

THE DEFENCE-AROUSAL SYSTEM AND ITS RELEVANCE FOR CIRCULATORY AND RESPIRATORY CONTROL

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SUMMARY

It was proposed some fifty years ago that the visceral and hormonal changes accompanying fear and rage reactions can best be understood as adaptations which prepare an organism to cope with an emergency and specifically to perform the extreme muscular exertion of flight or attack. This is well exemplified by the pattern of cardiovascular response which is characteristic of the alerting stage of these reactions and consists of an increase in cardiac output directed mainly to the skeletal muscles.

This group of behavioural responses has been collectively termed the defence reaction. The regions of the hypothalamus and brainstem which organize it have been mapped. They function as a reflex centre for the visceral components of the altering response as well as initiating the behavioural response. So far as the cardiovascular system is concerned, this is a preparatory reflex and not compatible with short-term homeostasis. Indeed, the baroreceptor reflex, which is homeostatic, is strongly inhibited. By contrast, the chemoreceptor reflex is facilitated. The input from peripheral chemoreceptors is itself an alerting stimulus.

The visceral alerting response has been studied in most detail in the cat, but there is evidence for the same cardiovascular pattern and an accompanying group of respiratory changes in other mammalian species (rat, rabbit, dog, monkey and man).

On the efferent pathway for the cardiovascular response pattern, there is a group of relay neurones near the ventral surface of the caudal medulla, which seem important for the maintenance of arterial blood pressure. The visceral alerting system may therefore be continually engaged to some extent in the awake state, as well as being acutely activated in response to novel, and especially to noxious, stimuli.

INTRODUCTION - FUNCTION AND STRUCTURE

Our understanding of the biological role of what is now called the defence reaction was firmly founded by W. B. Cannon (1929) in his book, 'Bodily Changes in Pain, Hunger, Fear and Rage'. It hardly needs emphasizing that the behavioural reactions of flight or attack are adaptive, in that they lead to the preservation of the organism. Cannon's invaluable contribution was to have shown in detail how all the internal

bodily changes then known to occur as components of the emergency reactions, as he called them, could be viewed in this light. Their fascination for the physiologist has derived from the attempt to unravel the complicated stories of the various visceral and hormonal changes occurring at different stages of these reactions, so as to understand how they contribute to the maximum efficiency of the organism when coping with the emergency.

When Cannon was carrying out his experiments, few of the now familiar details of sympathetic innervation or its effects had been discovered, so he based his speculations on the actions of adrenaline, which was known to increase limb volume and cause a decrease in volume of the intestine, kidneys and spleen. He argued that the sympathetic efferent discharges would probably exert the same differential effect during the reaction, so that blood would be driven out of the viscera and into the skeletal muscles, which would have to meet the urgent demands of struggle or escape. Even the small amount of information then available led him to the further suggestion that the blood supply to the brain would not be reduced, whereas the coronary flow would even increase. He concluded: 'This shifting of the blood so that there is an assured adequate supply to structures essential for the preservation of the individual may reasonably be interpreted as a fact of prime biological significance'.

Parallel with Cannon's work proceeded a further development, pioneered by his student, Bard (Bard, 1928; Bard & Rioch, 1937; Bard & Macht, 1958), who showed that a large part of the brainstem is concerned with the integration of the whole pattern of response and that the hypothalamus must be intact for the pattern to be well organized and of anything like normal intensity. Topographical detail of the regions most concerned was first provided by Hess (1949) and his collaborators, who employed the technique of localized electrical stimulation to chart the regions from which characteristic patterns of behaviour could be elicited in cats. Responses, which began as alerting and culminated, with sufficiently intense stimulation, in flight or attack, were most readily obtained from a localized area in the tuberal region of the hypothalamus just medial, ventral and lateral to the fornix (Hess & Brugger, 1943): These responses were indistinguishable from those seen in an animal responding to a natural environmental stimulus and were collectively termed the defence reaction (Abwehrreaktion).

With a number of colleagues over the years, we have made detailed maps of those regions in the hypothalamus, mid-brain and dorsal medulla of the cat that organize these responses (Abrahams, Hilton & Zbrożyna, 1960; Coote, Hilton & Zbrożyna, 1973). The early work was started because of an interest in the sympathetic vasodilator nerve supply to the skeletal muscles in the cat and dog, which was known not to be involved in homeostatic circulatory reflexes, but which had been shown to be activated on electrical stimulation in the hypothalamus and dorsal mid-brain (Uvnäs, 1954; Lindgren, 1955). We found such a remarkable identity of the regions from which defence reactions were elicited in the conscious animal and a characteristic pattern of cardiovascular response, including the muscle vasodilatation in the same animal under anaesthetic, that this vasodilatation seemed to be the best objective index of the reaction itself. It thus proved an invaluable aid to the exact location of the excitable regions for the defence reaction, because of the large amount of information that could

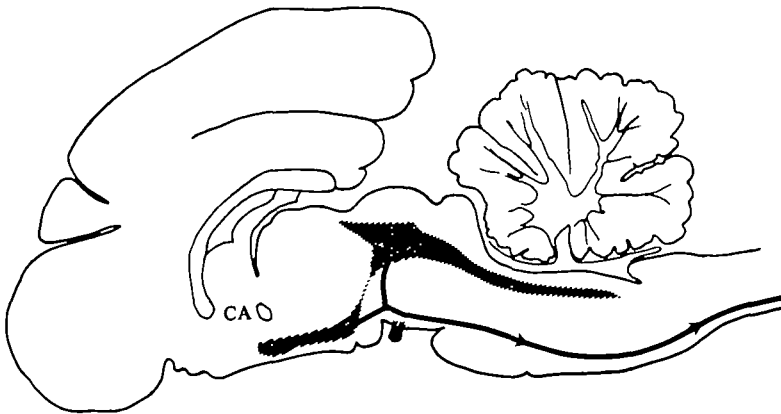


Fig. 1. Diagrammatic paramedian sagittal sections of cat's brain. Hatched areas represent regions in hypothalamus, mesencephalic tegmentum, central grey matter and medulla which integrate defence reactions; solid line indicates location of efferent pathway for cardiovascular pattern of response and other visceral components. CA, Anterior commissure. (Modified from Hilton, 1975).

be gained from exploratory experiments on anaesthetized cats with stereotactically orientated microelectrodes. The regions so mapped are illustrated diagrammatically in Fig. 1. When the behavioural reaction is observed in conscious animals, no matter whether in response to natural stimuli or appropriate electrical stimulation within the brain, the vascular response is fully developed during the early, alerting stage of the reaction, when the only outward signs are pupillary dilatation, pricking of the ears and an increase in rate of respiration (Abrahams, Hilton & Zbryozyna, 1964).

THE PATTERN OF CARDIOVASCULAR RESPONSE

Analysis of the details of the cardiovascular response that is part of the alerting stage of the defence reaction has revealed at every turn the depth of Cannon's insight. The pattern includes, in addition to vasodilation in skeletal muscle, vasoconstriction in the splanchnic area, kidneys and skin (Eliasson, Folkow, Lindgren & Uvnäs, 1951; Abrahams, Hilton & Zbrożyna, 1960; Feigl, Johannson & Löfving, 1964). Heart-rate, of course, increases and so does the contractile force of the heart (Rosén, 1961) and there is evidence of widespread venoconstriction (Folkow, Mellander & Öberg, 1961; Hilton, 1965). These changes lead to an increase of cardiac output, up to 140% of the resting level (Kylstra & Lisander, 1970; Timms, 1981), which is directed chiefly to the skeletal muscles. The whole pattern of response develops sufficiently quickly in the conscious animal for it to be fully prepared, within seconds of receiving a sudden stimulus, to meet the immediate demands of widespread muscular activity, as in flight or attack.

THE RESPONSE VIEWED AS A PREPATORY REFLEX

The regions of the hypothalamus and brainstem which are essential to the organization of this pattern of response are not solely motor. The ease with which the pattern

is regularly elicited as a stereotyped response in high decerebrate preparations led us to say, 20 years ago, that the regions concerned may be regarded as reflex centres in the usually accepted sense of the term (Abrahams *et al.* 1960). Indeed, there was already much evidence for the existence of sensory connexions with the core of the brainstem appropriate to this function: this was the so-called afferent collateral system of Starzl, Taylor & Magoun (1951) which, as we later showed, actually impinges upon all parts of the integrative centre for the defence reaction (Abrahams, Hilton & Malcolm, 1962). So the connexions undoubtedly exist that would enable these regions to function as a reflex centre for the reaction.

Such a simple concept has to be qualified; for the central nervous system acts as a whole, and the connexions to and from the telencephalon undoubtedly contribute to the reactions of the intact organism. There is no convincing evidence that they can be initiated from specific areas of the neocortex, even the motor cortex (Hilton, Spyer & Timms, 1979), although the cortex of the frontal lobe does include areas which can modulate them (Timms, 1977). There can be no doubt, however, of the prime significance of the limbic system, and we have direct evidence of the excitatory influences of a specific area of the amygdala (a group of nuclei within the temporal lobe), which connects directly by a short ventral pathway with the hypothalamus (Ursin & Kaada, 1960; Hilton & Zbrożyna, 1963; Timms, 1981).

Nevertheless, the idea that this response is as much a reflex as many another may be a fruitful one. In particular, it leads to the suggestion that it could be classified as a preparatory reflex, rather than a consummatory one. The significance of such a preparatory reflex for the survival of the individual is easily understood, as a means of mobilizing the resources of the organism to cope with an emergency, yet it must be emphasized that in so doing a reflex of this kind establishes for the time being a new state of equilibrium that represents a radical departure from the status quo. Mechanisms ordinarily operating to maintain the constancy of the internal milieu will therefore suffer a temporary interruption.

EFFECTS ON HOMEOSTASIS — INHIBITION OF BARORECEPTOR REFLEXES

A striking example of the changes in internal milieu is provided by the metabolic alterations induced by circulating adrenaline and cortisol which are released during defence reactions; for these are hormones exerting powerful effects, notably on carbohydrate metabolism, which can readily be understood within the framework of Cannon's concept but which are incompatible with short-term homeostasis and can greatly disturb the internal milieu. More relevant to the present discussion, however, is a particular feature of the cardiovascular response; that is, as a consequence of all the changes already described, the arterial blood pressure rises. Even more specifically, the pulse pressure increases simultaneously with the onset of the tachycardia — a combination of changes which must imply an inhibition of baroreceptor reflexes. This conclusion was tested by observing the well-known depressor effect of raising the pressure in a blind-sac preparation of the carotid sinus on one side, showing that this reflex effect of baroreceptor activation is strongly inhibited, and may be unobtainable, during stimulation in the hypothalamic region for the defence reaction

(Hilton, 1963; 1965). The reflex bradycardia is similarly inhibited. That this reflects a profound inhibition generated within the central nervous system has been demonstrated more recently by Coote, Hilton & Perez-Gonzalez (1979), who recorded activity in the cardiac and renal sympathetic nerves, in addition to heart-rate, blood pressure and regional blood flows. Thus, the hypothalamus can impose its own pattern of response and over-ride the homeostatic reflex organized at a lower level of the neuraxis. This is not because the hypothalamic stimulation simply activates the sympathetic outflows so strongly as to swamp any inhibitory effect; since stimulation at many points outside the defence area, which elicits similarly large increases in blood pressure and sympathetic activity, does not inhibit the vasomotor components of the baroreceptor reflex. One possible mechanism underlying this inhibition was demonstrated by McAllen (1976) who showed that neurones in the region of the nucleus of the tractus solitarius, which are early in the baroreceptor afferent pathway (possibly even second-order neurones), can be completely inhibited by a brief burst of stimulation of the hypothalamic defence area.

One qualification needs to be made, since inhibition of baroreceptor reflex bradycardia is not confined to stimulation within the defence area: it is frequently observed on stimulating around the area, as reported by Gebber & Snyder (1970) and Djojosingito *et al.* (1970). Electrical stimulation does not have to be strictly confined to the defence area to cause an increase in rate and depth of respiration, so this may reflect a special vulnerability of the baroreceptor reflex effect on the heart due to the inhibitory action of the central inspiratory drive on vagal cardio-inhibitory neurones (Lopes & Palmer, 1978). Augmentation of this drive is a feature of many patterns of response, hence suppression of baroreceptor reflex bradycardia on its own will not be confined to defence area activation.

Such complete suppression of the baroreceptor reflex has so far only been obtained as part of the defence reaction, and this indicates the potency of such a basic reaction not only for promoting the continued existence of the individual by helping it deal with an emergency, but also, if the reaction should be prolonged, for embarrassing the organism by weakening its defences and depleting its reserves.

COMPARISONS BETWEEN ANIMALS AND RESPONSES

So far, this account has dealt almost exclusively with experimental findings in one mammalian species, the cat, although with the implication that the ideas and conclusions may be more generally applicable. A full fledged defence reaction will show points of difference as an overt, behavioural response from one animal species to another. Even within a species, distinctions can be made, as has been well described by Leyhausen (1956) for the cat. Confronted by a potentially superior enemy, flight is the rule: if flight is impossible, a defensive posture is adopted, with dilated pupils, piloerection, flattened ears, head retraction, crouching and withdrawal, with growling and hissing. Facing an inferior enemy, a threatening posture is displayed, culminating in attack, biting and striking with the forepaws, with claws unsheathed. Thus, the detailed environment is an important factor determining the exact behavioural response. Notwithstanding these differences in behaviour, however, the observed

autonomic changes are always the same, and the pattern of cardiovascular response will be appropriate no matter whether the animal is displaying flight, threat or attack

This generalization seems equally valid between species also. In contrast to the cat, which is potentially an aggressive animal when threatened, the rabbit is relatively passive. Male rabbits can be aggressive when defending their territory against another male rabbit (Lockley, 1976); but faced with a predator or outside their territory they appear fearful, simply crouching or becoming immobile – in more popular parlance, freezing or playing dead. Stamping movements of a hindleg have also been observed by Lockley (1976) as part of an alarm reaction. In a recent study by Azevedo, Hilton & Timms (1980), it was found that electrical stimulation in anaesthetized rabbits in restricted regions of the hypothalamus and mid-brain, analogous to the defence areas in the cat, elicited a pattern of cardiovascular response comparable with that seen in the latter animal. It consisted of tachycardia, a rise of arterial pressure, with vasodilation in skeletal muscle and vasoconstriction in the kidney, accompanied by hyperventilation, pupillary dilation and a degree of exophthalmos. Stimulation in the same regions in the conscious rabbit sent it searching in the corners of its cage, as if looking for a means of escape (Azevedo, 1981). This was not preceded by clear signs of alerting, but was followed by apparent restlessness, usually accompanied by stamping of the hindlegs and preceded by a low pitched grunting. Here again, therefore, there is evidence that analogous forebrain and mid-brain regions organize and initiate a defence reaction which includes the same pattern of cardiovascular response as in the cat, in particular with a large muscle vasodilatation.

Exactly the same pattern organized by analogous areas of the brain has been found in dogs (Bolme, Ngai, Uvnäs & Wallenberg, 1967; Caraffa-Braga, Granata & Pinotti, 1973), monkeys (Schramm, Honig & Bignall, 1971) and rats (S. M. Hilton, R. J. Timms & C. P. Yardley, unpublished observations). It is readily provoked in human subjects, particularly in situations causing anxiety (Blair, Glover, Greenfield & Roddie, 1959). In the experiments of Brod, Fencl, Hejl & Jirka (1959) it was elicited by a simple test in mental arithmetic which the subjects were urged to perform rather rapidly. Patients suffering from chronic anxiety states exhibit the same pattern of response, with a muscle blood flow of almost double the normal (Kelly & Walter, 1968). The details of the pattern of cardiovascular response are close counterparts of those seen in animal experiments (cf. Hilton, 1965), even though a university academic, for example, fearful of being made redundant is unlikely to make a physical assault on his vice-chancellor, and if he is fortunate enough to find a job in Australia he will not have to run all the way there.

SPECIES DISTRIBUTION OF VASODILATOR NERVE FIBRES TO MUSCLE

There seems to be a common pattern of alerting response, at least so far as the cardiovascular system is concerned, for all the mammals which have been studied so far, including man; but there are interesting differences in the ways in which the muscle vasodilatation is brought about. In the cat, in which the phenomenon has been analysed the most carefully, it is mainly due to cholinergic vasodilator nerve fibres of

the sympathetic outflow, though a contribution is made by inhibition of on-going vasoconstrictor tone (Coote *et al.* 1973) and, in some animals, by circulating adrenaline (Marshall, 1977; Hilton & Marshall, 1982). The actual extent of each component varies from one individual experiment to another. Much the same combination would be expected in the dog, as this species also possesses cholinergic vasodilator nerve fibres in the sympathetic supply to skeletal muscle which are activated during defence reactions (Lindgren, 1955; Bolme *et al.* 1967). In the rat, rabbit and monkey, on the other hand, there is no evidence for cholinergic vasodilator nerve fibres supplying skeletal muscle (Bolme, Novotny, Uvnäs & Wright, 1970). Nevertheless, muscle vasodilation of sympathetic origin is as prominent a feature of the pattern of response in these species as in the others – (monkey – Schramm *et al.* 1971; rabbit – Azevedo, Hilton & Timms, 1981; rat – Folkow & Rubinstein, 1966; S. M. Hilton, R. J. Timms & C. P. Yardley, unpublished observations). The cause of this vasodilatation has been analysed most carefully in the rabbit (Azevedo, 1981). It is not affected by atropine in doses which block any vagal influence on the heart; it is unaffected by blockers of histamine receptors; and it is not reduced by doses of propranolol which block the vasodilator effect of large doses of the β -adrenoceptor agonist, isoprenaline. Close arterial injections of guanethidine or the α -adrenoceptor blocker, phenoxybenzamine, reduce the vasodilatation; but as the base-line level of vascular conductance is raised by these agents, the results are difficult to interpret. Thus, the dilatation could be due to a sudden cessation of on-going vasoconstrictor fibre activity, or there could be another vasodilator mechanism, as yet unidentified.

It is interesting, in this connexion, to look briefly at a further feature of the defence response, one to which Cannon paid no little attention, and which is a possible augmentation of the strength of contraction of fatigued muscle. Adrenaline can certainly produce this effect, though it is not known whether the concentration in the circulating blood during defence reactions would be sufficient to make a significant difference. Nevertheless, the emotional stress of mental arithmetic can prolong the period over which a maximal muscle contraction can be maintained in man, and this effect is sensitive to atropine and independent of blood flow (Berdina *et al.* 1972; Vinogradova *et al.* 1974). A similar cholinergic effect on prolonged isometric contractions has been demonstrated in cats during hypothalamic stimulation (Berdina *et al.* 1978), and this was interpreted as due to a direct effect on muscle metabolism, as evidenced by an activation of phosphorylase (Berdina & Rodionov, 1976): the flow change was thought to be secondary. We have recently shown a similar improvement of muscle performance in the rabbit on electrical stimulation in the hypothalamic defence area (Azevedo *et al.* 1981). The effect was only small, but it seemed to be produced through the nerve supply to the muscle, to be unaffected by atropine and independent of the increase in muscle blood flow. In some mammalian species, therefore, there may be sympathetic nerve fibres which release an as yet unidentified transmitter substance to cause vasodilatation and metabolic effects in skeletal muscle as part of an alerting reaction.

THE QUESTION OF A SECOND TYPE OF EMOTIONAL RESPONSE

This apart, however, the common pattern of response in a variety of mammalian species is striking, as might be expected in such a basic evolutionary adaptation. Only one study in cats has led to the description of a different pattern of response, and this was in experimental animals confronted by a second cat made aggressive by hypothalamic stimulation (Adams, Baccellii Mancia & Zanchetti, 1969). In these experiments, the cats were in two compartments of a cage separated by an opaque partition. Before the partition was raised to reveal the aggressive cat, the experimenter made noises to alert the experimental cat that the partition would be raised. The actual confrontation period lasted from 2–10 s and was ended after the first striking movements of the experimental cat, when the partition was closed. Adams *et al.* (1969) reported that no change, or only vasoconstriction, occurred in the inactive skeletal muscles during confrontation and this was often accompanied by bradycardia. They emphasize that their experimental cats were selected as subjects on the basis of strong behavioural responses on confrontation in these special conditions, and that at least six responses were recorded in each cat during actual experimental sessions. Thus, quite apart from the difficulty of categorizing their novel, experimental situation, Adams *et al.* (1969) would have had the unforeseen problem of observing animals that were far from naive, and whose confrontations, preparatory or experimental, were not associated with an actual attack or noxious stimulation. Martin, Sutherland & Zbrożyna (1976) have demonstrated the degree of habituation that occurs in such conditions.

Of the various features of the cardiovascular pattern of response, the muscle vasodilatation is the most rapidly extinguished (Sutherland & Zbrożyna, 1974;) and the behavioural responses can persist in the cat after extinction of all cardiovascular changes (Martin *et al.* 1976).

In a more recent review, Zanchetti & Bartorelli (1977) attempted to distinguish between the 'classical defence pattern', as described in this review, and a second pattern, including bradycardia and generalized vasoconstriction, which they suggested should be recognized as the accompaniment of the immobile emotional confrontation. But the latter was not in fact a stereotyped pattern regularly found in their experiments, and this is not surprising in view of the variability in habituation observed by Martin *et al.* (1976). On the other hand, under appropriate conditions the alerting pattern can readily be obtained as a conditioned response to a previously neutral stimulus, and such conditioned responses are remarkably stable (Abrahams *et al.* 1964; Bolme & Novotny, 1969). Indeed, the ease with which the alerting pattern of response may be conditioned is in keeping with the suggestion that it is preparatory, and hence anticipatory, of the actions that may immediately follow.

Unlike the cat or dog, however, there are some animals that commonly respond to frightening situations by 'freezing' or 'playing dead'. As remarked by Fokow & Neil (1971), this was so well recognized in the opossum as to have led to the expression 'playing possum'. Reference has already been made to this reaction in the rabbit, and it has also been studied in the woodchuck, *Marmota monax*, willow grouse, *Lagopus lagopus*, and deer fawn, *Odocoileus virginianus*, (see Smith & Woodruff (1980) for references). Bradycardia and reduced respiratory movements are characteristic of the

freezing type of behaviour, while in some species the animal may drop suddenly as if dead, almost apnoeic, with marked arterial hypotension. This really is a well authenticated, second type of emotional response, and it is therefore of no little interest that, in their experiments on anaesthetized rabbits, Azevedo *et al.* (1980) found that, on electrical stimulation within the hypothalamus around the area eliciting the characteristic defence pattern, there was still a large vasodilatation in skeletal muscle and vasoconstriction in the kidney but these were accompanied by bradycardia and apnoea.

As this grouping of responses was consistently observed on stimulation of a well-localized area, it seems likely to represent a second pattern of response, entirely appropriate to the freezing characteristic of a frightened rabbit. The same pattern would be appropriate to playing dead in those species in which this occurs, and may underlie emotional fainting in man; for this response includes in addition to a drastic bradycardia and an obvious vasoconstriction in the skin, a marked vasodilatation in skeletal muscle (Barcroft & Edholm, 1945). It will be interesting to explore these ideas further in future work on suitable animal species.

CHANGES IN RESPIRATION – THE CHEMORECEPTOR INPUT AS AN ALERTING STIMULUS

The discussion so far has concentrated on the cardiovascular pattern of response, but it must be emphasized that this is accompanied by a powerful effect on ventilation. More rapid and deep respiration is an obvious feature of the response to pain and excitement, and it has long been known as a component of the overall response on electrical stimulation of the defence areas in the hypothalamus and mid-brain (Hess, 1949). This led Hilton & Joels (1965) to test whether there is any interaction between the defence response and that to peripheral chemoreceptor stimulation. When carotid chemoreceptors were stimulated by a close arterial injection of a suitable stimulant, such as cyanide, and this was preceded by electrical stimulation of the hypothalamic defence area, the reflex hyperpnoea was greatly augmented. This result raises the question whether the chemoreceptor input may be able, on its own, to activate the defence areas of the brain.

This possibility had indeed already been indicated by experiments of Bizzi, Libretti, Malliani & Zanchetti (1961), who showed that, in cats decerebrated at a high level so as to spare the hypothalamus, sham rage responses could be evoked by carotid chemoreceptor stimulation. They were characterized by a dramatic rise in arterial blood pressure and hyperventilation, with dilatation of the pupils, retraction of the nictitating membranes, struggling and clawing movements, lashing of the tail, and the facial expression of rage. Hilton & Joels (1965) confirmed these observations, and registered at the same time a tachycardia and an increase in muscle blood flow which was not secondary to muscle contractions or the hyperventilation. Interestingly, inhalation of high concentrations of CO₂ did not elicit this pattern of response, though of course causing hyperventilation and some increase in arterial blood pressure (S. M. Hilton & N. Joels, unpublished observations).

It has recently become possible to study reflexly elicited alerting responses in

anaesthetized cats, with the introduction of the use of the steroid mixture, althesin (Glaxo), in animal experiments (Timms, 1976). Under this anaesthetic, unlike those conventionally used (chloralose, urethane, barbiturates), hypothalamic and mid-brain structures can be activated synaptically without serious distortion, with the result that the autonomic components of the alerting stage of the defence reaction can for the first time be evoked with full surgical anaesthesia on electrical stimulation of the amygdala (Timms, 1981) or noxious stimulation of the skin (Hilton & Marshall, 1982). Such experiments have revealed that stimulation of the carotid chemoreceptors is an effective alerting stimulus which can evoke the full pattern of autonomic response (Marshall, 1977; Hilton & Marshall, 1982), including all the characteristic cardiovascular features. This will have been missed in previous studies because of the depressant action of the commonly used anaesthetics on transmission in the hypothalamus and mid-brain.

The cardiovascular pattern of response has already been observed on carotid chemoreceptor stimulation in conscious dogs (Rutherford & Vatner, 1978), though it was not recognized as such and so was not analysed with this possibility in mind: moreover, no comment was made on any behavioural changes. In rabbits, however, hypoxia (probably acting through peripheral chemoreceptor stimulation) leads to clear signs of behavioural alerting, with sniffing in the corners of the experimental cage 'as though looking for a means of escape' (Korner, Uther & White, 1969). In such experiments, the heart-rate fell, but the pattern of response in the peripheral vasculature (Uther, Hunyor, Shaw & Korner, 1970) was similar to that of the alerting response, a combination which, as already mentioned, is readily evoked by hypothalamic stimulation in this animal (Azevedo *et al.* 1980).

These results pose the general biological question whether chemoreceptor stimulation may be a potent alerting stimulus in a number of mammalian species, and raise the more specific issue of the part played by this input in cardiovascular control. It has long been known to be important in the adjustment to haemorrhage, and the significance of this early finding is reinforced by the recent observation that the chemoreceptor input can engage the alerting system sufficiently strongly to suppress the baroreceptor reflex (Marshall, 1981). This hitherto unexpected result may have important implications. Finally, the question comes to mind whether a minor degree of hypoxia, insufficient to produce a response at rest, could become an effective respiratory stimulus during muscular exercise.

THE RESPIRATORY RESPONSE

The respiratory changes which are a constant feature of the defence reaction, and of rapid onset in the alerting stage, have hardly been given any serious consideration. Tachypnoea, rather than hypernoea, is the usual response to stimulation in the peripheral area of the hypothalamic region, and this particular pattern of respiration has been related to the hissing that is a prominent feature of the reaction in the cat (Hess, 1949). But the combination of tachypnoea and hyperpnoea, being characteristic of muscular exertion, in which condition its utility seems self-evident, led Cannon to two interesting speculations. One is that the important effect of these

changes, as part of the defence reaction, is to produce an anticipatory reduction of blood p_{CO_2} . Some findings of Douglas & Haldane (1909), quoted in this connexion, showed that forced breathing for a few minutes would relieve the subsequent respiratory distress of severe muscular exertion. It is difficult to understand why this speculation has received so little attention. In view of the obvious desirability of maintaining a minimal resistance to airflow, Cannon also considered the possibility that bronchiolar dilatation might be an additional mechanism helping to prevent a man or animal becoming 'winded' during the severe exertion resulting from a strong defence reaction; but this too has not been studied subsequently.

There is little information about any changes occurring in the pulmonary vascular bed itself. A decreased compliance of the pulmonary arteries has been demonstrated (Szidon & Fishman, 1971), which would make a contribution to the mobilization of blood reservoirs necessary to 'prime the pump' and increase cardiac output; but of course the overall rate of blood flow is greatly increased, so it would be important to investigate whether the pulmonary vasomotor innervation could in some way help to provide the most favourable conditions for gaseous exchange. It is possible, for example, that a redistribution of pulmonary blood flow could provide for an optimization of the ventilation-perfusion ratio throughout the lung, or that the shunting effect of the bronchial arterial supply could be reduced.

EFFERENT PATHWAY FOR THE CARDIOVASCULAR RESPONSE —
A RELAY NUCLEUS IN THE VENTRAL MEDULLA

A recent development in our study of the central nervous structures involved in the organization of the alerting response, and particularly the cardiovascular pattern, has come from an investigation of the efferent pathway from the hypothalamus and mid-brain to the spinal cord. Our early work (Abrahams *et al.* 1960), and that of Lindgren & Uvnäs (1953) had shown this pathway to run in the ventral part of the medulla, while later work by Schramm & Bignall (1971) had indicated that, in the more caudal medulla, it passes extremely close to its ventral surface.

For this reason, it is particularly interesting that local applications of pentobarbitone sodium bilaterally onto the ventral surface of the medulla can cause a profound fall of arterial pressure (Feldberg & Guertzenstein, 1972). Moreover, Guertzenstein & Silver (1974) have reported that bilateral applications of glycine to the same restricted region has the same vasodepressor effect, and so have small bilateral electrolytic lesions in the area to which glycine had been applied. As glycine readily blocks conduction through synapses, this evidence suggests that nerve cells situated near the ventral surface of the caudal medulla play an essential part in tonically maintaining arterial blood pressure at its normal level. It also leads to the question whether such nerve cells could be on the efferent pathway for the alerting response. Indeed, we were able to show that bilateral application of glycine to the sensitive area blocks all the autonomic components of the defence reaction ordinarily seen in electrical stimulation of the appropriate regions of the amygdala, hypothalamus, or mid-brain (Guertzenstein, Hilton, Marshall & Timms, 1978). A few minutes after the application, as the block deepens, the arterial blood pressure falls. The first component of the cardio-

vascular pattern of alerting response to be abolished is the splanchnic vasoconstriction. Electrical stimulation within the medullary area sensitive to glycine elicits the complete pattern of response characteristic of the defence reaction, including a strong vasoconstriction in the splanchnic area and kidney.

The response is elicited by stimulation on the surface of the medulla, or only just below it. A map of the points from which the response is obtained shows it to occupy a narrow longitudinal strip which is a few millimeters from the mid-line and extremely superficial within the glycine-sensitive area, which is 1–2 mm caudal to the trapezoid body. After an extremely small lesion restricted to this superficial section of the strip on one side, glycine applied to the contralateral medullary area produces all the changes that without the lesion are seen only after bilateral application of the amino acid. As anatomical evidence is now accumulating of connexions between the superficial region of the ventral medulla in its caudal one-third and the intermediolateral cell column of the spinal cord from which the preganglionic sympathetic neurones arise (Amendt, Czachurski, Dembowski & Seller, 1978; Loewy & McKeller, 1979), we have proposed that the resting level of blood pressure is largely determined by the level of activity ordinarily prevailing in the brainstem defence areas in the awake condition and relayed in the pathway in the caudal medulla.

This idea would link the observations just described with those reported by Coote (1982) at this symposium; for during desynchronized sleep in cats (Kumazawa *et al.* 1969), the arterial blood pressure falls to a level similar to that found in our experiments with glycine. This fall results from vasodilatation in the splanchnic area and kidney, there being a vasoconstriction in skeletal muscle (Mancia, Baccelli, Adams & Zanchetti, 1971). This is just the pattern that would be expected from the combined sympathetic nerve recordings of Coote & Futuro-Neto (1982) in the paradoxical sleep-like state, and this combination of changes is the exact opposite of that seen in the alerting response. As pointed out by Hilton, Marshall & Timms, (1980), this is what would be expected if desynchronized sleep entails a suppression of the activity of the defence areas. It is, however, the corollary of this idea that should be emphasized in the present review, and that is, that the general level of blood pressure in the normal awake animal is determined mainly by that level of activity in the 'defence' areas of the brain which is necessary for the state of arousal in the awake condition.

The results also make it possible to treat anew the age-old problem in mammalian physiology of the existence of a vasomotor centre. This was postulated over a century ago by Dittmar (1873) to lie in the caudal one-third of the medulla. He had shown by making cuts across the brainstem in the anaesthetized rabbit that the arterial blood pressure fell to a low level when the section encroached upon this level of the medulla. On the basis of further, careful lesioning, moreover, he put the area of special significance in the ventrolateral reticular formation. Our results are fully in accord with this early work, and make it possible to explain it without needing to postulate a special vasomotor centre. As illustrated in the schematic diagram of Fig. 2, we suggest that there is a group of relay neurones very near the ventral surface of the medulla that may form the final link in the efferent pathway to the pre-ganglionic autonomic effector neurones. In fact, we have very recently recorded from such superficial neurones which display convergent inputs from the hypothalamic and mid-brain

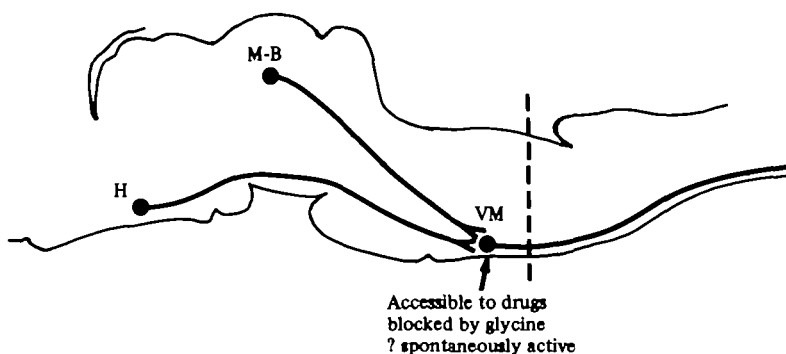


Fig. 2. Diagrammatic paramedian sagittal section of cat brainstem indicating locations of representative neurones in hypothalamic (H) and mid-brain (M-B) defence areas giving rise to axons hypothetically converging on neurones near the ventral surface of the medulla (VM) which generate the alerting pattern of cardiovascular response. Interrupted line indicates plane of section which, as shown originally by Dittmar (1873), eliminates vasomotor tone of central nervous origin.

defence areas (Donoghue, Hilton, Smith & Timms, 1981; Smith & Hilton, 1981). These neurones would thus constitute a functional nucleus in the caudal one-third of the ventral medulla essential for the normal level of sympathetic activity responsible for vasomotor tone.

CONCLUSION

In conclusion, therefore, there are specific and well-localized areas in the hypothalamus, mid brain and medulla that together are necessary for the expression of the integrated defence reaction, in all its aspects. This is a basic biological response, easily understood, so far as its visceral and hormonal manifestations are concerned, within the framework of Cannon's hypothesis that it enables the organism to cope with the exigencies of an emergency and even to anticipate it (Hilton, 1965). In its original form, this hypothesis has led to the association of the reaction only with acute episodes in daily life, in which an animal, or man, is suddenly aroused or alerted, and may be anxious. It now seems likely that essentially the same pattern of visceral response is continually imposed at a certain level during the hours of wakefulness, as a background upon which the other influences may play. The structures through which the response is organized would therefore be properly called the visceral alerting system, which amongst other effects including far-reaching cardiovascular adjustments as part of a preparatory reflex, may play a key role in setting the general level of arterial blood pressure in the awake state.

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