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Review

Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour

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ABSTRACT

Defensive behaviour evoked by mild or moderate psychological stress as well as increased activity and arousal are part of everyday life in humans and other animals. Both defensive behaviour and exercise are associated with marked and often quite stereotyped changes in autonomic and respiratory function. These patterned responses are generated by feed-forward or "central command" mechanisms, and are also modulated by feedback from peripheral receptors. In this review we first describe the pattern of autonomic and respiratory changes associated with defensive behaviour and exercise, and then discuss the central mechanisms that generate these patterned responses in the light of recent studies, with a particular focus on the role of the dorsomedial hypothalamus (DMH). We consider the hypothesis that the cardiorespiratory changes associated with defensive behaviour and exercise may, at least in part, be driven by common central mechanisms. Finally, we discuss the possible role of the DMH in generating circadian rhythms in arterial blood pressure and heart rate, and also in generating longer-term increases in sympathetic activity in some types of hypertension.

Contents

1. Introduction . . . 3
2. Naturally-evoked patterns of autonomic and respiratory changes . . . 4
   2.1. Acute psychological stress . . . 4
   2.2. Dynamic exercise . . . 4
3. Central mechanisms producing autonomic and respiratory changes . . . 5
   3.1. Psychological stress . . . 5
   3.2. Dynamic exercise . . . 7
4. Is there a common "central command centre" for cardiorespiratory activation during defensive behaviour and exercise? . . . 8
5. Role of the DMH in the long-term regulation of arterial pressure . . . 8
6. Conclusions . . . 9
Acknowledgements . . . 9
References . . . 9

1. Introduction

Homeostasis is maintained during different behaviours by the co-ordinated regulation of various physiological systems, including the somatomotor, cardiovascular, respiratory, and endocrine systems. In many of these behaviours, neural mechanisms within the hypothalamus play a key role. In this brief review, we shall consider in particular the role of hypothalamic mechanisms in regulating the autonomic and respiratory changes that occur as part of the complex physiological responses in two types of common behaviours: dynamic exercise and defensive behaviour. First, we shall briefly outline the pattern of autonomic and respiratory responses that are associated with these behaviours, emphasizing the fact that these have many features in common. Next, we shall discuss the potential central pathways and mechanisms that generate these responses, and then finally we will consider the question as to whether the central mechanisms that subserve cardiovascular responses to short-term challenges such as an acute psychological stress or exercise can also contribute to long-term changes in sympathetic activity, leading to hypertension.

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2. Naturally-evoked patterns of autonomic and respiratory changes

2.1. Acute psychological stress

An exteroceptive or psychological stress is one that is perceived by an animal as an actual or potential threat in the external environment. Such stress evokes defensive behaviour, which is associated with a characteristic pattern of physiological changes sometimes referred to as a "defence reaction" (Hilton, 1982). Psychological stress may be conditioned (i.e. is evoked by a stimulus which is normally innocuous, but which the animal perceives as threatening because of prior experiences) or else unconditioned (i.e. is intrinsically threatening or potentially threatening, such as a loud noise). It is important to make this distinction, because there is evidence that cardiovascular responses to conditioned and unconditioned psychological stress are mediated by different pathways within the brain. For example, lesions centred on the perifornical region in the hypothalamus have been shown to largely abolish the increases in blood pressure and heart rate associated with conditioned fear but have no effect on the increases in blood pressure and heart rate associated with restraint, an unconditioned psychological stress (Furlong and Carrive, 2007). In this review, we shall discuss only the unconditioned type of psychological stress. This may vary greatly in intensity, ranging from mild arousal to an extreme response evoked by a life-threatening stimulus (e.g. the approach of a predator).

In humans, mild psychological stress, such as that associated with mental arithmetic or the Stroop word-color conflict test, is known to evoke an increase in the secretion of adrenocorticotropic hormone (ACTH) (Altemus et al., 2001) and a rather characteristic pattern of cardiovascular and respiratory changes. Typically, these consist of an increase in arterial blood pressure, cardiac output and heart rate, together with a decrease in blood flow to the splanchnic and cutaneous vascular beds but often an increase in blood flow to skeletal muscles (Blair et al., 1959; Barcroft et al., 1960; Hjemdahl et al., 1989; Freyschuss et al., 1990; Chaudhuri et al., 1991; Wasmund et al., 2002; Lindqvist et al., 1996; Carter et al., 2005; Nicotra et al., 2005). The increase in skeletal muscle blood flow is due primarily to an increase in the level of circulating adrenaline as well as vasodilation mediated by endothelial nitric oxide (Cardillo et al., 1996; Lindqvist et al., 1996).

These cardiovascular changes are associated with a substantial increase in overall sympathetic activity, as assessed by total body noradrenaline spillover (Esler et al., 1989). The increase in noradrenaline spillover in different regions varies greatly, however, being very large for the heart but minimal for skeletal muscle beds (Esler et al., 1989). Direct measurements using microneurography generally show that in response to psychological stress there is little change or only a small increase in the activity of sympathetic nerves supplying skeletal muscle vascular beds (Hjemdahl et al., 1989; Freyschuss et al., 1990; Carter et al., 2005), whereas the activity of sympathetic nerves innervating skin vascular beds is markedly increased (Fagius and Traversa, 1994). Although there are no reports of direct or indirect measurements of renal or splanchnic sympathetic activity during psychological stress in humans, one study (Chaudhuri et al., 1991) has reported an increase in mesenteric vascular resistance during mental stress, which is indicative of sympathetically mediated vasoconstriction. Thus, in summary, psychological stress in humans generates a patterned sympathetic response, with marked increases in the activity of sympathetic nerves supplying the heart, skin, splanchnic beds and adrenal medulla, but with little effect on skeletal muscle sympathetic activity.

Respiratory activity is also increased during psychological stress in humans (Grossman, 1983), including the extreme case of panic disorder, in which hyperventilation is a characteristic feature (Sinha et al., 2000). An excellent example of a stress-induced increase in respiratory activity is illustrated in Fig. 1, taken from a study by Fenz and Epstein (1967), which shows that in novice parachute jumpers the heart rate and respiratory rate both increase progressively during the period preceding the jump. The magnitudes of these increases in heart rate and respiratory rate also correlate with the self-assessed level of anxiety during this period (Fenz and Epstein, 1967). The changes in tidal volume during anxiety are more variable, but overall there is an increase in ventilation, resulting in a decrease in the arterial blood pCO_2 (Grossman, 1983).

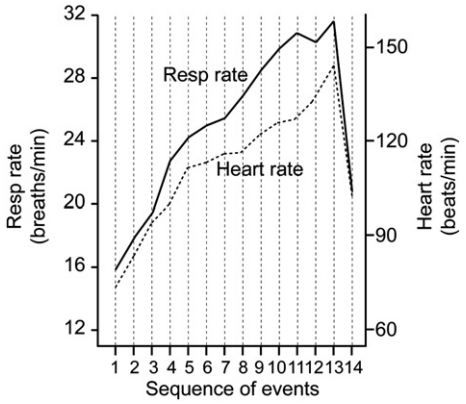

Fig. 1. The heart rate and respiratory rate in novice parachute jumpers during the sequence of events leading up to and after the jump. Event 1, previous day; events 2–9, from arriving at airport to flight take-off; events 10–12, during ascent of aeroplane; event 13, just before jumping; event 14, landing. Modified from Fenz and Epstein (1967), with permission.

The pattern of changes observed in experimental animals exposed to mild psychological stress is very similar to that observed in humans. In rats exposure to air jet or a novel environment leads to increases in arterial pressure, heart rate and renal sympathetic nerve activity (van den Buuse et al., 2001; Kanbar et al., 2007). Psychological stress in rats, as in humans, also evokes an increase in ACTH secretion (Neumann, 2001) and respiratory rate (King et al., 2005). Furthermore, in a rat model of panic disorder, increases in arterial pressure, heart rate and respiratory rate can be evoked by lactate infusion (Johnson and Shekhar, 2006), very similar to those that can be evoked by lactate infusion in panic-prone humans (Liebowitz et al., 1986).

2.2. Dynamic exercise

During dynamic exercise in humans and animals, the arterial pressure, heart rate, and cardiac output increases (Rowell, 1974; McAllister, 1998). There is also a major re-distribution of the cardiac output, such that blood flow to non-exercising regions such as the splanchnic bed and kidney is reduced, while blood flow to exercising muscles is greatly increased (Rowell, 1974; Rowell, 1997; McAllister, 1998). Direct or indirect measurements of regional sympathetic activity have demonstrated that there is an increase in the activity of sympathetic nerves innervating the heart and kidney (Hasking et al., 1988; Rowell, 1997; Miki et al., 2003). With regard to the skeletal muscle beds, current evidence indicates that there is an increase in sympathetically mediated vasoconstrictor activity in both active and inactive muscles during exercise (Rowell, 1997; Hansen et al., 1994). Thus, dynamic exercise is associated with a widespread increase in sympathetic nerve activity.

Like psychological stress, exercise is associated with an increased secretion of ACTH (Park et al., 2005), and an increase in ventilation, which during dynamic exercise consists of an initial rapid component followed by a more gradual component (Dejours, 1967). There is a close matching of the increased ventilation with the increased cardiac output, such that the arterial blood pO_2, pCO_2 and pH are not greatly altered during exercise, except under extreme conditions (Turner, 1991).