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CENTRAL CONTROL OF SYMPATHETIC CARDIO-ACCELERATION IN THE CAT

BY C. N. PEISS*

From the Department of Physiology, Stritch School of Medicine and the Graduate School, Loyola University, Chicago, Illinois, U.S.A.

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At the present time there is little conclusive evidence as to the location of a cardioaccelerator centre. It is a curious fact that the extensive series of investigations which have provided comprehensive information about the vasomotor centre (Scott & Roberts, 1923; Scott, 1925; Monnier, 1939; Wang & Ranson, 1939*a*; Alexander, 1946; Bach, 1952) has failed to clarify the anatomical basis for a medullary cardioaccelerator centre. In an early text-book of physiology (Howell, 1897) the statement is made that 'the situation of the centre for the augmentor nerves of the heart is not definitely known, although from analogy it seems probable that it will be found in the bulb'. It appears that current teaching about the cardio-accelerator centre is still based on analogy to a large extent. Aside from specific text-book descriptions of the location of the cardioaccelerator centre in the medulla close to the vasomotor centre, there are few reports in the research literature of this type. In reviewing the cardioaccelerator mechanism, Bard (1929) concluded that the centre is probably in the medulla oblongata. The chief basis for this conclusion appears to be the indirect evidence obtained from studies on heart-rate changes reflexly induced through the inhibitory and accelerator nerves (Hunt, 1899; Bayliss, 1908; von Brücke, 1917; McDowall, 1931, 1938; Bronk, Ferguson & Solandt, 1934). These papers are the chief basis for the concept of reciprocally innervated cardiac centres. It has also been stated (Bard, 1929) that Ranson & Billingsley (1916) observed cardiac acceleration during electrical stimulation of the floor of the fourth ventricle after section of the vagi. In fact, the paper of Ranson & Billingsley recorded no such result. It is a well documented fact that reflex activation of the vaso-motor centre is associated with cardiac acceleration. This fact, coupled with the known location of the vasomotor and cardio-inhibitory centres in the medulla, makes the postulate of a medullary cardioaccelerator centre in close proximity to the vasomotor centre a most attractive and reason-able hypothesis.

* John and Mary Markle Scholar in Medical Sciences.

Careful control of experimental procedures is necessary to test this hypothesis properly. There are four ways by which heart rate may be increased during electrical stimulation of the brain: (1) activation of sympathetic outflow to the heart; (2) central inhibition of vagal tone; (3) release of epinephrine and norepinephrine from the adrenal medulla; and (4) certain non-specific factors relating to the metabolic status of the heart.

Failure to evaluate these factors adequately has contributed to the uncertainty with regard to the cardioaccelerator centre. The conclusion that cardioaccelerator fibres are being activated is valid only when there is complete assurance that the other three mechanisms are inoperative. Once this point is reached, it must still be shown whether the fibres being stimulated in the brain are afferent or efferent. It is the purpose of this paper to present such a controlled analysis of the postulated medullary cardioaccelerator centre.

METHODS

The data in this paper were obtained from ninety-six young adult cats, of which fifty-five were anaesthetized with sodium pentobarbital 30 mg/kg intraperitoneally. The remaining forty-one animals were anaesthetized with alpha-chloralose 70–100 mg/kg intravenously. The differences in cardiovascular responses obtained from the two groups are discussed in detail below. Blood pressure was recorded from a carotid artery with a Statham P23Db transducer, Sanborn carrier wave amplifier and optical galvanometer. The pressure recording system was filled with heparin to prevent coagulation of the blood. Heart rate was recorded continuously with an integrating cardiotachometer (McCook & Peiss, 1959). Specific latency of changes in heart rate induced by electrical stimulation was determined by pulse-to-pulse measurements from high-speed recordings. Stimulation parameters were 2–7 V, 2 msec pulse duration and a frequency of 70 c/s. These parameters have been shown to be optimum for eliciting cardiovascular responses from the brain stem (Peiss, 1956). The positions of knife transections, hypothalamic lesions and stimulating electrodes were verified histologically from serial sections of the brain stem.

All animals were bilaterally vagotomized by dividing the vagosympathetic nerves high in the neck. This eliminated changes in vagal tone as a possible source of cardioacceleration. Increases in heart rate due to activation of the adrenal medulla were ruled out by the requirement that only cardioaccelerator responses which occurred with a latency of less than 6 sec would be considered as valid primary accelerator responses. The role of the adrenal medulla is shown below in the Results section. Since the metabolic status of the heart will have important consequences on its dynamic performance, we have eliminated from consideration any animals whose mean blood pressure was below normal limits. This was done solely to eliminate as far as possible non-specific factors (item 4 above) affecting the heart rate. It is conceivable that the blood-pressure rise following stimulation, with an attendant increase in coronary flow, might result in appreciable changes in heart rate in an animal with poor coronary circulation.

RESULTS

Areas stimulated in the medulla

There is general agreement that the vasomotor centre is located in the lateral reticular formation, extending dorsally to the floor of the fourth

ventricle (cf. Wang, 1955). It is our experience that the greatest pressor responses are obtained from an area extending 1–5 mm rostral to the obex, 1–3 mm to either side of mid line and from 0 to 3 mm ventral to the floor of the fourth ventricle. Although responses can be obtained from a much wider area than that outlined above, they generally are smaller in magnitude and less consistent from animal to animal. Whether this area of greatest responsiveness constitutes the integrative centre is not known. It is sufficient for our purposes to point out that large increases in mean pressure continue to be elicited from this region after mid-collicular transection, indicating that this area does not merely represent a site of afferent input to higher levels of the central nervous system. The picture is further complicated by the fact that an appreciable part of the blood-pressure rise resulting from stimulation of this area of the medulla is due to the activation of augmentor pathways to the heart (Peiss, 1958).

In these experiments the ventrolateral portion of the medulla has also been explored. Stimulation of this area, however, may not involve activation of a medullary vasomotor mechanism, but rather of efferent pathways from the hypothalamus (Magoun, Ranson & Hetherington, 1938; Wang & Ranson, 1939*b*). Since stimulation of the hypothalamus results in large increases in heart rate mediated through the cardiac sympathetics (Beattie, Brow & Long, 1930; Manning & Peiss, 1958, 1960; Rushmer, Smith & Franklin, 1959), it is vital to differentiate these two regions of responsiveness in the medulla. Cardioacceleration resulting from activation in the medulla of hypothalamospinal pathways affords no evidence for a medullary cardioaccelerator centre. Such inferences have been made in the older literature. In this paper, therefore, we shall distinguish between 'dorsal' and 'ventrolateral' medullary areas.

Responses under pentobarbital anaesthesia

Short-latency responses. Over one thousand stimulations of the dorsal medulla in fifty-five cats resulted in only a few clear-cut cardiac accelerations that could probably be ascribed to activation of sympathetic outflow to the heart. The heart-rate increases were never more than 15% of the pre-stimulation level. Since both vasomotor and augmentor responses could easily be elicited under this mode of anaesthesia (Peiss, 1958), it appeared reasonable to assume that a medullary cardioaccelerator centre would also be operative if it existed. Moreover, if the postulated close proximity of the medullary cardioaccelerator centre to the vasomotor centre, and its reciprocal relation to the cardio-inhibitory centre, were real, it appeared reasonable that we should have succeeded in activating it in the area of the medulla which yielded maximal vasoconstrictor and augmentor activity. The fact that the accelerator responses were rarely

evoked casts doubt on the postulated location of the cardioaccelerator centre.

On the other hand, in animals under the same anaesthesia it is common to obtain significant short-latency acceleration by stimulation of the ventrolateral medulla. It is our experience that these areas are usually devoid of the very large pressor responses observed when the dorsal medulla is

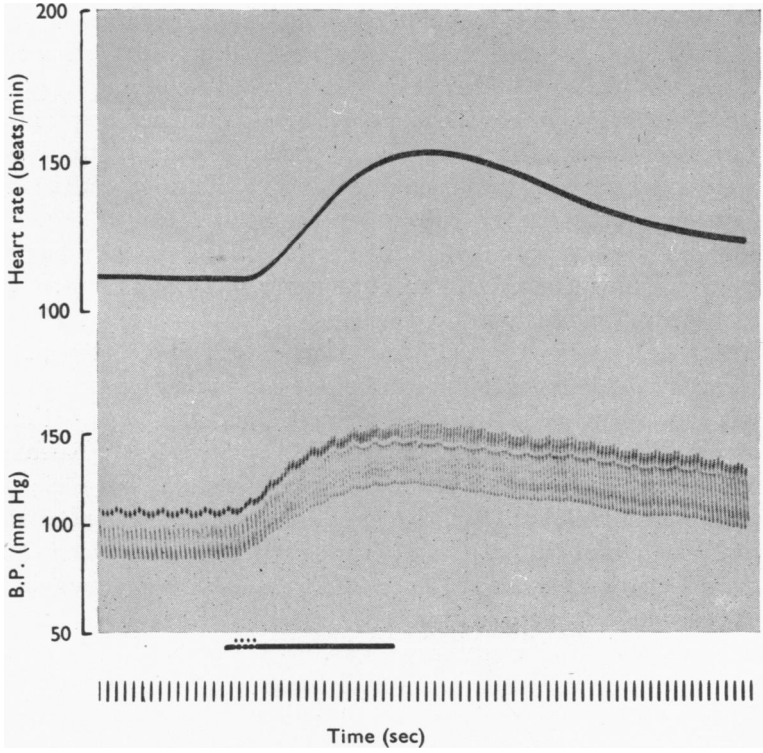

Fig. 1. Short-latency cardioaccelerator response to stimulation of ventrolateral medulla in the cat under pentobarbital anaesthesia. Stimulation parameters: 3·2 V, 2 msec, 70 c/s. Solid bar indicates period of stimulation.

stimulated. Figure 1 shows an example of a short-latency response from the ventrolateral medulla in a cat under pentobarbital. The electrode was located at the extreme border of the lateral reticular formation near the vestibulospinal tract. In other cats similar responses were obtained from the area of the ventral reticulospinal tract.

Long-latency responses. Stimulation of the dorsal medulla frequently elicited cardiac acceleration after a latency of 12–20 sec from the onset of stimulation. Figure 2 illustrates such a response, from a point 1·5 mm below the floor of the fourth ventricle, 2 mm right of mid line and 2 mm

rostral to the obex. Despite the fact that pressor and augmentor activity is observed within 5 sec, acceleration does not occur until 12·5 sec after onset of stimulation. It would be presumptive to assume that this is the result of peripheral delay at the effector sites on the heart, especially since cardioaccelerator responses obtained by hypothalamic stimulation have latencies of 1–5 sec. The delayed acceleration is most probably due to

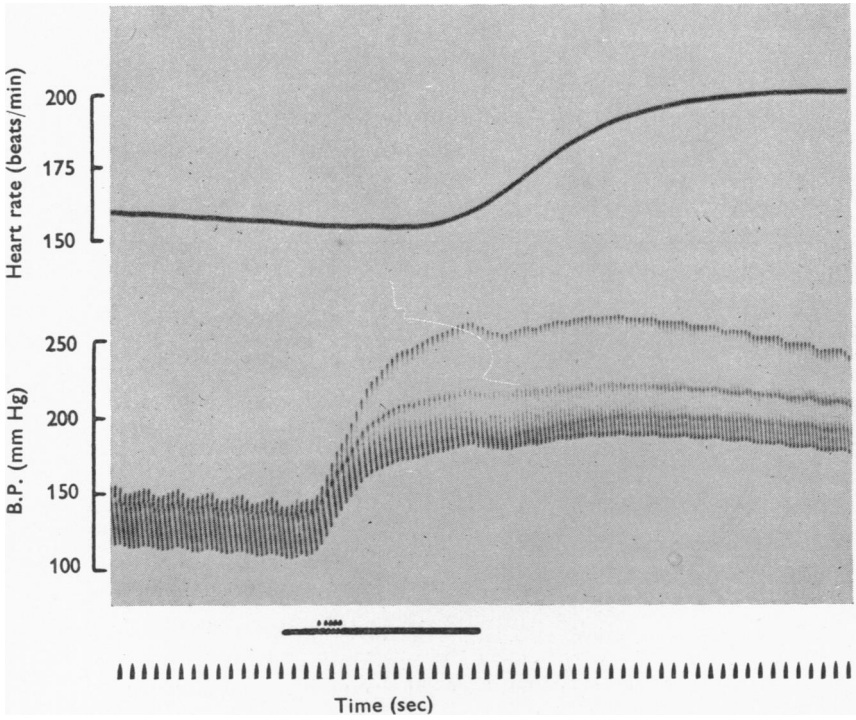

Fig. 2. Long-latency cardioaccelerator response to stimulation of dorsal medulla in the cat under pentobarbital anaesthesia. Stimulation parameters: 2·6 V, 2 msec, 70 c/s. Solid bar indicates period of stimulation.

activation of the adrenal medulla and subsequent arrival at the heart of its secretion. This possibility was tested in a series of seven animals, all of which showed delayed acceleration similar to that shown in Fig. 2. These seven cats were then subjected to acute bilateral adrenalectomy and restimulated at the same point in the medulla and at the same parameters of stimulation. The results of a typical experiment are shown in Fig. 3. It is apparent that most of the accelerator (and augmentor) response was eliminated by adrenalectomy, which supports our ideas concerning the origin of these long-latency accelerator responses. The decreased rise in blood pressure after adrenalectomy is due, in part, to elimination of the

accelerator and augmentor responses. In other animals most of the pressor response remained after adrenalectomy.

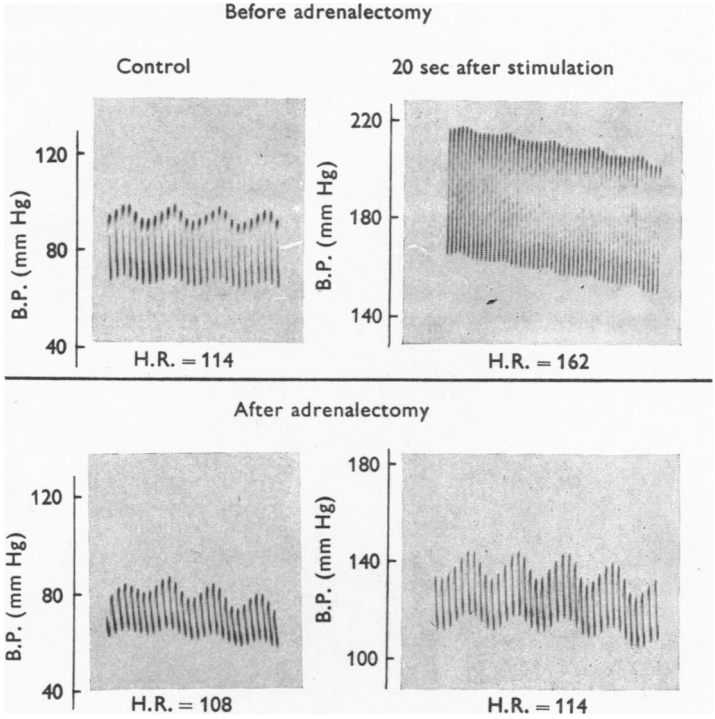

Fig. 3. Effect of bilateral adrenalectomy on long-latency cardioaccelerator response to stimulation of dorsal medulla in the cat under pentobarbital anaesthesia. Stimulation parameters: 3 V, 2 msec, 70 c/s; H.R., heart rate (beats/min).

Responses under chloralose anaesthesia

In striking contrast to results obtained with cats under pentobarbital, it was found that large increases in heart rate, with latencies of 1–5 sec, result when the dorsal medullary area is stimulated in cats under chloralose anaesthesia. A typical response is shown in Fig. 4. Although cardioacceleration is not obtained as consistently as augmentation and vasoconstriction, adequate exploration of the dorsal medullary area outlined above is usually successful in locating an active region in most cats. Moreover, increases in heart rate are consistently larger than those seen under pentobarbital, amounting to as much as an 80% increase over the prestimulation level. This greater response is not due to differing control levels of heart rate in the two sets of animals under different anaesthetics.

Heart rates in both series, after vagotomy, were in the range of 100–175 beats/min.

The question now arises as to the cause of the difference between cardioaccelerator responses to electrical stimulation of the dorsal medulla under the two anaesthetics. If the postulated existence and location of a medullary cardioaccelerator centre is valid, one must conclude that there is a

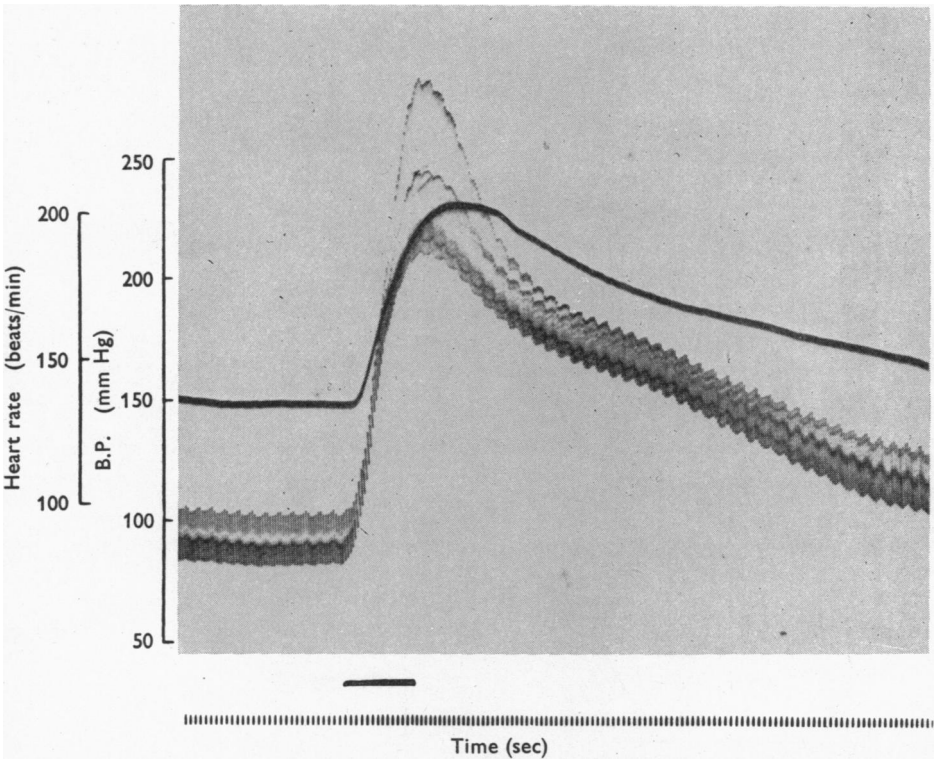

Fig. 4. Short-latency cardioaccelerator response to stimulation of dorsal medulla in the cat under chloralose anaesthesia. Stimulation parameters: 1·9 V, 2 msec, 70 c/s. Solid bar indicates period of stimulation.

differential effect of barbiturate on those cells and/or fibres subserving acceleration of the heart as compared with those subserving augmentation of myocardial contractile force and blood vessel constriction. This does not appear to be a reasonable assumption.

It has been shown previously (Manning & Peiss, 1958) that usual anaesthetic doses of pentobarbital severely depress or eliminate cardiovascular responses to electrical stimulation of the hypothalamus. On the other hand, these responses from the hypothalamus are readily elicited

under chloralose. A more logical conclusion from the above data is, therefore, that the accelerator area in the dorsal medulla, which is quite responsive under chloralose, is in fact an afferent pathway to higher levels of the central nervous system. If the fibres from this area relay in the hypothalamus, it might then be expected that the response to dorsal medullary stimulation would be blocked or severely depressed under pentobarbital anaesthesia.

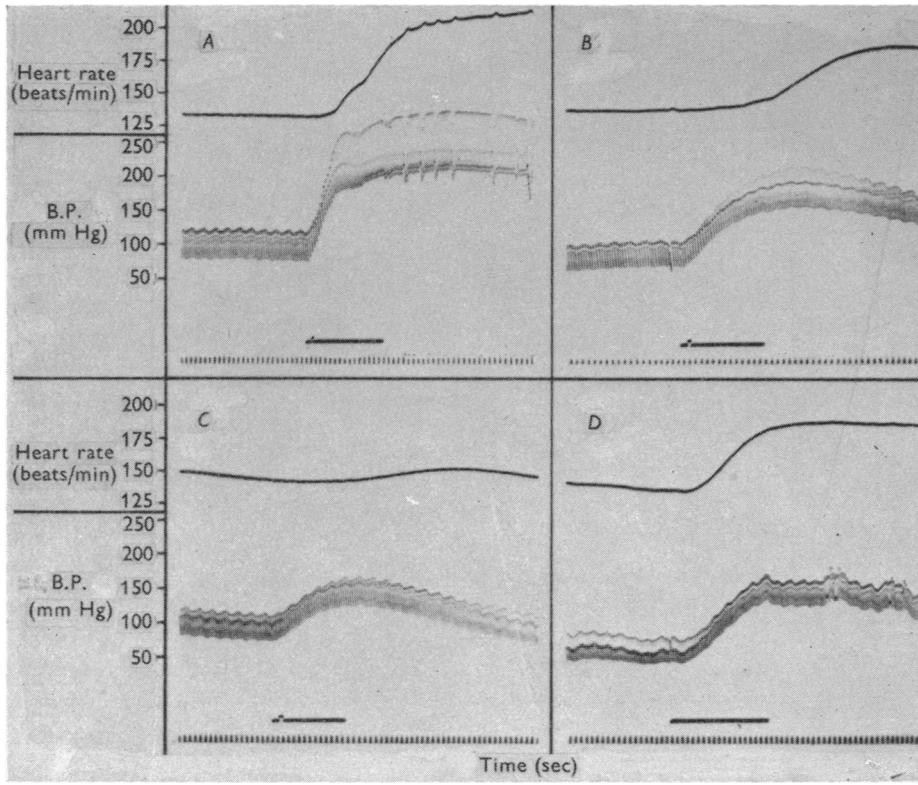

Fig. 5. Effect of lesions (just caudal to hypothalamus) on cardioaccelerator response to stimulation of dorsal medulla in the cat under chloralose anaesthesia. *A*. Pre-lesion response. *B*. Response after partial lesion (see text for details). *C*. Response after more extensive lesion (see text for details). *D*. Accelerator response from ventrolateral medulla after above lesion. All stimuli at 2·4 V, 2 msec, 70 c/s. Solid bars indicate periods of stimulation.

Figure 5 illustrates an experiment testing this critical point as to whether or not cardioacceleration following stimulation of the dorsal medullary area is due to stimulation of afferents to higher levels of the central nervous system. In Fig. 5*A*, a point in the dorsal medulla was stimulated

in a vagotomized cat under chloralose anaesthesia. The point stimulated was 1 mm below the floor of the fourth ventricle, 1·5 mm left of mid line and 2·5 mm rostral to the obex. Within 3 sec, heart rate, pulse pressure and mean pressure increased. At the peak of the response heart rate had increased from 134 to 220 beats/min, pulse pressure from 46 to 82 mm Hg, and mean pressure from 100 to 250 mm Hg. The recording shown in Fig. 5*B* was made after partial destruction of the brain stem with electrolytic lesions. A series of five electrodes were placed at 2 mm intervals across the brain stem. Each electrode carried a current of 5 mA for 20 sec. Since more extensive lesions were made subsequently, it is possible only to estimate the extent of the lesion present when the record shown in Fig. 5*B* was made. From the data of Carpenter & Whittier (1952), it is estimated that the lesion extended laterally on each side of the mid line to the nucleus ventralis posteromedialis, dorsally to a level at the dorsal border of the red nucleus and ventrally to a level at the ventral border of the red nucleus, involving a segment of the brain stem 10 mm wide, 2 mm in the dorsoventral plane and 1 mm in the rostrocaudal plane. The stimulus strength in Fig. 5*B* was the same as in Fig. 5*A*. It is apparent that the magnitude of response was greatly diminished by the lesion, and that the latency for cardioacceleration was greatly increased. Figure 5*C* shows a recording made some minutes later, after further electrolytic destruction of the brain stem. Histological examination of a cross-section at the level of the red nucleus revealed practically total destruction of the ventral two-thirds of the brain stem, extending approximately 5 mm to each side of the mid line and dorsally to a level at the dorsal border of the nucleus centralis. The recording indicates that the same stimulus which was applied to the same point in the dorsal medulla in Fig. 5*A* now produces a modest rise in mean blood pressure, practically no change in pulse pressure and very little cardioacceleration. It appears that the pathways which influence cardiac rate and contractility are no longer operative. It is presumed that the rise in diastolic pressure indicates the integrity of a vasomotor pathway. The integrity of the vasomotor reflex arc has been demonstrated in other experiments by using bilateral carotid artery occlusion. Figure 5*D* shows the response in the same animal to stimulation in the ventrolateral medulla shortly after the record in Fig. 5*C* was obtained. An appreciable acceleration of the heart resulted, after a latency of 3·5 sec. This response was similar to that shown in Fig. 1, which was recorded from another cat with the electrode in approximately the same position. The response in Fig. 5*D* also confirms that the trauma resulting from electrolytic destruction of the brain stem did not affect the peripheral mechanisms involved in the cardioaccelerator response. Two other lesion experiments were performed with the same results.

Similar experiments have been performed by knife transections of the brain stem at the mid-collicular level. In seven experiments of this type, transection resulted in complete loss of the cardioaccelerator response to dorsal medullary stimulation in four cats. The other three cats showed 80–90 % loss of response. In all animals the transections were accomplished without appreciable fall in mean blood pressure.

DISCUSSION

Taken as a whole, the data in this paper provide little evidence for the existence in the dorsal medulla of an area involved in the integration of sympathetic cardioacceleration. The postulated spatial proximity of a cardioaccelerator centre to the medullary vasomotor centre appears to have little basis in fact. Under pentobarbital anaesthesia the only region in the medulla which gives rise to fairly consistent short-latency cardiac acceleration, when stimulated electrically, is the ventrolateral area, which is usually devoid of great pressor activity. It is most probable, therefore, that these ventrolateral areas of the medulla represent the site of hypothalamo-spinal pathways. This view is supported by the loss of reflex acceleration in vagotomized animals induced by bilateral carotid artery occlusion following mid-brain transections (T. K. Akers & C. N. Peiss, unpublished results).

In cats under chloralose anaesthesia stimulation of the vasomotor area of the dorsal medulla gives relatively consistent short-latency accelerator responses, in contrast to the almost complete absence of these responses under full anaesthetic doses of pentobarbital. If the responses under chloralose were due to activation of pathways to higher levels of the central nervous system, this anaesthetic difference would be consistent with previous findings that the hypothalamus is severely depressed by the barbiturates (Manning & Peiss, 1958). Evidence supporting the hypothesis that the dorsal medulla contains afferent pathways involved in sympathetic cardioacceleration is provided by the loss of most of the accelerator responses to dorsal medullary stimulation following mid-collicular transection or massive electrolytic lesions in the brain just caudal to the hypothalamus. Hunt (1899) noted many years ago that the 'accelerator centre' is resistant to influences which depress the vasomotor centre. One of the influences was curare. We have shown recently (Peiss & Manning, 1959) that curare has a direct depressant effect on the excitability of the medullary vasomotor centre, with little or no effect on areas in the hypothalamus which are involved in cardiovascular control. These findings are consistent with an anatomical separation of cardioaccelerator and medullary vasomotor areas of integration. These findings do not exclude the possibility of some integrative activity in the bulb with regard to sym-

pathetic cardioacceleration. The 10–15% increases in heart rate in the cats under pentobarbital, as well as the persistence of up to 20% of the response under chloralose after transection, supports the view that there may be such bulbar integration. However, until all the hypothalamic pathways to the heart are known it is impossible to determine whether or not such residual acceleration is due to efferent pathways from the hypothalamus. The findings indicate that, of the sympathetic cardioacceleration that can be induced in a chloralosed cat, the great majority is dependent upon the integrity of brain-stem areas above the medullary vasomotor area. In the dog it has been shown that some cardiac acceleration occurs in a vagotomized, adrenalectomized, mid-brain-transected preparation following sciatic nerve stimulation (Chen, Lim, Wang & Yi, 1937). The heart rate in this experiment increased from a control level of 204 to a maximum response of 230 beats/min after stimulation.

The location of the integrative areas for sympathetic cardioacceleration in the cat are not known, although the bulk of the evidence points to the hypothalamus for one. This is well documented by the studies of Beattie *et al.* (1930), Manning & Peiss (1958, 1960) and Rushmer *et al.* (1959).

The experiments presented here seem to indicate that the over-all control of heart rate is integrated at several levels, the vagal nucleus in the medulla and at least one higher level, probably hypothalamic. The fact that various reflex responses induce slowing or acceleration of the heart by reciprocal inhibition has been known for many years (cf. McDowall, 1938). The experiments reported here indicate, therefore, that the afferent nerves involved in such reflex responses send off collaterals, at several levels of the central nervous system, to those areas involved in sympathetic and parasympathetic control of heart rate. It is not known whether the process of reciprocal inhibition operates in all reflexes affecting heart rate. In so far as the bulbar mechanism is concerned, it appears that change in vagal discharge is the primary mechanism. Sympathetic control of heart rate seems to operate chiefly at higher levels of the central nervous system.

In our experiments on cats under chloralose anaesthesia it was found that augmentor responses are elicited much more consistently than accelerator responses by stimulation of either the dorsal medulla or the hypothalamus. It is a reasonable assumption that the number of sympathetic fibres innervating the myocardium (augmentor fibres) is much in excess of the number of fibres innervating nodal tissue (accelerator fibres). If this is the case, one might reasonably expect a quantitative difference in the number of fibres involved in the central representation of these peripheral sympathetic fibres.

SUMMARY

1. Stimulation of the dorsal medulla, in regions producing maximal vasoconstrictor and augmentor responses, produced little short-latency cardiac acceleration in vagotomized cats under pentobarbital anaesthesia. Long-latency (12–20 sec) cardioacceleration in these cats was largely eliminated after bilateral adrenalectomy.

2. Stimulation of ventrolateral areas of the medulla produced large short-latency increases in heart rate in vagotomized cats under pentobarbital anaesthesia, presumably through activation of hypothalamospinal pathways.

3. In vagotomized cats under chloralose anaesthesia, stimulation of the dorsal medulla results in large cardioaccelerator responses with latencies of 1–5 sec.

4. These responses are partly or wholly eliminated by electrolytic lesions in the brain stem just caudal to the hypothalamus or by midcollicular transections, indicating that they are due to activation of afferent pathways to higher levels of the central nervous system.

5. The results in this paper do not support the concept of integration of sympathetic cardioacceleration in the medulla of the cat.

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