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Introduction

NANCY J. ROTHWELL

It is obvious to most biologists and clinicians that in mammals the central nervous system coordinates and regulates many complex physiological events. In order to do this, it must receive information from the internal and external environment, integrate this information and elicit appropriate efferent signals required to respond to a stimulus and maintain homeostatic function.

The concept of the brain as a regulator of responses to pathogenic insults is somewhat recent and still poses many unanswered questions. This may have resulted in part from a tendency for studies on injury and inflammation to focus on local tissue factors and immune mediators. It has, of course, long been known that certain aspects of the host defence response, such as fever, are under central nervous system control. However, concepts such as the effects of stress on susceptibility to disease, or the sustained psychological responses following trauma, were only poorly understood and were considered by some to be undefined and unsuitable for rigorous scientific analysis. This situation is changing rapidly, not least because of the identification of molecules and mechanisms underlying direct communications between the brain and the immune system, and the realisation that these are not distinct and unrelated biological entities.

The objectives of this book have been to discuss current knowledge about how the brain responds to and influences host responses to trauma, and to consider the mechanisms of these interactions, the clinical relevance and potential for novel therapeutic interventions. In spite of enormous advances in this field over the past decade, it will be clear that for each question that has been answered, a number of others have been raised. The planning of this book and most of the work in editing was carried out collaboratively with Dr Frank Berkenbosch at the University of
Amsterdam. Frank died tragically at the age of only thirty-nine, shortly before completion of this book. With the agreement of all of the contributors, the book has been dedicated to his memory. I believe that this is a fitting tribute, not simply because of his work on many of the subjects covered in this book, or because of his scientific and social interaction with several of the contributors, but also because the very nature of the subject closely reflects Frank’s outstanding contribution to scientific research. His work spanned neuroendocrinology, immunology, fever, responses to stress, injury and infection, and sought to answer basic scientific questions as well as to solve important clinical problems. He contributed novel findings and innovative approaches, collaborated with scientists in different countries with varied backgrounds and interests, and stimulated discussion and enthusiasm in science. Last, but not least, to those who knew him well, Frank Berkenbosch was an extremely likeable and warm individual with a great sense of humour, who will be sadly missed.
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Responses to injury

HARRY B. STONER

Historical aspects

Injury is such a frequent occurrence that its effects must have been among the earliest of the biological responses to have been investigated. Indeed, the salient features of the local response, inflammation, have been known from the time of Celsus (quoted by Majno, 1964) in the first century a.d. Realisation that there was a general response by the body to a local injury came later and was probably first described by Paré in 1582. Paré was a military surgeon, and later advances have almost always been linked to warfare. For most of the time injury and its effects can be conveniently ignored by doctor and lay-person alike but in wartime it obtrudes on general consciousness. Hence, our appreciation of these responses was advanced by military surgeons such as Clowes (1591), Hunter (1794), Guthrie (1815) and above all by Larrey (see Dible, 1970), who laid the foundations for the modern treatment of trauma.

Despite numerous conflicts, progress since the work of Larrey has been extremely slow for, although it was realised that injury provoked a response by the body, little attempt was made to understand the coordination of the response.

Causation of ‘shock’

Much of the time between the two World Wars was spent in the search for a single cause for what was usually called ‘shock’. This term was probably first used in the English literature by Latta (1795) but has never been clearly defined (Grant & Reeve, 1951). Three candidates were considered as possible causes – fluid loss, toxic factors and nervous influences. The last of these had been introduced by Crile (1899), who sought to explain the cardiovascular decline of the injured patient by
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### Table 2.1. Phases of response to injury

**Phases of response to injury**

1. **Pre-injury**
   - Defence reaction
   - Special senses

2. **Early, coagulation**
   - Activation of sympathetic-adrenal medulla system with redistribution of blood and liberation of energy stores
   - Hypoxemia

3. **Late, necrosis (shock)**
   - Activation of hypothalamic releasing hormones
   - Hypoxemia

4. **'Flow' (recovery)**
   - Failure of O2 transport
   - Lactate, protoplasmia, wound-organ
fatigue of the nervous centres involved. This was soon dismissed and interest in the later attempts by O'Shaughnessy & Slome (1934; Slome & O'Shaughnessy, 1938) and by Overman & Wang (1947) to determine the role of the afferent nervous barrage from the injured tissue was short lived.

The main argument was between fluid loss and toxic factors and was generally thought to have been decided by Blalock (1931) in favour of fluid loss – either externally as in haemorrhage or internally as in the oedema around damaged tissue. This seemed to bring together haemorrhage and tissue damage under a single umbrella. While it is true that the fluid loss into damaged tissue was often underestimated, real differences between the responses to haemorrhage and tissue damage were ignored. It is only during the last 50 years that the view has slowly developed that the responses to injury form a continuum, from the time of injury (even before in some cases) to eventual recovery or death, in which various factors play major roles at different times.

One reason for slow progress in this subject is scientific compartmentation. Although it has been recognised that the responses to injury involve many functions of the body each investigator seems to have seen them only in terms of his or her discipline – as a cardiovascular phenomenon, as an endocrine response or as a metabolic phenomenon. With over-specialisation few have been able to see the totality of the response. This has delayed the understanding of the order of events after injury. The existence of an order was pointed out by Cuthbertson (1942) and the subsequent development of his ‘ebb and flow’ idea (Stoner, 1993) indicated that injury was first followed by a period, the ‘ebb phase’, in which tissue oxygenation was adequate and during which widespread changes occurred. This was followed, either by a failure of O₂ transport and decline to death (shock/necrobiosis) or recovery through a ‘flow phase’. Each phase has clear markers and a different causation (Table 2.1).

**Endocrine response**

It might have been thought that the study of the endocrine response to trauma would have led quickly to that of the role of the central nervous system. This was not to be and compartmentation again seems to have been to blame. Physiologists engrossed in the experimental study of ‘sham rage’ and the defence reaction did not pass on to surgeons the relevance of their findings that showed that changes usually associated with injury could have begun even before it happened, if the danger was appreciated. Similarly, when knowledge of the endocrine response to injuries began to
grow from the work of Cannon (1929) on the adrenal medulla and sympathetic nervous system, endocrinologists seemed more concerned with the peripheral effects of the hormones than with the way in which the endocrine response was triggered through the central nervous system.

This was also the case when the importance of the adrenal cortex in the response to injury began to be appreciated in the 1940s. Although the link between the anterior lobe of the pituitary and the adrenal cortex was soon discovered, it was some time before the role of the hypothalamus in stimulating the pituitary–adrenal axis was realised. Before that, other mechanisms such as positive feedback and stimulation of the anterior hypophysis by adrenaline were considered. Positive feedback due to early consumption of adrenocortical hormones was never demonstrated and although adrenaline is a factor in the release of adrenocorticotropic hormone (ACTH) (Buckingham, 1985) and the circulating levels of adrenaline can be very high after severe injury (Little et al., 1985; Frayn et al., 1985), high enough to penetrate those parts of the brain with a poor blood–brain barrier, it is not the main stimulus. Understanding of this followed the demonstration of the direction of flow in the pituitary portal system and the isolation of the corticotrophin-releasing hormone produced by the parvocellular nuclei of the paraventricular hypothalamus.

Despite this, people seemed able to continue to view the hypothalamus as different, almost separate, from the rest of the brain in spite of its wealth of anatomical connections. Little was done to investigate how the parvocellular nuclei of the paraventricular hypothalamus were stimulated by distant trauma. An exception is the work by Swingle et al. (1944), Gibbs (1969a, b), Greer et al. (1970) and Feldman et al. (1971). From their work it would seem that, after trauma, noxious impulsive, not necessarily associated with pain, ascend in the contralateral spinohypothalamic tracts and stimulate the appropriate hypothalamic neurones, although the precise intracerebral pathways are not known.

Although, since the work of Cannon, there has been a growing appreciation of the importance of the early activation of the sympathetic–adrenal medullary system in diverting blood to the brain, heart and muscles and in liberating energy-yielding substrates from the stores of glycogen and triacylglycerol and, later, of the importance of the hypothalamic–pituitary–adrenal axis, the role of the posterior hypophysis has often been ignored. It was shown by Ginsburg & Heller (1953) that vasopressin was very rapidly released in response to haemorrhage and it is also released in response to accidental trauma (Anderson et al., 1989).
Responses to injury

In fact, vasopressin is probably the first of the pituitary hormones to be secreted. Vasopressin will reinforce the effects of the sympathetic–adrenal medullary system, since it is a pressor compound and induces hepatic glycogenolysis (Clark, 1928). Hems & Whitton (1980) have pointed out that the early breakdown of glycogen will have a bonus because it will free the water associated with the glycogen molecule, which can then be used to counteract a volume deficit.

The clinician should realise that the endocrine response to trauma is very rapid and is usually fully developed by the time the patient reaches hospital, say, in an urban area, 20–30 min after the accident.

Role of the central nervous system

Despite the growing appreciation of the importance of the endocrine response to injury, it was still some time before a role in response to injury was allotted to the brain as a whole. By the 1950s it had been shown that there were differences between the response to simple fluid loss, as in haemorrhage, and loss of fluid accompanying tissue damage (Tabor & Rosenthal, 1947). It has also been shown that the effects of fluid loss were aggravated by afferent nerve stimulation (Overman & Wang, 1947). The implications of these findings were widely ignored, particularly by clinicians. An exception was Tibbs (1956), who pointed out that patients could tolerate much greater blood loss if it was not accompanied by tissue damage.

Control of body temperature in the ‘ebb’ phase

Tabor & Rosenthal (1947) showed that whole body O₂ consumption by mice after haemorrhage or bilateral hind-limb ischaemia was less than appropriate at environmental temperatures below thermoneutral. After haemorrhage this was due to failure of O₂ transport and could be corrected by administering O₂, but this was not the case in the early stage of the response to limb ischaemia. A detailed examination of the reasons for this difference has shown that the animals with bilateral hind-limb ischaemia were unable to thermoregulate properly. This disability is found in other species and after other injuries (e.g. burns; Stoner, 1991). It also occurs earlier than was described by Tabor & Rosenthal (1947), for it commences during the period of limb ischaemia, not just after the tourniquets have been removed (Stoner, 1971). At this early stage after an injury, the reduced response to cold was not due to failure to appreciate...
the stimulus (Stoner, 1972) or to failure of the peripheral response mechanism. Trauma inhibits both the non-shivering and shivering thermogenic responses to a cold stimulus so that a colder stimulus has to be applied to the exterior of the animal or to the hypothalamus in order to produce a response. However, once the response had been initiated the gain of the response was the same as in the normal state (Stoner, 1969, 1971, 1974).

Further work showed that the alterations in thermoregulatory heat production were due to nociceptive afferent impulses, not necessarily painful ones, carried from the injured areas by non-medullated and fine medullated fibres i.e. C and Aδ, with the impulses from the dorsal horns ascending in contralateral spinothalamic tracts. The primary target for these impulses appears to be noradrenergic pools in the hindbrain. When these neurone pools are stimulated, impulses ascend in the ventral bundle to liberate noradrenaline in the region of the dorsomedial nucleus of the hypothalamus and so inhibit shivering (Stoner & Elson, 1971; Stoner et al., 1973; Stoner & Marshall, 1975a, b, 1977; Stoner & Hunt, 1976; Stoner, 1977; Marshall & Stoner, 1979a, b). It is not known if the same neurone pools and transmitters are involved in the inhibition of non-shivering thermogenesis, which is apparently more resistant to inhibition than shivering thermogenesis. For instance, in the injury produced in the rat by hindlimb tourniquets, Q₁ consumption can still be increased to maintain body temperature in response to the postural decrease in insulation during the period of limb ischaemia (Stoner & Marshall, 1971), although shivering is inhibited at that time (Stoner, 1971).

An effect of these changes in the small mammal is a fall in core temperature in environments where it would normally be maintained. However, the acute effects of injury on thermoregulation are not confined to heat production, for the heat loss pathway is also inhibited. In the injured rat more heat has to be applied to the hypothalamus to dilate the arteriovenous anastomoses in the tail than in the normal rat (Stoner, 1972).

The central neural network for thermoregulation is probably similar in all mammals (Bligh, 1979), but the relative importance of the two controlling paths, heat production and heat loss, varies with body weight (Holdmaier, 1971). In a small mammal like the rat, the main variable is heat production, whereas in larger mammals, including adult humans, it is heat loss. A consequence of differences in body weight can be seen in the changes in core temperature after trauma when the environmental temperature is below the thermoneutral zone. In rats and mice under these
conditions trauma leads to a rapid fall in core temperature, whereas in humans such falls are seen only after severe injuries, when failure of O₂ transport may be a factor (Little & Stoner, 1981). Nevertheless, the same type of central change after injury can be demonstrated in the human as in the rat. For instance, shivering is not seen in injured patients when their body temperature falls below the normal threshold for its onset (Little & Stoner, 1981; L. Martineau, personal communication). On the other hand the threshold for the onset of sweating is raised in the child with burn injury (Childs et al., 1990b).

Behavioural thermoregulation is important in all species and this too is affected by injury. In humans there is a very good negative relationship between the preferred temperature for water sprayed on the back of the hand and the core temperature. This relationship is lost in patients with moderately severe injuries (fractures). The injured patients examined all opted for a high water temperature irrespective of core temperature (Little et al., 1986). The desire for a warm environment has been described after burn injury (Wilmore, 1977; Henane et al., 1981).

The overall effect of these changes is to reduce the responses to both heat and cold and widen the ‘dead space’ (thermoregulatory zone) between the onset of thermoregulatory heat production and loss. In the human and the rat the normal bounds of this zone are 28–32°C. The effect of injury, in the ‘ebb’ phase, does not represent a change in thermoregulatory set-point, for then the thresholds would have moved in the same, not opposite, direction. This is confirmed in humans, since the change in behavioural thermoregulation after trauma is very different from that seen after a change in set-point (Cabanac & Massonnet, 1974).

**Cardiovascular homeostasis**

Thermoregulation is not the only homeostatic system to be disrupted by trauma, for the baroreceptor control of the cardiovascular system is also disturbed. Again this is due to nociceptive afferent impulses generated in damaged tissue and reaching the spinal cord via C and Aδ fibres. In this case the primary target in the brain is different and is probably in the periaqueductal grey matter (PAG). From there, impulses go to the hypothalamus and vagal nuclei leading to inhibition of a number of reflex responses. Noradrenaline is not involved as a central transmitter in these effects but is important in another reflex response to damaged tissue, particularly ischaemic muscle, namely the rise in systolic blood pressure.
in the Alam and Smirk reflex (Alam & Smirk, 1937, 1938a,b; Stoner & Marshall, 1975a). A detailed description of the cardiovascular or homeostatic changes following trauma are given in Chapter 3; they may be summarized here as follows.

In addition to the Alam and Smirk reflex, tissue damage leads to inhibition of those reflexes in which the afferent limb arises from the arterial baroreceptors. Consequently in injured patients and animals there is a reduced reflex response to body tilting, the Valsalva manoeuvre, phenylephrine infusion or direct stimulation of the carotid baroreceptors by neck suction (Little, 1979; Little & Stoner, 1983; Little et al., 1984; Redfern et al., 1984; Anderson et al., 1990). Not only is there a decrease in the sensitivity of the responses but, in the case of the last two, there is also resetting of the responses. The difference between the effects of simple fluid loss and tissue damage is even greater than in the case of thermo-regulation, as after haemorrhage the sensitivity of the baroreceptor reflexes can be increased.

These effects of nociceptive afferent stimuli may explain why the outlook after haemorrhage combined with tissue damage is worse than after haemorrhage alone. Nevertheless, it is surprising that an injury should be accompanied by impairment of a homeostatic system on which so much is thought to depend. It is also remarkable that in humans these changes appear after injuries of very moderate severity (injury severity scores 4 and 9) (Baker et al., 1974) that are not life-threatening.

A further action of the nociceptive stimuli on a response to a very severe injury should be mentioned. When haemorrhage is sufficiently severe to reduce cardiac filling to such a degree that it deforms the heart and stimulates cardiac C fibres it leads to vagal bradycardia. This vagal response is also inhibited by nociceptive afferent impulses from damaged tissue so that the blood loss required to produce the bradycardia is increased (Little, 1989).

It would seem from what has been written above that inhibition of homeostasis, both thermoregulatory and cardiovascular, is likely when muscle is damaged either directly by vascular occlusion or indirectly by fractures, which will also interfere to a varying degree with local muscle nutrition. It is likely that the afferent nociceptive impulses that arise from these damaged tissues commence their centripetal journey from polymodal receptors stimulated by such factors as a change in pH (Mense & Stahnke, 1983; Hoheisel & Mense, 1990). The fibres that carry these impulses are themselves resistant to hypoxia (Ochoa et al., 1972).