normally nembutalized cat (Fig. 3). Biphasic responses similar to those described after a second dose of nembutal were often observed. Injection of more nembutal at this stage again led to a pressor response.

The return of the depressor response could be very markedly accelerated by administration of picrotoxin, which is extensively used in the clinical treatment of barbiturate poisoning. Intravenous injection of approximately 1–1·5 mg./kg.

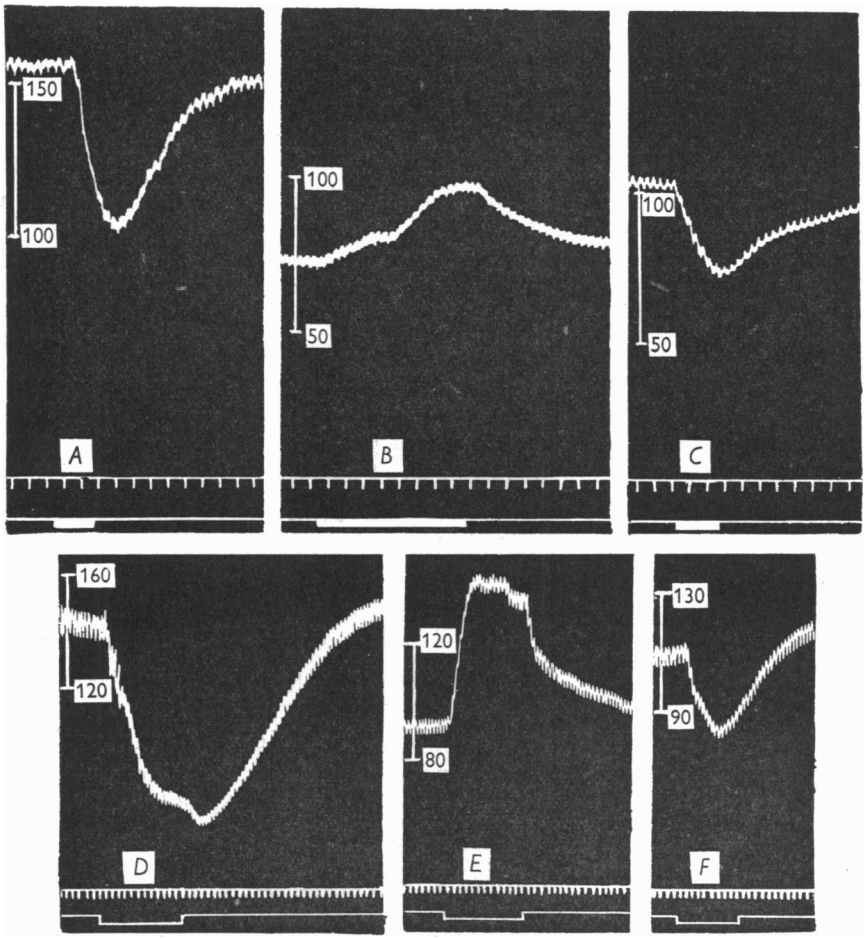

Fig. 3. Cat. Nembutal. Both vagi and left sinus nerve cut. Open pneumothorax by intubation through diaphragm. Artificial respiration. B.P. in left carotid artery in mm. Hg. Time 5 sec. Stimulation of right sinus nerve with neon tube stimulator, 40 V., 30 cyc./sec. *A*, after 50 mg./kg. nembutal; *B*, after 80 mg./kg.; *C*, 3 hr. later; *D* another cat, after 43 mg./kg. nembutal; *E*, after 83 mg./kg.; *F*, after 1·1 mg./kg. picrotoxin.

picrotoxin led within 5–10 min. to the reappearance of the depressor response, and usually to a rise of blood pressure (Fig. 3). Biphasic responses were sometimes observed in the transition period. Injection of nembutal at this stage re-established the pressor response.

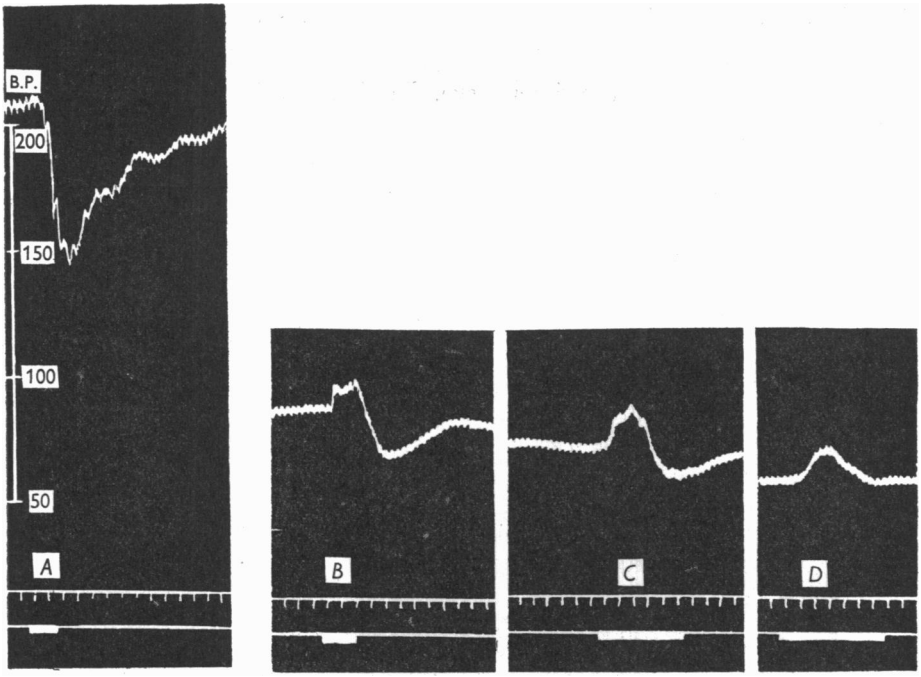

Fig. 4. Cat. Nembutal. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left carotid artery in mm. Hg. Time 5 sec. Stimulation of right sinus nerve with neon tube stimulator, 20 V., 30 cyc./sec. *A*, after 40 mg./kg. nembutal; *B*, 12 min. after additional 20 mg./kg.; *C*, 4 min. after *B*; *D*, 9 min. after *C*.

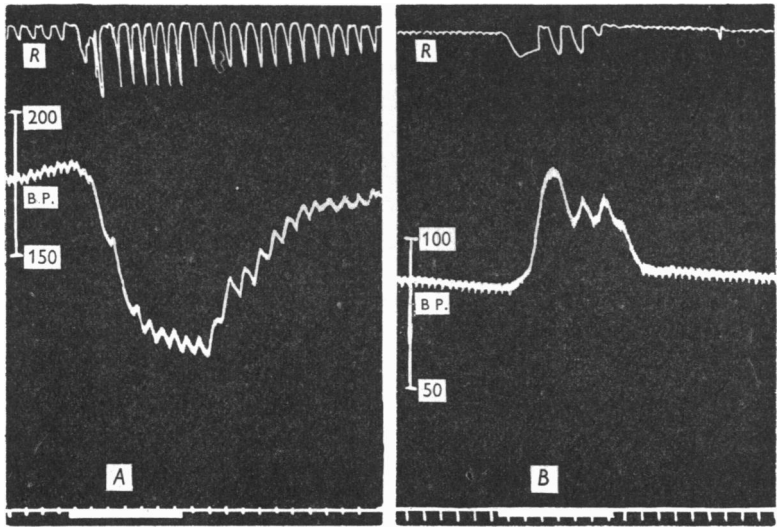

Fig. 5. Cat. Nembutal. Both vagi cut, both sinus nerves intact. Bilateral open pneumothorax. Artificial respiration. *R*, respiratory movements, inspiration downward. B.P. in femoral artery in mm. Hg. Time 5 sec. Stimulation of left sinus nerve with neon tube stimulator, 20 V., 30 cyc./sec. *A*, after 50 mg./kg. nembutal. *B*, 25 min. after additional 20 mg./kg. nembutal.

Very large doses of nembutal abolished all effects on the blood pressure of electrical stimulation of the sinus nerve. In view of this depressant action, it was held likely that doses between the normal anaesthetic dose and the dose

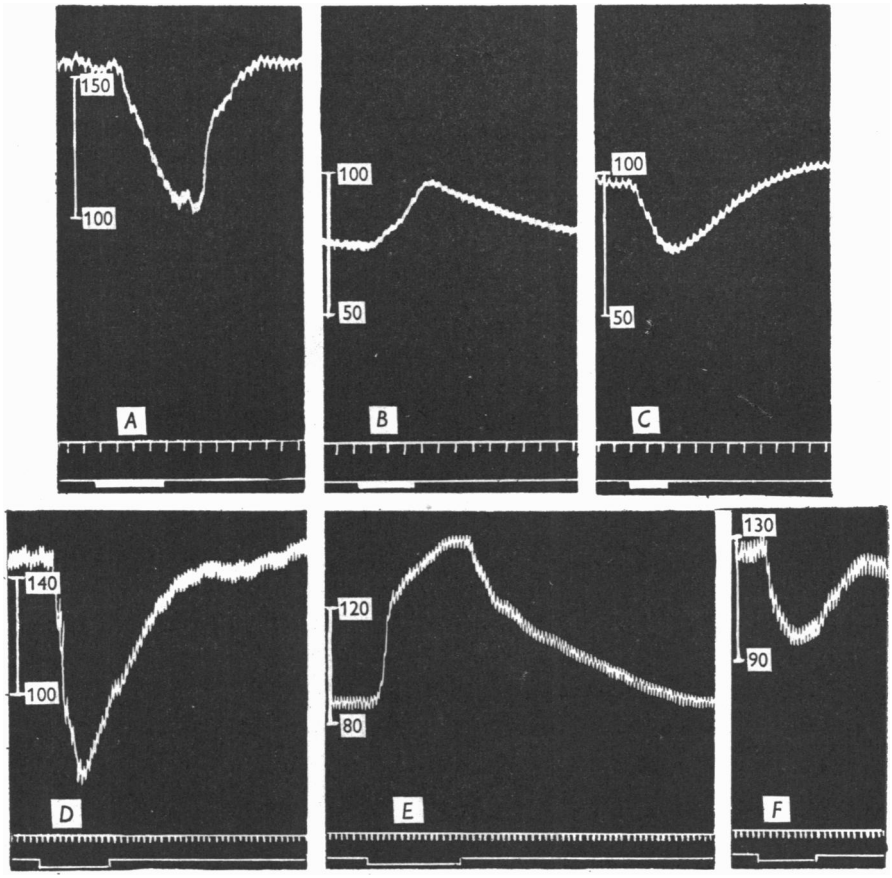

Fig. 6. Cat. Nembutal. Both vagi and left sinus nerve cut. Open pneumothorax by intubation through diaphragm. Artificial respiration. B.P. in left carotid artery in mm. Hg. Time 5 sec. Stimulation of right vagus nerve with neon tube stimulator, 40 V., 30 cyc./sec. *A*, after 50 mg./kg. nembutal. *B*, after 80 mg./kg. *C*, 3 hr. later. *D*, another cat, after 43 mg./kg. nembutal. *E*, after 83 mg./kg. *F*, after 1·1 mg./kg. picrotoxin.

causing complete absence of response would cause a rise in the threshold of both pressor and depressor reflexes. It was possible to observe in some over-nembutalized cats such an increase in the threshold of both reflexes so that in order to obtain depressor responses the strength of stimulus had to be increased. If, however, still more nembutal were given only pressor responses were obtained, no matter how strong the stimulus. In negative attempts still to

obtain depressor response, stimuli were applied of sufficient strength to destroy the nerve.

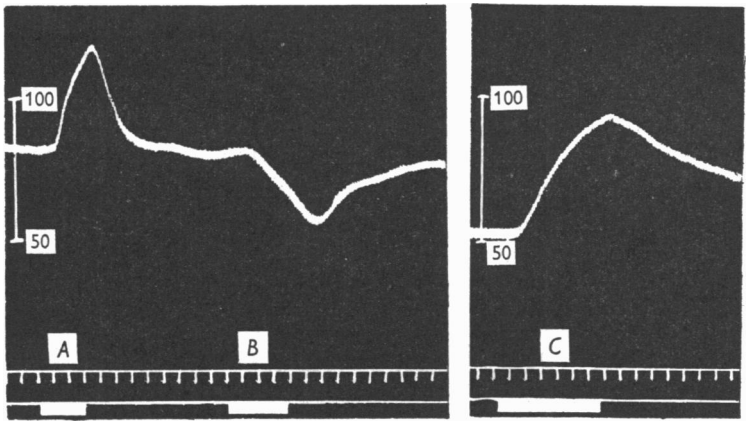

Fig. 7. Cat. Nembutal. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left carotid artery in mm. Hg. Neon tube stimulator, 40 V., 30 cyc./sec. *A*, right sinus nerve after 65 mg./kg. nembutal. *B*, right vagus nerve after 65 mg./kg. *C*, right vagus nerve after 80 mg./kg.

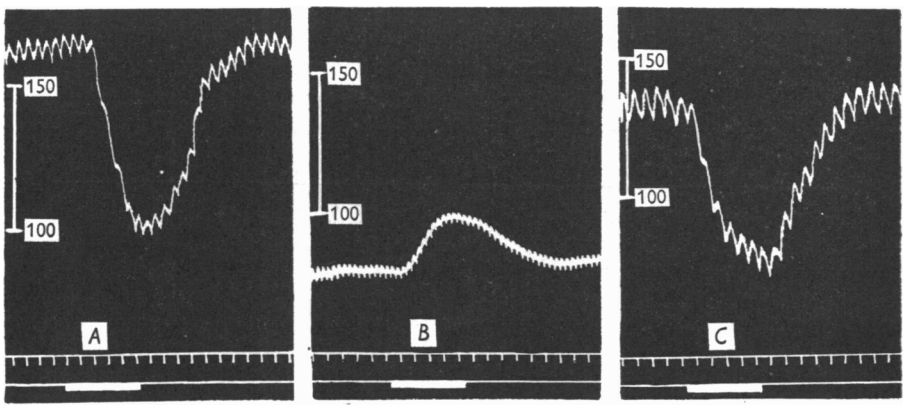

Fig. 8. Cat. Nembutal. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left femoral artery in mm. Hg. Time 5 sec. Stimulation of left aortic nerve, 1 msec., square wave, 10 V., 70 cyc./sec. *A*, after 45 mg./kg. nembutal. *B*, after 70 mg./kg. *C*, after 2·4 mg./kg. picrotoxin. (Respiratory waves are absent from *B* due to cessation of spontaneous respiratory movements during nembutal overdosage.)

The vagus nerve. In the cat, given the normal anaesthetic dose of nembutal, electrical stimulation of the central ends of the vagus nerves with a strong stimulus usually led to a marked depressor response. After a second dose of nembutal of about half the amount required for the initial anaesthesia,

this response became pressor. Spontaneous recovery, and recovery due to picrotoxin, did not show any difference from similar phenomena already described for the sinus nerve (Fig. 6). It was, however, obvious that the vagal reflexes were less sensitive to overdosage with nembutal than the sinus nerve reflexes, that is to say, with a suitable dose of nembutal normal depressor responses were still elicited by stimulation of the vagus while the sinus nerve response was pressor (Fig. 7).

With the strength of stimulus required to obtain a depressor response in the normally nembutalized cat an inhibition of respiration was observed. After the reversing dose, spontaneous respiration ceased and in thirteen out of thirty-four cats the stimulus previously causing inhibition of respiration now caused stimulation.

The aortic nerve. Stimulation of the central end of the left aortic nerve in three cats led to a fall in arterial blood pressure in the cat anaesthetized with nembutal (40–50 mg./kg.). Further injection of half the original anaesthetic dose converted the depressor to a pressor response. Picrotoxin re-established the depressor response (Fig. 8).

The effect of low blood pressure on the response to electrical stimulation of the sinus and vagus nerves

Since the arterial blood pressure in the overdosed animal was often low, it was necessary to test whether low arterial blood pressure could by itself 'reverse' the response. This is of importance in view of the results of McDowall (1925) and Wright (1932), who found that in animals with low arterial blood pressure pressor fibres may be active in the vagus nerve.

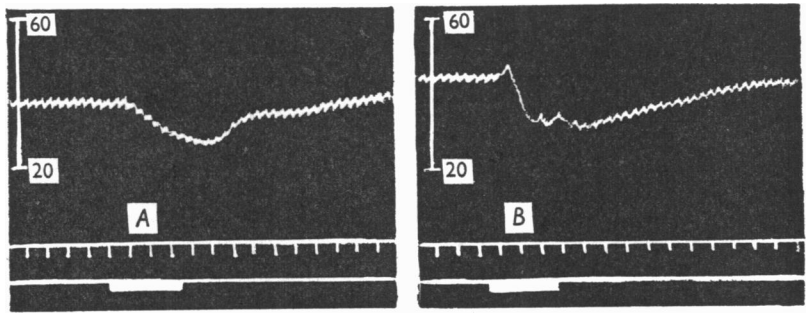

Fig. 9. Cat. Nembutal, 40 mg./kg. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left carotid artery in mm. Hg. Time 5 sec. Neon tube stimulator, 40 V., 30 cyc./sec. *A*, right vagus nerve; *B*, right sinus nerve.

Low pressures in cats given the normal anaesthetic dose of nembutal were obtained either at the end of lengthy experimental procedures (two cats), or after repeated bleedings (two cats). Two more cats were under urethane

anaesthesia, the low pressure being consequent upon the combined effects of operative interference and bleeding. In all these animals, stimulation of the vagus and sinus nerves resulted in depressor responses, even when the pressure was initially as low as 40 mm. Hg (Fig. 9). It is also of interest to note that administration of picrotoxin to cats overdosed with nembutal may raise the blood pressure without converting the pressor response to a depressor while, on the other hand, it may cause depressor responses to reappear without raising the blood pressure.

Effect of decerebration at various levels

In these experiments, cats were first given the normal anaesthetic dose of nembutal and the responses to stimulation of the vagus and sinus nerves tested. This was repeated after administration of the 'reversing' dose. Then decerebration was performed. In four out of five cats, stimulation of the buffer nerves after decerebration at the level of the superior colliculi gave pressor responses similar to those obtained before; picrotoxin still converted the pressor to depressor as in the animals with the brain intact (Fig. 10). In the fifth animal, the responses, pressor before decerebration, were depressor after. On administration of more nembutal, however, they again became pressor. Sectioning below the superior colliculi down to the entry of the ninth and tenth nerves did not affect the pressor responses nor the efficacy of picrotoxin in abolishing the nembutal reversal. This fact indicates that no centres higher than the medullary vasomotor centres are involved in the action of nembutal or picrotoxin on these vasomotor reflexes.

The traction test in nembutal overdosage

In cats with both vagi and the left sinus nerve cut, traction on the occluded right common carotid artery caused a fall in arterial blood pressure if the normal anaesthetic dose had been given, and a rise in blood pressure if the animal had been overdosed with nembutal. These effects were still present, although diminished, when the sinus nerve was frozen but were absent after severing the nerve. Traction of the cut sinus nerve in the overnembutalized cat gave a pressor effect similar to that observed after traction of the carotid artery with the nerve frozen (Fig. 11). At least part of the effect of the traction test is therefore due to mechanical stimulation of the axons in the nerve itself central to the frozen area. In nembutal overdosage such traction results in a rise of blood pressure, traction on the depressor fibres being ineffective.

The effect of overdosage of urethane

For the analysis of the effects of electrical stimulation of the sinus nerve with stimuli of varying *Vt* it was of importance to compare the results obtained on nembutalized cats with those obtained on cats given an anaesthetic which, even

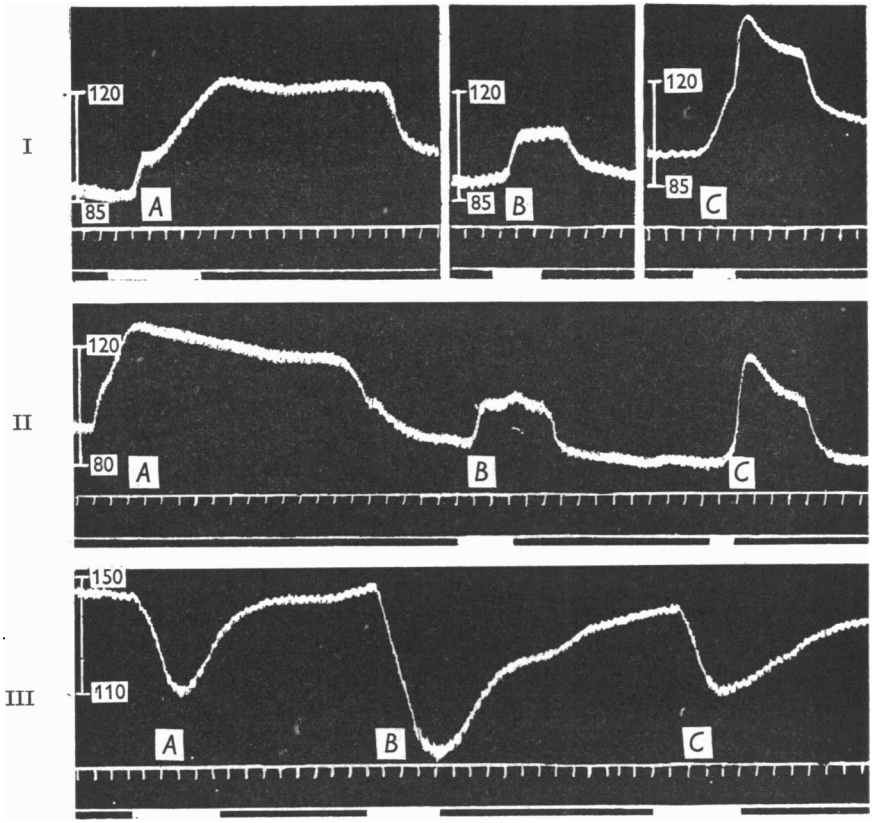

Fig. 10. Cat. Nembutal. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. B.P. in left carotid artery in mm. Hg. Neon tube stimulator, 40 V., 30 cyc./sec. *A*, left vagus nerve; *B*, right vagus nerve; *C*, right sinus nerve. I: after 78 mg./kg. nembutal. II: 16 min. later, after decerebration at level of superior colliculi. III: after 1·8 mg./kg. picrotoxin. (Signal for II *A* is missing.)

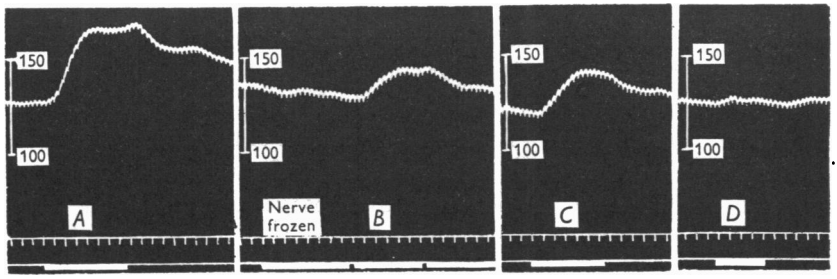

Fig. 11. Cat. Nembutal, 65 mg./kg. Both vagi and left sinus nerve cut. Bilateral open pneumothorax. Artificial respiration. Right common carotid artery occluded throughout. B.P. in left carotid artery in mm. Hg. Time 5 sec. *A*, traction applied to the right common carotid artery. *B*, repeated with the right sinus nerve frozen. Right sinus nerve cut between *B* and *C*. *C*, traction applied to the cut right sinus nerve. *D*, traction on the carotid artery repeated after sinus nerve section.

in large doses, did not lead to a 'reversal'. It was found that urethane fulfilled these conditions.

Cats were anaesthetized with urethane (1–1·5 g./kg. in 25% solution, intraperitoneally). When suitable stimuli had been selected which gave depressor responses on stimulation of the vagus and sinus nerves, the animals were given intravenously, at intervals, additional doses of one-quarter of the original anaesthetic dose. The magnitude of the responses tended to diminish as the anaesthesia became deeper, but there was no 'reversal' as in nembutal overdosage, even in cats which had received a total of three times the anaesthetic dose.

DISCUSSION

From studies of the action potentials of the sinus nerve it has been known for some time that it contains large barosensory and smaller chemosensory fibres (Bronk, 1931; Bronk & Stella, 1932; Heymans & Rijlant, 1933; Zotterman, 1935). In addition, Euler, Liljestrand & Zotterman (1939, 1941) adduced evidence that apart from the large barosensory fibres, the sinus nerve also contains small fibres which respond to variations in endosinusal pressure and are insensitive to chemical stimuli. They found that sometimes the large spikes due to activity of the large barosensory fibres were absent. If, in such preparations, they silenced the chemosensory fibres by hyperventilation with O_2, small spikes were observed when the arterial blood pressure was raised. Since these small spikes were very numerous, it was concluded that the small barosensory fibres might be of greater importance in the sinus pressure reflexes than the large ones. The amplitude of the action potentials was similar to that of the chemosensory fibres.

In the light of these findings, the following interpretation of the response of the sinus nerve to electrical stimulation suggests itself: weak stimuli of low *Vt* activate the large barosensory fibres with a low threshold, causing a fall in blood pressure. A small increase in the *Vt* of the stimulus also activates the chemosensory fibres with a slightly higher threshold, leading to a rise in arterial blood pressure as soon as the effect of the stimulation of the numerous chemosensory fibres overcomes that of the large barosensory fibres. A further rather considerable increase of the *Vt* of the stimulus at first intensifies the pressor and then successively diminishes it and converts it into a depressor response as more and more of the small barosensory fibres with a high threshold are brought into play. The magnitude of the stimulus required to activate the small barosensory fibres indicates that they are smaller than the chemosensory fibres. It also suggests that their threshold is of the order usually found in C fibres (Blair & Erlanger, 1933). If this is the case, the powerful stimulus required to activate them is in agreement with the findings of Gordon (1943), who stressed the difficulty of exciting vasomotor C fibres in mixed sensory nerves with brief condenser shocks.

The view that the pressor responses are due to stimulation of the chemosensory fibres is supported by the following facts:

(1) Stimuli of low *Vt*, which activate the large depressor fibres only, have no effect on the respiratory centre. Stimuli of medium *Vt*, which activate the large depressor and the small pressor fibres, yielding a pressor response, stimulate the respiratory centre as shown by the increase in respiratory movements. Stimuli of high *Vt* which stimulate also the small depressor fibres, yielding a depressor response, have little or no additional effect on the respiratory centre.

(2) After the 'reversing' dose of nembutal, the pressor responses due to stimuli of high *Vt* are in the majority of animals still accompanied by a stimulation of the respiratory centre.

The physiological significance of the two types of barosensory fibres is not clear at present. There will, however, be a considerable difference between the times taken for the conduction by the large and small fibres of barosensory impulses from the carotid sinus to the medulla. It is at least possible that in this way the variations in endosinusal pressure caused by the cardiac cycle are minimized so far as impulses arriving at the vasomotor centre are concerned. Further, the large and small fibres probably have different characteristics of adaptation and summation, similar to the differences found for large tactile and small pain fibres in mixed sensory nerves (Adrian, 1932). If this is so, the reflexes subserved by the small barosensory fibres would probably be more effective in maintaining the arterial blood pressure at a constant level than those subserved by the large fibres.

In urethane overdosage, the thresholds for both pressor and depressor responses obtained by electrical stimulation of the sinus nerves rise at about equal rates and the character of the responses remains unchanged. In nembutal poisoning, however, the depressor reflexes suffer more than the pressor ones: when the anaesthesia is deep enough seriously to interfere with the activity of the respiratory centre but not so deep as to cause complete abolition of all vasomotor reflexes, then the depressor responses are no longer obtainable after stimulation of the sinus, aortic and vagus nerves while the pressor responses are still present. This phenomenon is reversible. On recovery from the overdosage with nembutal, either spontaneous or accelerated by picrotoxin, the normal depressor responses are again obtained. Proof has been given that the 'reversal' is not caused by a low arterial blood pressure and that centres higher than the vasomotor centres are unnecessary.

So far as the nature and the site of the 'reversal' are concerned, evidence is still incomplete. The following interpretation may serve as a tentative hypothesis. It is suggested that, while a strong stimulus activates chemosensory and both types of barosensory fibres in the sinus nerve in nembutal overdosage, the rise in blood pressure is brought about by the fact that the barosensory reflexes

are in abeyance. This is probably due to the barosensory reflex mechanisms of the medulla being more susceptible to nembutal than the chemosensory. This hypothesis could also explain why the vagal depressor response is converted to pressor in nembutal overdosage. However, the fact has to be taken into consideration that the fibre composition of the vagus is much more complex than that of the sinus nerve.

Of other anaesthetics, urethane has been found to have no selective effect on the barosensory mechanism. Neil, Redwood & Schweitzer (1948, 1949) have also recently described a 'reversal', apparently similar to that here described in nembutal overdosage, in cats anaesthetized with the normal dose of chloralose.

SUMMARY

1. Cats, anaesthetized with urethane or nembutal, had their lungs artificially ventilated after bilateral open pneumothorax. After section of both vagi and the left sinus nerve electrical stimulation of the right sinus nerve gave the following responses: (*a*) stimuli of low voltage and very short duration caused in many, but not in all, cats a fall in blood pressure; (*b*) when the voltage or the pulse duration was increased, a pressor response was obtained; (*c*) further increase, either in voltage or in pulse duration, caused at first an after-fall, then a biphasic and finally a depressor response. In responses (*b*) and (*c*), but not in (*a*), there was increased activity of the respiratory centre. It is suggested that response (*a*) is due to stimulation of large barosensory fibres with a low threshold, response (*b*) is due to smaller chemosensory fibres and response (*c*) is due to small barosensory fibres of high threshold.

2. Injection of half the original anaesthetic dose of nembutal in a cat, already anaesthetized with the normal dose of nembutal, resulted in a general fall in arterial blood pressure and in conversion of depressor responses, due to electrical stimulation of the sinus, vagus and aortic nerves, to pressor responses. No depressor response could be obtained while the cat was thus overdosed with nembutal, whatever the voltage or pulse duration of the stimulus. On spontaneous recovery from the effects of nembutal overdosage, or more rapidly after injection of picrotoxin, the normal depressor response reappeared. The depressor reflexes subserved by the vagus were less susceptible to the action of nembutal than those subserved by the sinus nerve.

3. Low arterial blood pressure by itself did not lead to a loss of the depressor reflexes.

4. Removal of the brain just cranial to the level of the entry of the 9th and 10th nerve in overnembutalized cats had no effect on either the pressor response or on the efficacy of picrotoxin.

5. Overdosage with urethane, unlike overdosage with nembutal, did not cause a selective loss of the depressor response. With increasing doses both pressor and depressor responses diminished and eventually disappeared.

6. Traction on the common carotid artery in the overnembutalized cat led to a pressor response which, although diminished, was still present after a cold block had been applied to the sinus nerve and which was similar to the pressor response obtained by traction on the cut sinus nerve.

7. Strong stimuli may activate the chemosensory and both types of barosensory fibres in the sinus nerve, yielding a depressor response in the cat under the normal anaesthetic dose of nembutal. The selective loss of the depressor responses found in over-nembutalized cats is assumed to be due to the barosensory reflex mechanism of the medulla being more susceptible to nembutal than the chemosensory. The vagal pressor response in nembutal overdosage can be similarly explained.

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