Central command: control of cardiac sympathetic and vagal efferent nerve activity and the arterial baroreflex during spontaneous motor behaviour in animals

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Feedforward control by higher brain centres (termed central command) plays a role in the autonomic regulation of the cardiovascular system during exercise. Over the past 20 years, workers in our laboratory have used the precollicular–premammillary decerebrate animal model to identify the neural circuitry involved in the CNS control of cardiac autonomic outflow and arterial baroreflex function. Contrary to the traditional idea that vagal withdrawal at the onset of exercise causes the increase in heart rate, central command did not decrease cardiac vagal efferent nerve activity but did allow cardiac sympathetic efferent nerve activity to produce cardiac acceleration. In addition, central command-evoked inhibition of the aortic baroreceptor–heart rate reflex blunted the baroreflex-mediated bradycardia elicited by aortic nerve stimulation, further increasing the heart rate at the onset of exercise. Spontaneous motor activity and associated cardiovascular responses disappeared in animals decerebrated at the midcollicular level. These findings indicate that the brain region including the caudal diencephalon and extending to the rostral mesencephalon may play a role in generating central command. Bicuculline microinjected into the midbrain ventral tegmental area of decerebrate rats produced a long-lasting repetitive activation of renal sympathetic nerve activity that was synchronized with the motor nerve discharge. When lidocaine was microinjected into the ventral tegmental area, the spontaneous motor activity and associated cardiovascular responses ceased. From these findings, we conclude that cerebral cortical outputs trigger activation of neural circuits within the caudal brain, including the ventral tegmental area, which causes central command to augment cardiac sympathetic outflow at the onset of exercise in decerebrate animal models.

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Heart rate (HR) during voluntary exercise is controlled via cardiac autonomic nerve activity resulting from a feedforward mechanism by higher brain centres termed central command (CC; Goodwin et al. 1972; Ninomiya et al. 1988; Mitchell, 1990). However, the characteristics of the centrally induced responses to cardiac autonomic outflow have not been clear owing to the technical difficulty of obtaining direct recordings from efferent nerves, especially cardiac vagal outflow. At rest, the arterial baroreflex has a strong influence on cardiac autonomic outflow (Ninomiya et al. 1988; Matsukawa et al. 1993), and we hypothesized that interactions between CC and arterial baroreflexes contribute to producing the cardiac autonomic responses during exercise. Furthermore, the specific neural networks involved in generating CC remain unclear, because it is also difficult to accomplish a comprehensive study with voluntary exercise. In order to address the questions raised, we conducted a series of experiments in our laboratory using conscious or decerebrate animals. The present report provides novel information concerning the following aspects: (1) central control of cardiac sympathetic and vagal outflows during exercise; (2) central modulation of the arterial baroreflexes during exercise; and (3) the central site responsible for generation of CC.
Central control of cardiac sympathetic and vagal nerve activities during exercise

It has been thought that the change in HR during exercise is predominantly controlled by cardiac vagal withdrawal at the early phase of exercise or throughout a low to moderate intensity of exercise and then by additional recruitment of stimulation of cardiac sympathetic outflow as the exercise intensity is raised (Robinson et al. 1966; Rowell & O’Leary 1990). Then, Mitchell et al. (1989) demonstrated that atropine attenuated the increase in HR during attempted static exercise with partial curarization, suggesting that the centrally generated HR response is in part caused by vagal withdrawal. However, atropine greatly elevates the baseline HR and has an influence on the CNS, which may in turn modify cardiac autonomic outflow itself. This traditional view has been challenged by a recent finding that cardiac sympathetic efferent nerve activity (CSNA) increases rapidly at the beginning of treadmill exercise in conscious cats, irrespective of the exercise intensity (Tsushimauchi et al. 2002). In addition, it was recently found that β1-adrenergic receptor blockade at the beginning of treadmill running in rats (Wakasugi et al. 2010) and hand-grip exercise in humans (Fisher et al. 2010) attenuated the exercise-induced tachycardia more than muscarinic blockade. It would be expected that if cardiac vagal withdrawal played a dominant role in the initial tachycardia, the HR increase of tetraplegic subjects who have an intact vagal nervous system but have lost supraspinal control of the sympathetic nervous system would have been similar to that of healthy control subjects. Indeed, the initial tachycardia at the onset of static arm exercise at 35% of maximal voluntary contraction was blunted in subjects with complete cervical spinal cord injury (C6–C7; Takahashi et al. 2004). The high-frequency component of the power spectrum of HR variability, an indirect estimate of cardiac vagal efferent nerve activity (CVNA), showed a gradual decrease throughout the static exercise in both normal and spinal-cord-injured subjects (Takahashi et al. 2007). From these studies, we hypothesized that in contrast to the traditionally accepted view, that central stimulation of CSNA must play an important role in cardiac acceleration at the onset of exercise, rather than that of cardiac vagal withdrawal.

We tested this hypothesis in our laboratory by directly recording CSNA and CVNA from nerve branches close to the right atrium in cats decerebrated at the precollicular–premammillary body level, which are able to induce spontaneous motor nerve discharge under paralysis (Kadowaki et al. 2011). In this preparation, the cardiac autonomic responses are caused by CC alone and are not influenced by the exercise pressor reflex. As shown in Fig. 1, CSNA increased immediately before spontaneous motor activity, whereas CVNA did not decrease at that time, but slightly increased throughout the motor activity. As clear cardiac vagal withdrawal was never found, HR is predominantly controlled by the increase in cardiac sympathetic outflow during spontaneous motor activity in decerebrate animals. Hence, unlike the traditional concept of cardiac vagal withdrawal, CC allows cardiac sympathetic outflow to increase at the onset of exercise and it does not appear to produce cardiac vagal withdrawal in a decerebrate animal model. Whether this idea is true for autonomic control of HR during exercise in the intact and conscious state requires further investigation.

In another experiment, we cut the bilateral carotid sinus nerves and the left aortic nerve, but not the right aortic nerve; this preparation is called partial sinoaortic denervation (SAD; Kadowaki et al. 2011). We found that the initial increase in cardiac sympathetic outflow at the onset of motor activity still existed, but the size of the increase was blunted (Fig. 2). In contrast, the increase in cardiac vagal outflow was abolished by partial SAD, indicating that the increase in vagal outflow is induced by the arterial baroreflex and appears to be dependent on the blood pressure elevation. The surprising result that the size of the initial increases in CSNA and HR during exercise is blunted by SAD indicates that some kind of central modulation of the arterial baroreflex is involved in producing stimulation of cardiac sympathetic outflow and HR (Sadamoto & Matsukawa 1997; Matsukawa et al. 1998; Nishida et al. 2002; Kadowaki et al. 2011).

Central modulation of arterial baroreflexes during exercise

When arterial blood pressure (AP) decreases, CSNA is increased to raise HR and cardiac output; conversely, when AP increases, CSNA is decreased by the baroreflex (Ninomiya et al. 1988; Matsukawa et al. 1993). At the same time, CVNA is increased in response to the rise in AP (Murata & Matsukawa 2001; Simms et al. 2007; Kadowaki et al. 2011). The slope of the baroreflex curve between AP and HR represents baroreflex sensitivity, indicating the strength of the arterial baroreceptor–HR feedback loop. Bristow et al. (1969) found that a reduction in baroreflex sensitivity occurs at the beginning of ergometer exercise in humans. To further identify the dynamic characteristics of the arterial baroreflex at the onset of exercise, HR and AP have been simultaneously recorded during voluntary static exercise in conscious animals (Matsukawa et al. 2006). Heart rate increased at the onset of exercise, and this increase was followed by a rise in AP. To manipulate afferent input from arterial baroreceptors to the CNS, baseline blood pressure was decreased by nitroprusside and increased by noradrenaline. As a result, the baseline HR was increased and decreased by the arterial baroreflex, respectively. When static exercise was evoked...
at different baseline blood pressures, the size of the initial tachycardia was strongly dependent on baseline blood pressure (Matsukawa et al. 2006). The higher the blood pressure, the more the HR was increased. Furthermore, the slope of the baroreflex relationship between AP and HR became much less at the onset of voluntary exercise, in comparison with the control values before exercise, and returned to the control slope during the later period of

Figure 1. A typical example of the responses of cardiac sympathetic nerve activity (CSNA), cardiac vagal nerve activity (CVNA), heart rate (HR), arterial blood pressure (AP) and tibial motor nerve discharge during spontaneous fictive motor activity in a decerebrate cat with intact baroafferents. In A, CSNA increased before the onset of the motor activity (⋆), which was followed by rises in HR (⋆) and AP. In B, CVNA slightly increased throughout the motor activity. (Reproduced with permission from Kadowaki et al. 2011.)
exercise (Matsukawa et al. 2006). Thus, it is likely that central command blunts the sensitivity of the arterial baroreceptor–HR baroreflex at the onset of exercise, allowing an upward shift of HR with the same blood pressure.

To examine whether the central modulation of the arterial baroreflex occurs within the brainstem, Komine et al. (2003) electrically stimulated the aortic nerve with a constant intensity at various phases of voluntary static exercise in conscious cats. Electrical stimulation of the aortic nerve induces a marked bradycardia and hypotension at rest (Fig. 3). The amplitude of the response reflects the central property of the cardiac and vasomotor component of aortic baroreflex, respectively. Aortic baroreflex bradycardia was markedly attenuated immediately before and at the onset of voluntary exercise and remained blunted during the later period of exercise, indicating that CC plays a more important role in causing the inhibition of the component of the aortic baroreflex than the exercise pressor reflex (Fig. 3). In contrast, aortic baroreflex hypotension was not affected by the exercise. The summarized data, obtained from three cats, indicate a consistent response (Fig. 3). The same type of central modulation of the aortic baroreflex has

![Figure 2](image_url)

**Figure 2.** The time courses of the average changes in CSNA, CVNA, HR and mean arterial blood pressure (MAP) during spontaneous fictive motor activity in decerebrate cats with intact baroafferents (grey lines) or partial sinoaortic denervation (SAD; filled circles)

The initial increase in CSNA at the onset of spontaneous motor activity appeared even following partial SAD, but the size of the increase was blunted by partial SAD. In contrast, the slight increase in CVNA during the motor activity was abolished by the partial SAD. ∗ Significant differences (P < 0.05) from the baseline in the partial SAD condition. (Reproduced with permission from Kadowaki et al. 2011.)
Figure 3. The effects of central command on the arterial baroreflex function during voluntary exercise

A, an example of the baroreflex bradycardia and depressor response evoked by electrical stimulation of the aortic depressor nerve (ADN) before, during and after voluntary static exercise in a conscious cat. The horizontal line shows the duration of voluntary static exercise. Stimulation of the ADN caused baroreflex bradycardia and a depressor response at rest. When the ADN was stimulated at the onset of exercise, the evoked baroreflex bradycardia was markedly attenuated. Subsequently, when the ADN was stimulated in the middle of static exercise, the baroreflex bradycardia was also blunted but became greater than that evoked at the onset of exercise. When the ADN stimulation was given after static exercise, the same bradycardia was produced as before exercise. In contrast to the baroreflex bradycardia, the depressor response evoked by ADN stimulation was not altered by static exercise. In B, relative percentage values of the ADN stimulation-induced baroreflex bradycardia and depressor response are compared before, during the initial period of exercise (up to 8 s from the onset of exercise), during the later period of exercise until the end of exercise, and after exercise in three cats. Vertical columns and bars show means ± SEM. The baroreflex bradycardia during the initial period of static exercise was significantly attenuated from the control value, whereas the bradycardia during the later period of and after exercise was not significantly different. In contrast, the depressor response was not influenced by static exercise. * Significant difference (P < 0.05) from the pre-exercise response. (Reproduced with permission from Komine et al. 2003.)
been recognized during spontaneous muscle contraction in decerebrate cats (Murata et al. 2004). Therefore, CC associated with spontaneous motor activity in decerebrate cats can modulate the aortic baroreflex according to a similar mechanism to that in conscious cats. It is likely that the cardiac component of the aortic baroreflex is inhibited at the onset of exercise, while the vasomotor component of the aortic baroreflex is preserved. Central command appears to organize selective inhibition of the cardiac component of the aortic baroreflex within the brainstem, which in turn allows increases in cardiac sympathetic outflow to rapidly increase HR at the onset of exercise (Komine et al. 2003). This conclusion is supported by a recent study (Fisher et al. 2007) demonstrating that the carotid sinus baroreflex bradycardia elicited by a transient increase in carotid sinus transmural pressure was blunted at the onset of static hand-grip exercise with a higher intensity in humans.

In contrast, neither evoked muscle contraction nor passive mechanical stretch of skeletal muscle affected the bradycardia elicited by aortic nerve stimulation in decerebrate cats (Murata et al. 2004). Thus, afferent input from muscle mechanoreceptors and metaboreceptors does not modify the sensitivity of the aortic baroreflex within the brainstem.

In contrast, the effect of the exercise pressor reflex on carotid sinus baroreflex function is controversial. McWilliam et al. (1991) reported that the cardiac vagal component of the carotid sinus baroreflex was inhibited at the start of evoked muscle contraction in decerebrate cats.

Figure 4. The effects of chemical stimulation of neurons in the ventral tegmental area (VTA) on the sympathetic nervous and motor systems

A, typical recordings showing the effects of microinjection of bicuculline into the VTA on renal sympathetic nerve activity (RSNA), AP, MAP and integrated tibial motor nerve activity in an unanaesthetized, decerebrate rat. B, the same changes during chemical stimulation of the VTA are shown at a faster chart speed. C, relationships between the location of the tip of the micropipettes and the size of the increase in RSNA elicited by injecting bicuculline into the VTA, substantia nigra (SN) and a dorsolateral part of the periaqueductal grey matter (PAG). Chemical stimulation by bicuculline of neurons in the VTA and the dorsolateral PAG increased RSNA, whereas chemical stimulation of neurons in the SN did not alter RSNA. Abbreviations: cp, cerebral peduncle; ml, medial lemniscus; MM, medial mammillary nucleus; RN, red nucleus; SNCD, the dorsal tier of SN pars compacta; and SNR, SN pars reticularis. (Reproduced with permission from Nakamoto et al. 2011.)

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cats, and Drew et al. (2008) reported a marked reduction in its maximal gain during combined muscle chemoreflex and mechanoreflex activation in resting human muscles, suggesting that muscle afferents may change the sensitivity of the cardiac vagal component of the carotid sinus baroreflex. However, Potts & Mitchell (1998) and McIlvven et al. (2001) reported that stimulation of the muscle receptors shifted the operating point of the carotid sinus baroreflex towards a higher blood pressure but did not affect the sensitivity of the baroreflex in anaesthetized dogs and decerebrate cats.

Central site responsible for generation of central command

The anatomical location and structures responsible for CC activity remain obscure. In order to answer the question of whether cerebral cortical structures are essential for the generation of CC during exercise, a decerebration of the precollicular and premammillary bodies in the cat was established (Eldridge et al. 1981; Hajduczok et al. 1991; Sadamoto & Matsukawa, 1997; Matsukawa et al. 1998). The decerebrate animals can usually stand up and perform spontaneous locomotion without any artificial stimulation. In this model, it was found that renal sympathetic nerve activity and HR abruptly increased in association with starting the locomotion (Hajduczok et al. 1991; Matsukawa et al. 1998). The same cardiovascular responses occurred at the onset of spontaneous fictive motor activity in paralysed, decerebrate cats (Eldridge et al. 1981). Based on this evidence, it is considered that cerebral cortical output is not an essential component of the generation of CC but does seem to require a process that triggers activity in neural circuit(s) in the caudal brain to generate CC. As spontaneous motor activity and the associated cardiovascular response are lost after decerebration at the midcollicular level (Hayashi 2003), it is hypothesized that a region from the caudal diencephalon to the rostral mesencephalon plays an important role in the generation of CC. Interesting evidence has come from the data obtained in Parkinson's disease patients, who lose dopaminergic neurons in the midbrain. In normal subjects, HR and AP change in parallel over a 24 h period, and there is a significant positive relationship between them (Murata et al. 1997). In addition to the parallel changes in HR and AP, a positive relationship between renal sympathetic nerve activity and AP in different behaviours (moving, grooming, resting and non-rapid-eye-movement sleep) has been noticed in conscious rats (Miki et al. 2004). The increases in HR, renal sympathetic nerve activity and AP during exercise contributed to the positive relationships, which cannot be explained by the arterial baroreflex but are caused by central command in concert with the exercise pressor reflex. However, such a positive relationship between HR and AP is lost or weakened in Parkinson's disease patients with the same age as control subjects (Murata et al. 1997). Collectively, these data lead to an interesting idea that central dopaminergic neurons may play a role in producing CC during exercise.

The midbrain dopaminergic system is classified into three cell groups, the substantia nigra (SN), the ventral tegmental area (VTA) and the retrorubral nucleus. Of the three cell groups, it is most likely that the VTA is involved in generation of CC during exercise, because neurons in the VTA represent not only an ascending projection to the cerebral cortex and basal ganglia, but they also send a projection to the hypothalamic and mesencephalic area (Beckstead et al. 1979; Simon et al. 1979; Oades & Halliday 1987; Kirouac & Pittman 2000). As both VTA and SN contain dopaminergic cells, glutamatergic cells and GABAergic cells (Steffensen et al. 1998; Olson & Nestler 2007; Yamaguchi et al. 2007; Dobi et al. 2010), Nakamoto et al. (2011) have examined, for the first time, the effect of chemical stimulation of neurons in the VTA and SN by an antagonist of GABA<sub>A</sub> receptors (bicuculline) on renal sympathetic outflow and haemodynamics, as shown in Fig. 4. Bicuculline stimulation in the VTA evoked long-lasting increases in renal sympathetic nerve activity, AP and HR in anaesthetized rats, whereas bicuculline
in SN did not affect these parameters (Nakamoto et al. 2011). Moreover, the chemical stimulation of VTA induced tibial motor discharge in anaesthetized, decerebrate rats (Nakamoto et al. 2011). There was good synchronization of renal sympathetic nerve activity and tibial motor discharge (Fig. 4), indicating that chemical stimulation of the VTA can promote repetitive motor discharge and corresponding sympathetic nerve responses. In addition, either electrical or chemical stimulation by bicuculline of the VTA evoked neurogenic vasodilatation of the femoral vascular bed in the rat and the cat (Matsukawa et al. 2011; Nakamoto et al. 2011). If the VTA is involved in generation of spontaneous cardiovascular events associated with motor activity, inactivation of neurons in the VTA may interrupt the spontaneous cardiovascular changes. It has been observed that when lidocaine was injected into the VTA, spontaneous blood pressure fluctuations ceased and baseline haemodynamics were maintained (K. Matsukawa, K. Ishii & N. Liang, unpublished observation). These findings indicate that the VTA is involved in generation of cardiovascular events associated with spontaneous motor activity.

Conclusion

A schematic hypothesis of central command is presented in Fig. 5. It appears that cortical output is needed to trigger neural circuit(s) in the caudal brain responsible for generation of CC. Neural circuits, including the VTA in the midbrain, appear to be involved in the generation of CC. Excitation of neurons in the VTA evokes rhythmic discharge not only of sympathetic nerves but also of motor nerves. However, it is not yet known whether the VTA itself is a CC generator or whether the VTA may excite a CC generator. Central command allows cardiac sympathetic outflow to increase prior to spontaneous motor activity, which contributes to the tachycardia at the onset of motor activity. The increase in cardiac sympathetic outflow at the beginning of exercise is partly produced by selective inhibition of the cardiac component of the aortic baroreflex resulting from increases in CC.

References


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