

from the amygdala and periphery. This might be facilitated by reciprocal connections between the regions, for example, the hypothalamus and periaqueductal grey. On the other hand, it appears that the regions can also act independently. Therefore the full pattern of response can still be evoked from the hypothalamus after extensive lesions involving much of the dorsal midbrain, while animals in which the hypothalamus has been removed — by sectioning rostral to the periaqueductal grey — can show patterned defensive behaviour in response to strong noxious stimulation.

► The cardiovascular pattern of the alerting response, which is mediated by patterned changes in parasympathetic and sympathetic activity, is integrated in localized regions of the forebrain and brainstem, from the amygdala through the hypothalamus to the dorsal midbrain and medulla. All of these regions funnel into an efferent pathway which synapses onto neurones in the rostral ventrolateral medulla (RVLM).

► Experiments involving DLH, which stimulates cell bodies but not nerve fibres, indicate that the cell bodies of the neurones that mediate the alerting response are in the basal nucleus of the amygdala, possibly in the rostral hypothalamus, but certainly in the periaqueductal grey matter of the midbrain and medulla. The output from these regions can be modulated by inputs from frontal cortex and can modulate reflex pathways at the medullary level.

The ventral medulla

The activity from the defence areas apparently funnels through the single ventral medullary pathway, which has itself been the subject of recent investigation. Using electrical stimulation in the Althesin-anaesthetized cat, the full cardiovascular pattern of the alerting response could be evoked from a longitudinal strip running caudally through the midbrain and as far as a region just caudal to the trapezoid bodies (Fig. 7). At sites more caudal than this, electrical stimulation seemed to evoke individual components but not the whole pattern of the response. The region where the response seemed to fractionate corresponded closely with what had been called the 'glycine-sensitive area', since

bilateral application of glycine to this region produced respiratory apnoea and a dramatic fall in arterial pressure [17] (see Chapter 1). Since glycine depresses the activity of neuronal cell bodies, this implied that there are neurones in the glycine-sensitive area that play an important tonic excitatory role in setting the normal level of arterial pressure. However, Hilton and co-workers [18] also found that bilateral application of glycine, or application of glycine to one side and electrolytic lesion of the other, abolished the cardiovascular components of the alerting response evoked from the amygdala, hypothalamus or midbrain (Fig. 7), indicating that the ventral defence pathway synapses in these regions on to the neurones with tonic excitatory drive.

Since then, electrophysiological and neuronal tracing studies on this region, which is anatomically defined as the nucleus paragigantocellularis lateralis, but is now widely known as the RVLM (rostral ventrolateral medulla), have demonstrated that these neurones receive direct projections from the defence areas (Fig. 8) and also from many other regions of the brain, including the parabrachial nucleus, ventral periaqueductal grey matter and nucleus tractus solitarius (see Chapter 1, Fig. 4) and that they project to the intermediolateral cell column to the region of the sympathetic preganglionic neurones (see Chapter 1).

Furthermore, microinjection of excitatory amino acids into this region can selectively produce vasoconstriction in mesenteric or renal circulation, vasoconstriction or vasodilatation in muscle, tachycardia or bradycardia and other autonomically mediated responses, depending on exactly where the injection is made. The obvious conclusion is that these neurones are already functionally dedicated and represent a major pathway to the sympathetic preganglionic neurones that is used to generate different patterns of autonomic response; the alerting pattern is just one of these patterns (see Chapter 1).

It has been proposed that the neurones of the RVLM have their own intrinsic activity but that this activity is also constantly moderated by afferent inputs. In as much as the defence areas have activity in the waking state, which is raised in response to alerting or noxious stimuli, the defence areas may provide one of the excitatory inputs that not only produces a characteristic pattern of cardiovascular response,

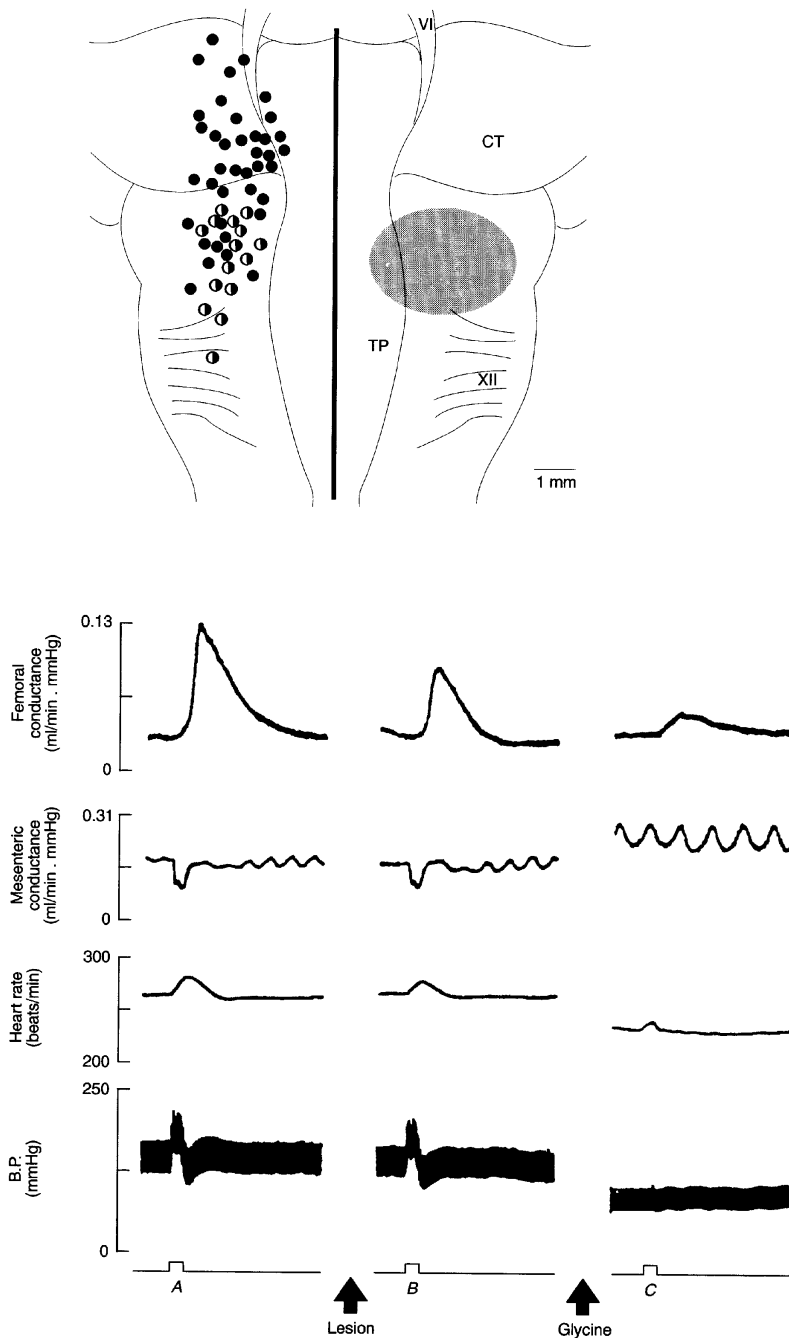


Fig. 7. A diagrammatic plan view of the ventral medulla of the cat (top) and the effects of an electrolytic lesion and glycine application to the ventral medullary surface on the alerting response evoked from the amygdala (bottom)

In the top diagram, filled circles indicate sites at which electrical stimulation evoked the full pattern of the alerting response; half-filled circles indicate sites at which electrical stimulation evoked responses similar to, but not identical with, the alerting response. The shaded area indicates the area to which glycine was applied. Abbreviations used: TP, pyramidal tract; CT, trapezoid body; VI and XII, abducens and hypoglossal nerves respectively. In the bottom diagram, traces show effects

on resting levels of femoral (muscle) and mesenteric vascular conductance, heart rate and arterial blood pressure, and on changes evoked by stimulation in the amygdala of a ventral medullary lesion in the efferent pathway from the defence areas (middle) and of subsequent application of glycine to the contralateral glycine-sensitive area (right). Bars beneath traces indicate periods of stimulation. Modified and reproduced with permission from [17].

but contributes to the prevailing level of arterial pressure. However, it is also clear that the neurones of the RVLM are not the only excitatory pathway to the sympathetic preganglionic neurones. For example, bilateral application of glycine to the RVLM rapidly abolished the cardiovascular components of the alerting response evoked by peripheral chemoreceptor or radial nerve stimulation; but generalized vasoconstriction could be evoked by both stimuli until the arterial pressure became so low that the sympathetic preganglionic neurones were

probably too far below their thresholds to be activated.

It should also be remembered that the role of the RVLM is not restricted to autonomic function. The surface of the ventral medulla has also been proposed as the site of central chemosensitivity to carbon dioxide. This has been questioned by some. However, it is clear that respiration is severely depressed or abolished by bilateral application of glycine to the RVLM, and by bilateral cooling or electrolytic lesion of this same region, and that this respira-

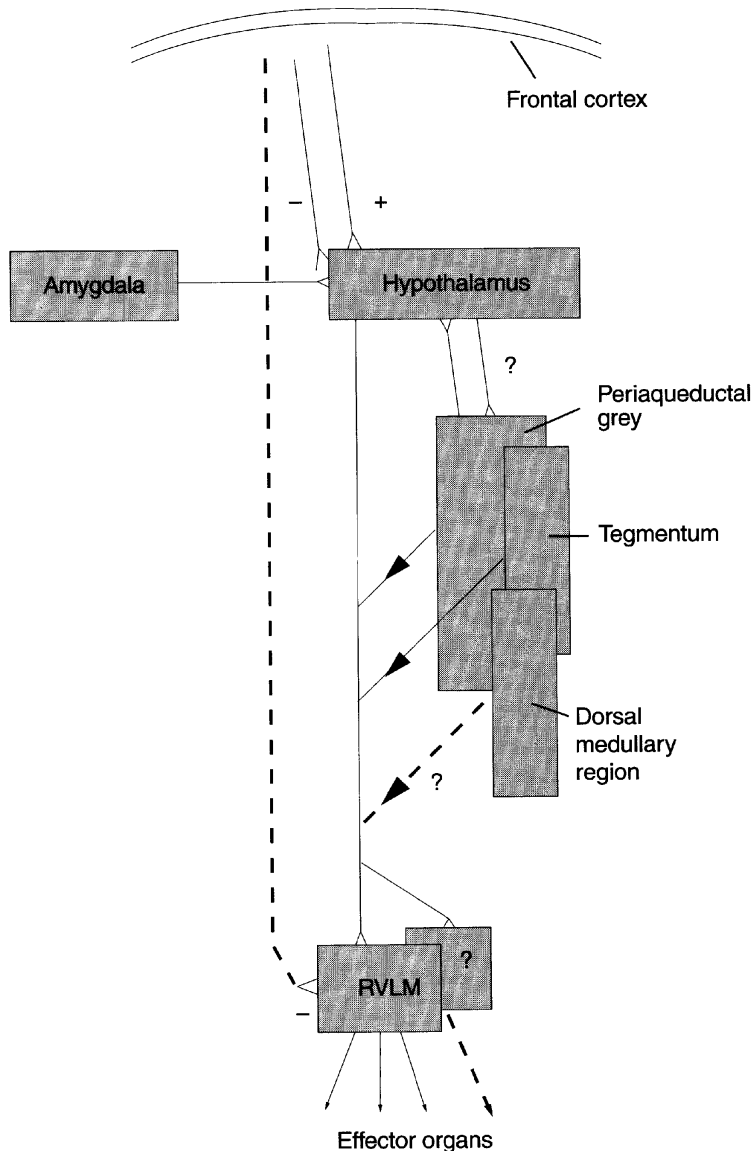


Fig. 8. Schematic diagram showing the brain regions that are thought to be involved in the integration or modification of the alerting response

+ and - indicate excitatory and inhibitory influences, respectively. Dashed lines indicate proposed pathways. For further details, see text.

tory depression is accompanied by loss of responsiveness to carbon dioxide. In fact, this region has been called Area S, or Intermediate Area, by those investigating central chemosensitivity. It obviously provides a major tonic excitatory drive to respiration and has been proposed as the site of relay from more caudal and rostral chemosensitive areas: Areas M and L, respectively [18].

Thus it seems likely that the RVLM is an important site of integration of cardiovascular and respiratory regulation. It is, therefore, particularly interesting that in the cat, inhalation of carbon dioxide not only caused the expected increased respiration, but reduced the muscle vasodilatation and enhanced the splanchnic vasoconstriction of the alerting response evoked by stimulation in the amygdala. Similar effects upon these cardiovascular changes were induced by superfusion of the ventral medulla with cerebrospinal fluid of low pH, while opposite effects were induced by superfusion with high pH. It may be that these effects are exerted by the modulatory influence of changes in pH upon synaptic transmission within the RVLM onto neurones that mediate the alerting response, rather than by effects on specific chemoreceptors for carbon dioxide, or hydrogen [19].

► The activity of the RVLM neurones, on to which the pathway for the alerting response synapse, provides a major tonic excitatory drive to sympathetic preganglionic neurones. Therefore, changes in the level of alertness, and thereby in the output from the defence areas to those medullary neurones, may play an important role in setting the level of arterial pressure.

► The region of the RVLM also contains neurones that are of major importance in the control of respiration. It seems probable that this ventral medullary region is an important site for integration of cardiovascular and respiratory function.

Habituation and sensitization of the response

The discussion so far may have given the impression that the cardiovascular pattern of the alerting response is stereotyped and consis-

tent in response to a given stimulus. This may be true when the response is evoked by electrical or chemical stimulation in the brain. However, when evoked by more natural stimuli, in the conscious animal, the response pattern may show habituation or sensitization upon repetition of the stimulus [21]: habituation means that the response gradually becomes smaller, while sensitization means that it becomes larger. Of the two, habituation is the more common [21].

Habituation of the alerting response has been observed, for example, in the baboon when confronted by a snake, in the cat when confronted by a dog (Fig. 9), and in man when subjected to the cold pressor test (Fig. 10) or to auditory stimuli. Sensitization seems more likely to occur when the individual is already aroused or anxious, leading to the idea that this process is favoured when ongoing activity in the defence areas is high. It has been proposed that during repeated exposure to a given stimulus, the two processes of habituation and sensitization are activated in parallel within the central nervous system and that it is their interaction which determines the magnitude of the response observed. The outcome of this interaction is apparently dependent on the intensity and specificity of the stimulus, the frequency of repetition, as well as on the level of arousal of the individual [21].

Whether habituation or sensitization occurs in a given individual, there is not necessarily any correlation between the rate of change of the behavioural response and the cardiovascular response. Thus the magnitude of the behavioural response does not give a reliable indication of the cardiovascular response; it may persist when the cardiovascular response has been completely extinguished. In addition, the individual components of the cardiovascular response may change at different rates. Generally speaking, the muscle vasodilatation seems to be the component of the response that is most susceptible to habituation, and it may disappear completely at a time when the tachycardia, rise in arterial pressure, and renal and splanchnic vasoconstriction are almost as great as those seen in response to the first stimulus. On the other hand, experiments on dogs, baboons and human subjects suggest that in some individuals the renal vasoconstriction and other pressor components of the response habituate very readily as well [21].

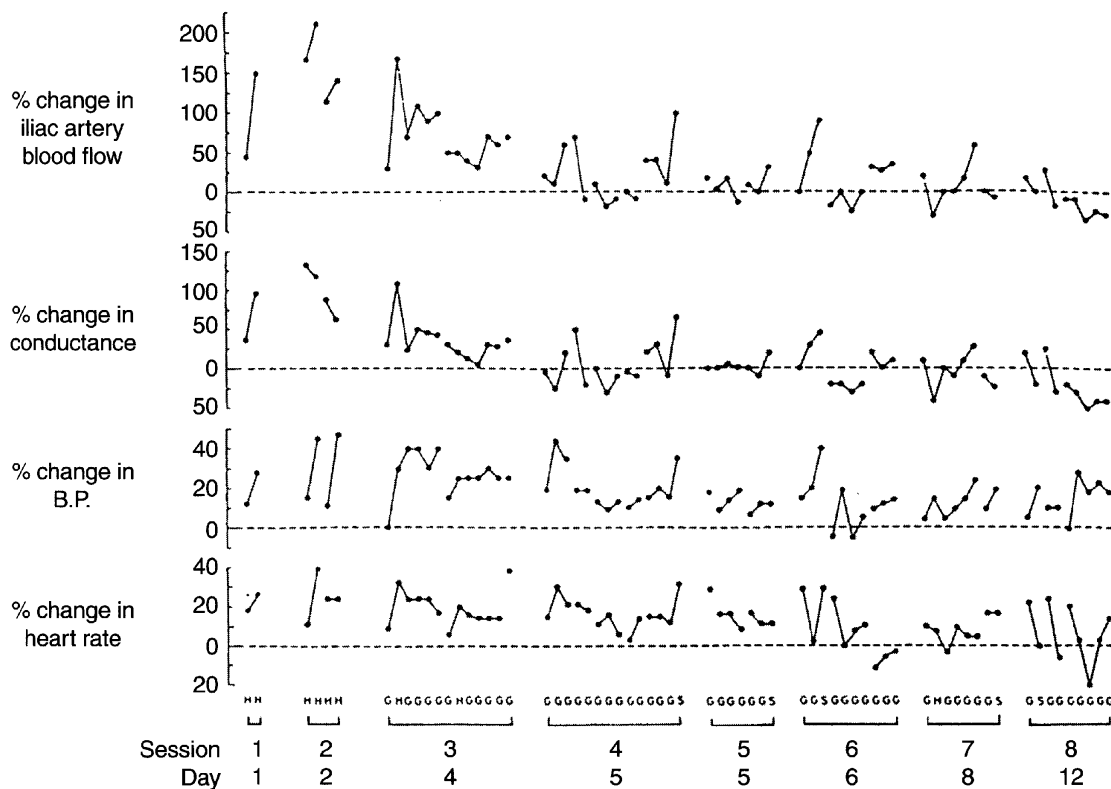


Fig. 9. Habituation of the cardiovascular components of the alerting response evoked in a cat confronted by a dog

Each point corresponds to one bout of rage during confrontation. Abbreviations used: H, hissing; G, growling; S, striking with the front paw. Reproduced with permission from Martin, J., Sutherland, C.J. and Zbrozyna, A.W. (1976) *Pfluegers Arch.* **365** 37–47.

► The alerting response can be habituated or sensitized on repetition of the stimulus. Individual components of the response may habituate or sensitize at different rates. The muscle vasodilatation seems the most vulnerable to both processes.

Hypertension

It has been proposed that those individuals who most readily develop renal vasoconstriction in response to aversive stimuli, and who show little or no habituation of it, are most likely to develop essential hypertension [4,21,22]. This is consistent with a large body of evidence suggesting that the defence response plays an important role in the genesis of essential hypertension. For example, the following observations have been made:

- hypertensive patients show a marked tendency towards nervous tension, anxiety, or so-called 'type A behaviour', and it has been found that conditioning, or yoga, can lower blood pressure in some hypertensives;
- labile hypertensives have a higher 'resting' level of muscle blood flow and muscle vascular conductance than normotensive subjects, which would be consistent with a high level of ongoing activity in the defence areas of the hypertensives (Fig. 10);
- labile hypertensives and established hypertensives show larger increases in muscle blood flow and muscle vascular conductance in response to stressful stimuli (Fig. 10), and the increases in arterial pressure evoked by mental stress are greater in labile hypertensives, and even in the normotensive, adolescent children of hypertensive subjects, than they are in normotensives with no family history of hypertension;

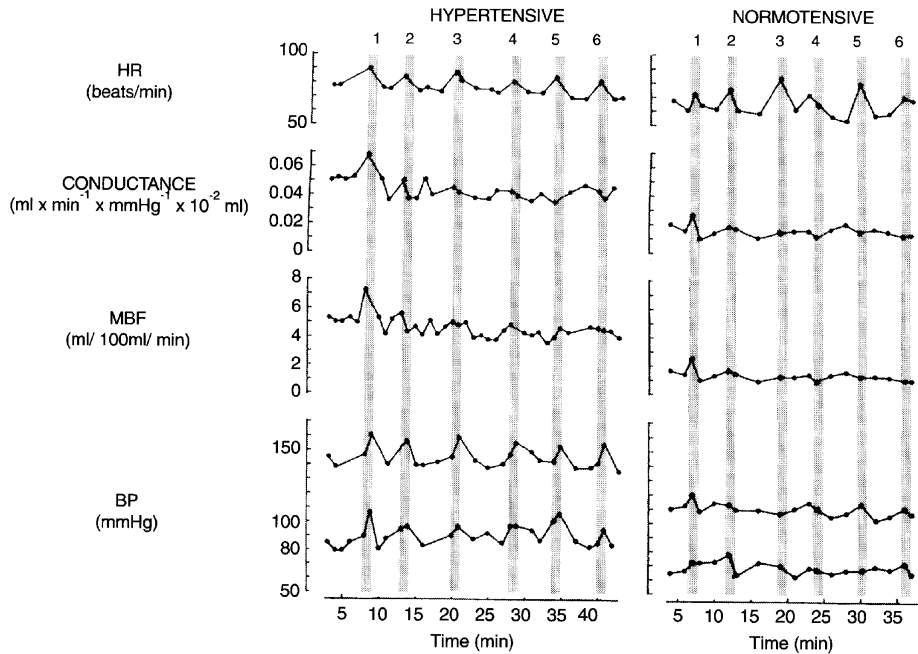


Fig. 10. Cardiovascular responses evoked in a hypertensive subject (left) and in a normotensive subject (right) on repeated immersion of one foot in cold water

Abbreviations used: BP, mean arterial pressure; MBF, forearm muscle blood flow; conductance, muscle vascular conductance calculated as MBF/BP ; HR, heart rate.

Reproduced with permission from Zbrozyna, A.W. and Kriebel, F. (1985). *Eur. J. ppl. Physiol.* **54**, 136–44.

— the renal vasoconstrictor response to mental stress is more pronounced and longer lasting in established hypertensives than in normotensive subjects;

— while the muscle vasodilatation evoked by the cold pressor test showed some habituation in both labile hypertensives and normotensives, the increases in blood pressure, particularly the increases in diastolic pressure, remained of similar magnitude on repetition of the stimulus in the labile hypertensives, but gradually decreased in the normotensives, as would be consistent with lack of habituation of the renal vasoconstriction in the labile hypertensives (Fig 10).

Thus it seems that an individual who persistently shows pronounced alerting responses to the many unexpected and unpleasant stimuli of everyday life, and little habituation of the vasoconstrictor components, may be caught in a vicious circle. It is well-established that the increase in tension of blood vessel walls that results from increase of arterial pressure causes hypertrophy of the vascular smooth muscle

and, consequently, a reduction in vessel internal diameter, so providing a physical reason for increased vascular resistance and arterial pressure [22].

▶ There is evidence that the alerting response plays a role in the genesis of essential hypertension.

Central processing

The fact that the alerting response can show sensitization or habituation raises the possibility that there are regions of the brain that can increase or decrease the response by influencing the 'interpretation of the incoming sensory information', by altering the level of activity in the defence areas, or by modifying the outgoing pathway to the effectors. The fact that sensitization and habituation may have differential effects on individual components of the alerting response suggests that at least one of the sites of modification must be at a level within the central nervous system where there is separate

representation of those individual components [21]. There has been relatively little experimental investigation of these possibilities. However, there is evidence from experiments on cats anaesthetized with Althesin that electrical stimulation within restricted regions of the frontal cortex produced no measurable cardiovascular responses when applied alone, but caused a significant reduction of the cardiovascular components of an alerting response evoked by simultaneous stimulation of the amygdala, the muscle vasodilatation being affected most [23]. Since stimulation at these same cortical sites had no effect on the alerting response evoked by stimulation in the hypothalamus, it seems likely that the modulating influence is exerted at synapses in the efferent pathway from the amygdala to the hypothalamus (Fig. 8). On the other hand, stimulation at other sites within a different region of the frontal cortex substantially facilitated the amygdaloid response, with no effect on the hypothalamic response, suggesting that the cortex can also facilitate synaptic transmission in the amygdalo-hypothalamic pathway (Fig. 8).

In contrast, experiments on rats anaesthetized with Saffan showed that electrical or chemical stimulation with DLH within a restricted region of the frontal cortex had no cardiovascular effect when applied alone, but reduced or abolished both the muscle vasodilator and renal vasoconstrictor components of the alerting response evoked from both the amygdala and the hypothalamus [24]. Since stimulation at the effective sites inhibited the alerting response evoked from the hypothalamus, as well as from the amygdala, the site of inhibition must be at synapses in the efferent pathway from these areas. The only site of synapses in the pathway from the defence areas that has been identified is in the RVLM (see Fig. 6), where the fibres synapse onto neurons that descend to produce the individual components of the response; this must, therefore, be a favoured site. The fact that stimulation in the frontal cortex alone had no detectable effect on cardiovascular variables suggests that the inhibitory influence is presynaptic. Interestingly, it has been shown in the rat that lesions of the frontal cortex can prevent habituation of the tachycardia evoked by noxious stimuli, while electrical stimulation in this region accelerated habituation of this response.

► The output from the defence areas of the brainstem can be modulated by inputs from the frontal cortex, and can modulate cardiovascular reflex pathways at the medullary level, probably at the RVLM. Such modulation may underlie habituation and sensitization.

Functional importance of the alerting response

It has been argued that the cardiovascular pattern of the alerting response provides a split-second advantage in a life-threatening situation by ensuring an increased nutritional supply to muscle even before exercise, defensive or aggressive behaviour begins. This is open to discussion, since functional or active hyperaemia begins immediately the muscle contracts. In any case, in the initial period of muscle contraction, muscle metabolism is not limited by oxygen supply (see Chapter 7). It may be that vasodilatation of the arteriolar vessels of muscle is more important in allowing the venous vessels to fill, so that as soon as the muscles contract, the skeletal muscle pump provides an immediate increase in venous return to the heart and a consequent increase in cardiac output according to Starling's Law.

On the other hand, it can also be argued that this response pattern is a potential threat to life. For example, the acute rise in arterial pressure is hazardous to an individual who is stroke-prone or has impaired coronary circulation, while repetition of the response in individuals who show little habituation may lead to the development of hypertension.

'Playing dead' or 'vasovagal syncope'

Although the pattern of the alerting response may be the most common and well-known response to novel, noxious or emotional stimuli, it is clear that under some conditions a very different pattern of response occurs. Playing dead seems to be particularly common in some species, for example, in the opossum (from which we get the expression 'playing possum'), in the rabbit and in deer fawn. This behavioural response is accompanied by bradycardia and a decrease in respiration. The term vasovagal syncope is used to describe sudden fainting, associated with a fall in arterial pressure, which

results from bradycardia and vasodilatation. It is known to occur in human subjects who experience what is, to them, an extremely stressful situation from which there is no escape; for example, the sight of blood, news of the death of a close relative or the thought of a danger that must be faced can serve as triggers. It is not clear whether, from the point of view of the underlying physiological mechanisms, playing dead and the vasovagal syncope are the same response. However, it has been said that both occur in situations when 'looking dead is preferable to being dead'. The discussion that follows is mainly concerned with the vasovagal syncope in human subjects, because this has received more attention.

True emotional fainting is difficult to evoke under laboratory conditions. For some of the classical experiments in the field (Fig. 11), the investigators selected medical students who knew that they were likely to faint at the sight of blood. On finding that fainting did not occur in the laboratory when blood was removed

from the subject by venepuncture, the investigators insisted that they would make the subject drink the blood — a faint ensued! Such experiments clearly demonstrated that before the faint there was an increase in arterial pressure, tachycardia and vasodilatation in forearm muscles, as would be expected during the alerting response. Then, suddenly, as if at the flick of a switch, there was pronounced bradycardia, further vasodilatation in the forearm and a fall in arterial pressure culminating in the faint [25]. It has been established that the bradycardia is mainly due to activation of the cardiac vagal fibres, while the vasodilatation in muscle has been attributed to inhibition of sympathetic noradrenergic fibre activity and to the actions of circulating adrenaline (Fig. 12). It has been claimed that the muscle vasodilatation is also mediated by increased sympathetic cholinergic activity, but acceptance of this idea is open to similar criticisms as discussed above in connection with the proposed involvement of sympathetic cholinergic fibres in the alerting response.

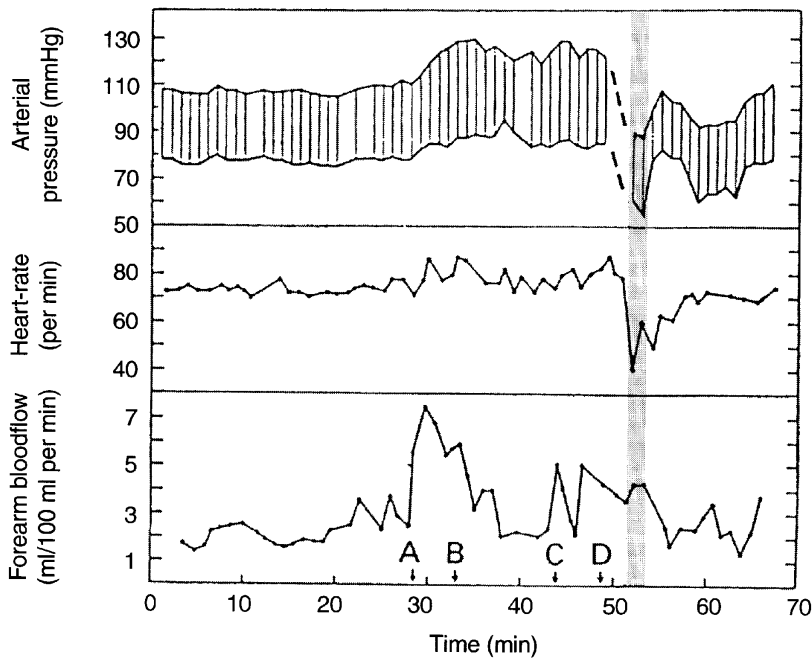


Fig. 11. Cardiovascular changes in a male student during vasovagal syncope

The student showed forearm vasodilatation and tachycardia as part of the alerting response while watching the preparation for venepuncture (A) and venepuncture of a colleague (B); however, he did not faint as he had on an earlier occasion. Insertion of a needle into his own arm (C) again produced forearm vasodilatation, but no faint. When he was asked to drink some of the blood taken

from his colleague (D), he yawned and then fainted (stippled area). No heart beat was detectable for 11 s and then heart rate was 37 beats/min. Forearm blood flow remained well above the resting level despite the profound fall in arterial pressure, showing that vasodilatation had occurred. Consciousness was regained after 2 min. Reproduced with permission from [25].

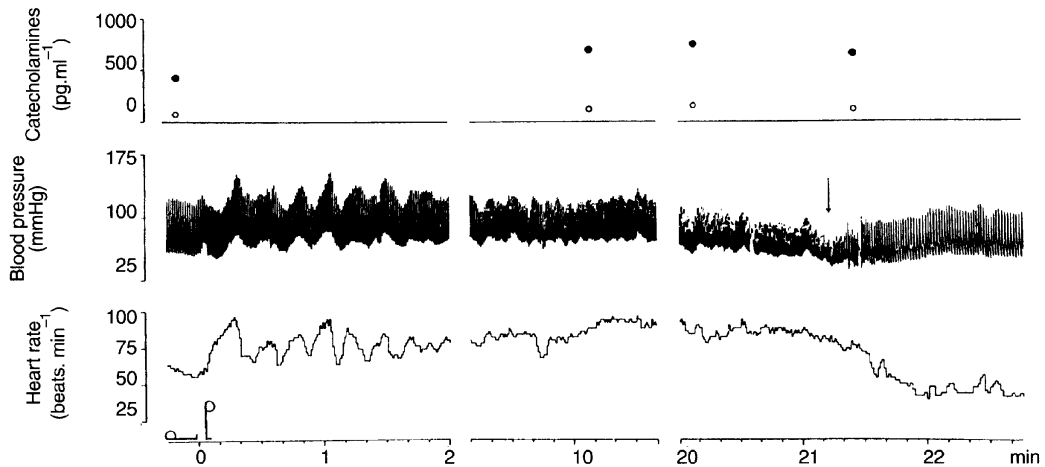


Fig. 12. Cardiovascular and plasma catecholamine changes recorded from a 40-year-old woman during vasovagal syncope induced by prolonged standing

Upon standing up (at time 0) there was an increase in heart rate and arterial pressure (recorded non-invasively). By 11 min, when heart rate had reached an even higher level, there was an increase in both plasma noradrenaline (○) and adrenaline (●) levels. Thereafter, plasma noradrenaline did not rise further, despite the gradual fall in arterial pressure and heart rate, while the rise in plasma adrenaline was maintained. At 21 min of standing, both

heart rate and arterial pressure declined more rapidly until fainting occurred (arrow). At this time plasma adrenaline was still above the baseline level. After transition to the supine position at 21.2 min, arterial pressure rose again towards the original control level (before time 0). Reproduced with permission from Van Lieshout, J.J. (1989) *Cardiovascular reflexes in orthostatic disorders*. PhD Thesis, University of Amsterdam.

From a haemodynamic point of view, the vasovagal syncope evoked by strong emotion seems to be identical with the vasovagal syncope evoked by other stimuli that are far easier to use in the laboratory, for example, prolonged standing, particularly in a hot environment, passive head-up tilt or lower body negative pressure. An apparently similar response can also occur after heavy exercise, if the individual stops exercising suddenly and attempts to stand upright. Bradycardia, peripheral vasodilatation and syncope have also been reported when a large haemorrhage occurs over a short period of time. Further, a persistent slow heart rate together with a low arterial pressure is sometimes noted in otherwise healthy subjects who have suffered blood loss as a result of an accident (see Chapter 8), even though under these conditions one might expect a baroreceptor-mediated tachycardia as a reflex response to the hypotension. Whatever the provoking stimulus, it seems that vasovagal syncope is preceded by profuse sweating, nausea, yawning and pupillary dilatation, which supports the idea that we are dealing with the same response.

It is known from experiments on anaesthetized animals that electrical stimulation in a localized region of the hypothalamus, lateral to the 'defence area', evokes a pattern of bradycardia and peripheral vasodilatation which leads to a fall in arterial pressure. It is possible that this region contains the neurones that are involved in integrating the pattern of the vasovagal syncope, or that it contains the efferent pathway from an integrating region, as described above for the defence areas. The sudden switch from the alerting response to vasovagal syncope in acute emotional stress might be explained if the defence areas 'trigger' the area concerned with the vasovagal syncope. Alternatively, it may be that the area concerned with vasovagal syncope is itself activated by emotional inputs, but has a higher threshold to them than the defence areas. Neither of these ideas has been tested experimentally.

However, there is experimental evidence that the vasovagal syncope can be elicited by a discrete group of cardiac afferent fibres whose endings are in the walls of the ventricles [26]. These unmyelinated afferent fibres seem to be particularly sensitive to ventricular wall defor-

