Autonomic Neuroscience: Basic and Clinical 188 (2015) 10–18

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Autonomic responses to exercise: Cortical and subcortical responses during post-exercise ischaemia and muscle pain

Vaughan G. Macefield [a,b,*], Luke A. Henderson [c]

[a] School of Medicine, University of Western Sydney, NSW, Australia
[b] Neuroscience Research Australia, Sydney, NSW, Australia
[c] Department of Anatomy and Histology, University of Sydney, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Received 28 June 2014
Received in revised form 27 August 2014
Accepted 13 October 2014

Keywords:
Central command
fMRI
Metaboreflex
Microneurography
Muscle pain

ABSTRACT

Sustained isometric contraction of skeletal muscle causes an increase in blood pressure, due to an increase in cardiac output and an increase in total peripheral resistance—brought about by an increase in sympathetically-mediated vasoconstriction. Both central command and reflex inputs from metaboreceptors in the contracting muscles have been shown to contribute to this sympathetically mediated increase in blood pressure. Occluding the blood supply and trapping the metabolites in the contracted muscle (post-exercise ischaemia) has shown that, while heart rate returns to baseline following exercise, the increase in MSNA and blood pressure persists in the absence of central command—sustained by peripheral inputs. Post-exercise ischaemia activates group III and IV muscle afferents, which are also activated during noxious stimulation. Indeed, post-exercise ischaemia is painful, so what is the role of pain in the increase in blood pressure? Intramuscular injection of hypertonic saline causes a deep dull ache, not unlike that produced by post-exercise ischaemia, and we have shown that this can cause a sustained increase in MSNA and blood pressure. We have used functional Magnetic Resonance Imaging (fMRI) of the brain to identify the cortical and subcortical sites involved in the sensory processing of muscle pain, and in the generation of the autonomic responses to muscle pain, produced either by post-exercise ischaemia or intramuscular injection of hypertonic saline. During static hand-grip exercise there were parallel increases in signal intensity in the contralateral primary motor cortex, deep cerebellar nuclei and cerebellar cortex that ceased at the end of the exercise, reflecting the start and end of central command. Progressive increases during the contraction phase occurred in the contralateral insula, as well as the contralateral primary somatosensory cortex, and continued during the period of post-exercise ischaemia. Decreases in signal intensity occurred in the perigenual anterior cingulate cortex during the contraction phase; these too were sustained during post-exercise ischaemia. That similar changes occurred with intramuscular injection of hypertonic saline suggests that much of the cortical and subcortical changes seen during post-exercise ischaemia reflect the sensory and affective attributes of the muscle pain, rather than in furnishing the cardiovascular responses *per se*.

1. Introduction

Unlike the rapid vasodilatation and fall in blood pressure seen during intermittent contractions of skeletal muscle (Reeder and Green, 2012), sustained isometric contractions cause an increase in blood pressure through an increase in cardiac output and sympathetically-mediated vasoconstriction (Mitchell, 1990). Indeed, it is well known that fatiguing isometric exercise is associated with increases in sympathetic outflow to the heart and the vascular beds of muscles not engaged in the exercise, resulting in increases in heart rate, cardiac contractility and systemic arterial pressure. What happens to sympathetic outflow to contracting muscle is less well-understood, with decreases (Wallin et al., 1992) or no change (Hansen et al., 1994) in muscle sympathetic nerve activity (MSNA) having been reported; differences in experimental paradigm and analytical approach may account for these disparate findings. We recently showed that, during static isometric contractions of tibialis anterior, MSNA actually increases in an intensity-dependent manner, which—together with the increase in intramuscular pressure—would tend to counteract the effects of local vasodilatory mechanisms (Boulton et al., 2014). Experimental records from one subject, performing a static dorsiflexion of the ankle at ~10% of maximum, are shown in Fig. 1. It can be seen that both burst amplitude and incidence increase during the contraction.

* Corresponding author at: School of Medicine, University of Western Sydney, Locked Bag 1797, Penrith NSW 2751, Australia. Tel.: +61 2 94620 3779; fax: +61 2 94620 3890.
E-mail address: v.macefield@uws.edu.au (V.G. Macefield).

http://dx.doi.org/10.1016/j.autneu.2014.10.021
1566-0702/

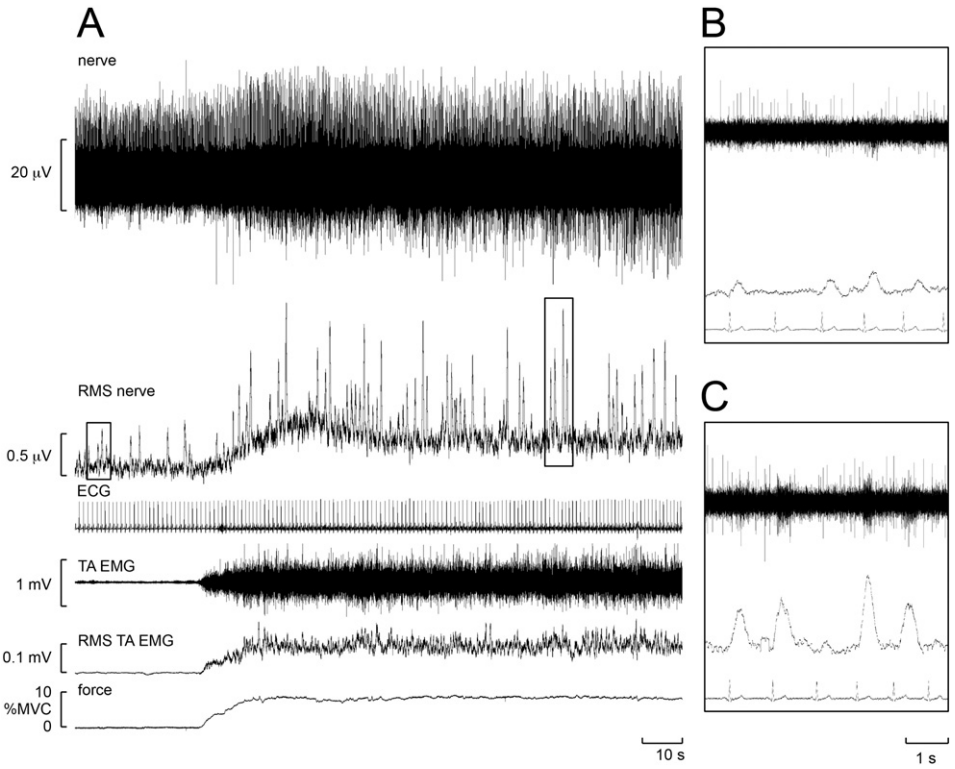

Fig. 1. Experimental records from one subject during an isometric control contraction of the ipsilateral tibialis anterior muscle at ~10%MVC. Note that an increase in muscle afferent activity occurs during the contraction, resulting in a baseline shift in the RMS-processed nerve signal. Despite this, bursts of MSNA remained clearly identifiable and increased in amplitude. (A) Raw recordings of the neurogram (top) and root-mean-square processed version of this recording (RMS nerve) which shows spontaneous bursts of MSNA. (B) Expanded view of the selected area in A prior to the contraction. (C) Expanded view of the selected area in A during the contraction, highlighting the increased amplitude of each burst compared with resting activity in (B). Reproduced from Boulton et al (2014).

It is generally accepted that both central and peripheral mechanisms contribute to the physiological changes in exercise: increases in MSNA, heart rate and blood pressure can occur in conscious humans trying to contract muscles which have been pharmacologically paralysed (Victor et al., 1989; Gandevia et al., 1993), while the increase in MSNA and blood pressure can be sustained at the conclusion of exercise by trapping metabolites in the contracted muscles (Victor et al., 1987). It is known that thinly myelinated (group III) and unmyelinated (group IV) muscle afferents respond to mechanical and metabolic events in the muscle (Kniffki et al., 1981; Kaufman et al., 1983; Hayes et al., 2005). These muscle afferents have been shown to excite neurones in nucleus tractus solitarius (NTS) in the medulla (Potts et al., 2000). A subset of the NTS neurones activated by muscle afferents is thought to directly excite neurones of the rostral ventrolateral medulla (RVLM)—the primary output nucleus for MSNA (Dampney et al., 2003)—while another subset of the activated NTS neurones are thought to be interneurones acting within the NTS to inhibit the baroreceptor-sensitive neurones of the NTS, which normally inhibit RVLM via the caudal ventrolateral medulla (CVLM) and hence bring about disinhibition of RVLM neurones (Potts, 2005). Both of these mechanisms would lead to increases in activity within RVLM, producing an increase in sympathetic outflow to muscle and the gut and blood pressure. This peripherally derived sympathoexcitatory reflex can occur independent of neuronal circuitry rostral to the brainstem: in decerebrate animals increases in sympathetic traffic, heart rate and blood pressure occur when muscle contraction is produced electrically (Smith et al., 2001); in humans, increases in blood pressure and heart rate can occur during evoked contractions in the absence of motor command (Coote et al., 1971; McCloskey and Mitchell, 1972; Mark et al., 1985; Gandevia and Hobbs, 1990), and during post-exercise ischemia sympathetic activity and blood pressure remain elevated (Victor et al. 1987).

1.1. Cortical and subcortical changes during exercise and post-exercise ischaemia

Over the last few years we have been using functional magnetic resonance imaging (fMRI) to identify brainstem nuclei involved in the control of muscle sympathetic nerve activity during manouevres known to cause a sustained increase in MSNA. One such manouevre is a maximal inspiratory breath-hold. This manoeuevre caused significant changes in BOLD (Blood Oxygen Level Dependent) signal intensity in three discrete regions of the medulla: increases in RVLM and decreases in CVLM and NTS (Macefield et al., 2006). These changes in neuronal activity were expected, given that the increase in MSNA during this manouevre is believed to be due to unloading of the low-pressure baroreceptors (Macefield et al., 2006) Moreover, by recording MSNA concurrently with fMRI of the brainstem we recently showed that activities within these three medullary nuclei covaried with the *spontaneous* bursts of MSNA at rest: increases in signal intensity occurring in RVLM, and deceases in NTS and CVLM, when bursts of MSNA were present (Macefield and Henderson, 2010).

Sustained activation of RVLM could also be seen during static handgrip exercise and post-exercise ischaemia (Sander et al., 2010). In this experiment we asked subjects to squeeze a pneumatic bulb at 40% of maximum pressure for 2 min with their right hand, and then inflated a sphygmomanometer cuff around the upper arm for 6 min immediately prior to the conclusion of the static exercise. It can be seen in Fig. 2 that, in addition to the progressive increase in BOLD signal intensity in RVLM during the contraction phase there was a parallel increase in the region of the medulla encompassing NTS. The time-course of activation in these two medullary nuclei mimics the progressive increase in MSNA during static handgrip and the subsequent steady state increase in MSNA during the period of post-exercise ischemia. The increase in NTS activity can be explained by several sources of input: