International Journal of Psychophysiology 71 (2009) 149–155

Contents lists available at ScienceDirect

International Journal of Psychophysiology

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

Sympathetic nerve and cardiovascular responses to auditory startle and prepulse inhibition

Derek N. Eder [1], Mikael Elam, B. Gunnar Wallin *

Department of Clinical Neurophysiology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy of Göteborg University, Gothenburg Sweden

ARTICLE INFO

Article history:
Received 5 May 2008
Received in revised form 26 August 2008
Accepted 4 September 2008
Available online 11 September 2008

Keywords:
Muscle sympathetic nerve activity
Arousal
Prepulse inhibition
Startle
PPI
Sensorimotor gating

ABSTRACT

While sudden (startling) sensory stimuli are generally thought of as inducing sympathetic excitation, in humans there is a short-lasting inhibition of limb muscle sympathetic nerve activity (MSNA). This study is the first to examine and contrast the effects of acoustic startle and the prepulse inhibition of startle (PPI) on MSNA, blood pressure, heart rate, and eye blinks. Startle elicited a two-component withdrawal of MSNA: an early inhibition of one sympathetic burst followed by a second inhibition. PPI abolished the early, but not the late MSNA inhibition. Prepulse stimuli alone had no early inhibitory effects on MSNA. Early MSNA inhibition, which may occur at latencies of approximately 100 ms, appears to be part of a CNS-generated startle reflex which subserves automatic defensive responses to potential threats. The late MSNA inhibition coincided with the stimulus-induced blood pressure increase and is probably an inhibitory reflex response.

1. Introduction

This paper describes, for the first time, the dynamics of muscle sympathetic nerve activity (MSNA), heart rate, and blood pressure responses during both acoustic startle and the prepulse inhibition of startle (PPI).

Sympathetic post ganglionic neurons innervate target organs such as the heart, blood vessels, and sweat glands. Mechanisms controlling the outflow of impulses in different sympathetic nerves vary between tissues and in principle, each sympathetic subdivision is governed by its own specific and independent reflexes (Morrison, 2001). In humans, most vascular sympathetic nerves cause vasoconstriction and because the skeletal muscle circulation receives a large proportion of cardiac output, the neural control of this vascular bed is fundamental for meeting homeostatic demands and for rapidly adapting to new functional challenges. Microneurographic recordings of vasoconstrictive sympathetic nerve traffic to the peripheral vasculature provide a relatively non-invasive window on this neural control (Wallin and Charkoudian, 2007).

Preparations for responses to environmental threats, including cardiovascular upregulation for intense or sustained physical effort, are initiated before the eliciting event has reached consciousness (Eliasson et al., 1952). Reflex increases of muscle blood flow by nociceptive or loud auditory stimuli were first described in intact and decerebrate cats (Abrahams et al., 1960b). These responses habituated rapidly and could be elicited using classical conditioning with paired sound and nociceptive stimuli. In addition, these cardiovascular responses were associated with evoked slow-wave potentials in areas of the brainstem associated with so-called "defense" behaviors (Abrahams et al., 1960a; Abrahams and Williams, 1967).

In humans as well as in experimental animals, startling sensory stimuli are known to evoke short-lasting sympathetic *activation* with vasoconstriction in the skin, the kidney and the splanchnic vascular bed (Caraffa-Braga et al., 1973; Forsyth, 1972; Yu and Blessing, 1997). In the skeletal muscle vasculature on the other hand, sudden somatosensory stimulation induces an immediate and short-lasting *inhibition* of MSNA in many healthy subjects. This inhibition was most marked when stimuli were applied 200 to 400 ms after the R-wave of the ECG (Donadio et al., 2002a) and was reproducible in repeated recordings with several months interval (Donadio et al., 2002b).

Intense acoustic stimulation is a well studied and widely used experimental protocol to elicit reflexive physiological and behavioral responses related to the engagement of threats. The eye-blink response to transient (usually<100 ms) high intensity (typically 100–110 dB) stimuli is paradigmatic of the "acoustic startle response". The neural circuitry mediating the acoustic startle reflex in animals has been identified as a short latency (~8 ms) spinal-motor reflex that is mediated by only three synapses between the auditory nerve, nucleus reticularis pontis caudalis, and spinal-motor neurons (Lee et al., 1996). In humans, a comparable brainstem primary acoustic

* Corresponding author. Department of Clinical Neurophysiology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden. Tel.: +46 31 3421197; fax: +46 31 821268.
E-mail addresses: derek.eder@lungall.gu.se (D.N. Eder), gunnar.wallin@neuro.gu.se (B.G. Wallin).
[1] Present address: Vigilance and Neurocognition Laboratory, Center for Sleep and Wakefulness Disorders, The Sahlgrenska Academy of Göteborg University, Sweden.

0167-8760/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpsycho.2008.09.001

startle circuit is suggested by activation of the postauricular muscle at latencies under 10 ms (Hackley and Valle-Inclan, 2003) and eye-blink latencies typically under 40 ms (Wu et al., 1988).

Startle eye-blink reflexes can be inhibited, however, if the startle stimulus is preceded (within certain inter stimulus intervals) by another stimulus. This phenomenon, known as sensorimotor gating, preserves information processing in rapidly changing sensory environments by inhibiting some motor reflexes and higher-level processing of sensory information. The experimental paradigm prepulse inhibition of startle (PPI) measures the efficiency of sensorimotor gating on eye-blink responses by presenting a relatively weak acoustic "prepulse" stimulus shortly prior to an acoustic startle (Braff et al., 2001; Swerdlow et al., 2001). Although PPI is a rich paradigm for the study of information processing, little is known about the effects of PPI on cardiovascular aspects of startle responses.

Cardiovascular responses to intense stimuli have been differentiated as either startle or defense responses by parameters of the stimuli which elicit them and by patterns of habituation over repeated exposures. Stimuli shorter than 250 ms evoke immediate acceleration and then deceleration of heart rate which resolves within 10 s and is slow to habituate. Stimuli durations greater than 500 ms evoke a secondary longer latency cardiac acceleration which peaks after approximately 35 s and habituates after the first exposure (Ramírez et al., 2005). This latter response has been characterized as part of a generalized stress-defense engagement. The relative predominance of vagal/parasympathetic mediation of the first acceleration and sympathetic mediation of the second acceleration is suggested by the onset latencies of these components, pharmacological blockade studies (Reyes del Paso et al., 1994), as well as by indirect measures of cardiac neural control, including pulse transit time, stroke volume, respiratory sinus arrhythmia, and baroreflex sensitivity (reviewed in Vila et al., 2007). We use the term "startle" in reference to our findings of both autonomic and eye-blink responses.

The present study uses the technique of microneurography to record directly from human vascular-muscle sympathetic nerves (Vallbo et al., 2004). MSNA consists solely of vasoconstrictor impulses, the outflow of which is modulated from arterial baroreceptors located in the carotid sinuses and the aortic arch. Thus, short-lasting spontaneous variations in blood pressure cause marked opposing changes in MSNA which act to reverse or "buffer" changes in pressure. Since each systolic pressure wave causes sympathetic inhibition, MSNA appears as neural bursts that display cardiac rhythmicity and which occur preferentially during transient reductions of blood pressure. Data on MSNA and its responses to various types of perturbations have provided substantial mechanistic information about baroreflex control of blood pressure, about inter- and intra-individual sympathetic responsiveness, and about changes with aging and disease (Wallin and Charkoudian, 2007). In contrast to the reported effects of acoustic startle on the end organ responses of heart rate and blood pressure, relatively little is known about the corresponding modes of sympathetic control of vascular blood flow.

The primary aims of our study were: first, to characterize the mechanism underlying the inhibition of MSNA using the acoustic startle paradigm. Specifically, we hypothesized that MSNA responses to acoustic startle are mediated by reflexes that were sensitive to prepulse inhibition, paralleling the eye-blink startle response. Second, we sought to describe MSNA responses within the larger context of cardiac and blood pressure responses.

2. Methods

2.1. Participants

We studied 16 (8 women) healthy subjects (mean age 38 years, sd 9, range 27–54), recruited among staff and students in a university hospital environment. Mean (sd) supine blood pressures at rest were 116(10)/72 (8) mm/Hg. The average MSNA burst density (sd) at rest was 60 (14) bursts per 100 heart beats. Criteria for recruitment were ages between 18 and 65 years, freedom from acute or major illness/disease, the absence of medication with psychotropic or cardiovascular effects, and no history of alcohol or drug abuse. The study was performed in accordance with the Helsinki guidelines for Human Subjects research and received institutional ethical committee approval. All subjects were fully informed about the study and gave written consent.

2.2. Physiological recording

All signals were recorded on synchronized microcomputer data acquisition systems (sampling rates: 200 Hz cardiovascular, 1000 Hz EOG, EEG). The detection of waveform features from MSNA, blood pressure, ECG, and EOG was performed using software developed in our laboratory. Other post acquisition signal processing and statistical analyses were performed using software written by us in the R language (R Development Core Team, 2004).

2.2.1. Microneurography

Multi-unit MSNA was recorded with a tungsten microelectrode (0.2 mm wire with a 1–5 μ tip) in the peroneal nerve, posterior to the fibular head of the knee, as described by Sundlöf and Wallin (1977). The nerve activity was amplified (×50,000), referenced to a nearby subcutaneous low impedance tungsten electrode, bandpass filtered (700–2000 Hz) and integrated (time constant 0.1 s). MSNA bursts were identified automatically and burst identification was controlled visually by a single investigator, who was blind to the stimuli.

2.2.2. EOG eye blinks

We measured eye blinks using bilateral EOG with supra- and suborbital Ag–AgCl electrodes and amplified using a Microtronics SAC preamplifier (passband 0.05–150 Hz) (Neurotronics, Gainesville Florida, USA). Blink amplitudes were identified manually from the EOG after removing baseline offsets, calculated from the mean EOG of a 200 ms window prior to the presentation of the stimulus (the prepulse in the case of PPI trials). Although less common than ocular EMG, the EOG has been validated as an equally sensitive measure of startle reflexes (Blumenthal et al., 2005; Waters and Ornitz, 2005; Gehricke et al., 2002; Schmidt and Fox, 1998).

2.2.3. Blood pressure, ECG, and respiration

Continuous measurements of arterial finger blood pressure were made using the volume-clamp method (Portapress Model-2, Amsterdam, The Netherlands) with a single cuff around the third finger. The Portapress cuffs were deflated every 15 min for several minutes during pauses in the stimulus trials. The Portapress blood pressures were calibrated against cuff blood pressure measurements taken during these pauses.

ECG was recorded using chest Ag/AgCl electrodes and R–R intervals were calculated offline by computer from R-wave detections. The 5 ms sampling resolution of the digitized ECG allowed measurements of the average cardiac acceleration to startle and PPI with accuracies of 1.5% and 3% respectively. The ECG also provided R-wave triggering of stimuli presentations through an analog comparator. Respiratory related chest movements were monitored using a belt strain gauge transducer in order to verify that experimental effects were not confounded by inadvertent apneas.

2.3. Procedure

The subjects were instructed not to eat and to avoid exposure to caffeine and nicotine for at least 3 h prior to the experiment, which began at 9 a.m. The subjects were studied in a darkened room while seated in a reclining "lounge" chair with their legs semi-extended. No specific task demands were made other than instructions that they