Neuroscience Letters 463 (2009) 140–144

Contents lists available at ScienceDirect

Neuroscience Letters

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

Sympathetic skin responses evoked by muscle contraction

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ARTICLE INFO

Article history:
Received 28 April 2009
Received in revised form 2 July 2009
Accepted 21 July 2009

Keywords:
Sympathetic skin response
Isometric contraction
Central motor command

ABSTRACT

Introduction: Voluntary muscle contraction is accompanied by an increase in sympathetic nerve activity. The sympathetic skin response (SSR) is a simple and non-invasive method of autonomic assessment that reflects a synchronized activity of the sweat glands. The aim of our study was to examine the possible relationship between isometric muscle contraction (IC) and changes in the SSR. *Methods*: In 11 healthy right-handed volunteers, we recorded the SSR from the palm of the hand induced by contralateral triceps IC (mSSR) of variable intensities and durations. We measured the latency, duration, amplitude, waveform and habituation index (HI) of the mSSR, in comparison to the SSR induced by supramaximal electrical stimulation (eSSR) of the brachial plexus at the axillae. *Results*: A single mSSR was always present at a mean latency of 1.34 ± 0.5 s after the onset of IC. Response amplitude, but not latency or duration, correlated positively with the intensity of IC ($r = 0.67$; $p < 0.001$). The latency was shorter, the duration was longer and the HI was reduced in the mSSR in comparison to the eSSRs (ANOVA; $p < 0.05$ for all comparisons). *Conclusions*: The mSSR is likely generated endogenously together with the motor commands since inputs from muscle afferents cannot account for response onset. This, together with its low level of habituation, underscores the possibilities of physiological and clinical studies using the mSSR, especially in the assessment of autonomic function in patients with nerve afferent problems.

Muscle exercise is known to evoke a variety of physiological responses, determined mainly by an increase in sympathetic nerve activity [10,16,20,21,27]. Apart from the changes in heart rate and blood pressure, isometric contraction (IC) also induces an increase in skin sympathetic nerve activity (SSNA) directed to sudomotor targets [20,21,27]. However, the increase in SSNA is not always paralleling with responses in cutaneous end-organs, i.e., sweat glands [29]. For instance, no consistent changes of sweat rate or of electrodermal activity (EDA) have been reported with IC [20,21,27,2,17].

Sympathetic skin responses (SSRs) result from synchronized activity of sweat glands and is commonly obtained using physiological stimuli, such as deep breath, coughing or gasping [8,23]. Although far from the detail of microneurographic assessment of SSNA, the recording of SSR is methodologically simple and feasible in most neurophysiological laboratories. Therefore, we thought that it would be worth increasing our knowledge on the relationship between IC and the SSR. In the study reported here, we investigated the physiological characteristics of the SSR induced by IC of varying strength and duration (mSSRs) in comparison to the SSRs induced by an electrical nerve stimulus (eSSRs).

Eleven healthy right-handed volunteers (6 women and 5 men; mean age of 28.2 years, range 22–43) participated in the experiment. None of them were on medication or disease known to interfere with autonomic nervous system functions. All subjects gave their written informed consent for the study, which was approved by the Ethical Committee of the Hospital Clínic from Barcelona, Spain.

We used conventional methods to record the SSR from the non-dominant hand [1]. We also recorded the EMG activity of the triceps muscle of the dominant arm with surface electrodes attached in a belly-tendon configuration and the respiratory movements using an abdominal band. We used a myometer (Penny & Giles Transducers, London, England) to monitor force. The EMG activity (20–500 Hz), the SSRs (0.1–100 Hz) and the signal from the respiratory band (0.1–10 Hz) were all recorded with a Neuropack-8 electromyograph (Nihon-Khoden; Kyoto, Japan) using a time window of 10 s and a variable gain. The signals were then fed, together with those from the myometer, into a personal computer for

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doi:10.1016/j.neulet.2009.07.062

off-line analysis and measurement using *Acknowledge MP100* (Biopac Systems, Bionic, Barcelona, Spain). Sampling rate was 2000 Hz.

Subjects were sitting on a comfortable chair. Their left hand, which had the electrodes attached for SSR recording, was resting on top of a small table that also contained a myometer securely fixed, standing on top of the table. The subject's right elbow joint was flexed at 90° and the wrist joint attached to the myometer's lever. Subjects were requested to extend their forearm against the lever using variable muscle force (low, medium and high intensity) and duration (brief, long and very long). In a different session, subjects were asked to imagine doing ICs with the same set up.

Electrical stimuli were delivered to the axillae in order to activate most upper limb muscles. Stimulus duration was 0.5 ms and the intensity was chosen to cause a supramaximal compound muscle action potential in the triceps muscle. We checked that subjects were at rest and with no visible ongoing EDA oscillations before applying each electrical stimulus.

All experiments were done by the same examiner at a similar daily time window in the evening, in a quiet, semidark room, with a constant, controlled temperature of 24.0 °C. Initially we asked the subjects to perform a series of 3 maximum voluntary contractions (MVCs) against the myometer lever to measure their maximum force in kg-F units (the mean of the 3 contractions) for later calculation of the percentage of MVC used in experimental trials. We divided the experiment in four sessions, separated by resting periods of at least 15 min. All trials throughout the same session were performed with an inter-trial interval of 30 s and subjects had the feedback of their force displayed on a computer screen.

The first session was intended to analyze the correlation between IC intensity and SSR characteristics. Subjects were asked to perform brief contractions of less than 1 s. They were free to choose among low, medium and high levels of IC. After each trial we calculated the percentage estimate of MVC as the exact percentage of peak force generated in that trial with respect to the individual's maximum force and the duration of the burst of EMG activity in the triceps. One of the experimenters helped the subject to keep control of the trial number and the intensity of IC. The session ended when 8 trials were completed for each level of muscle force, reaching a total of 24 trials per subject.

The second session was intended to analyze the effect of the duration of IC on mSSR characteristics. Based on previous studies [13,28], we asked subjects to perform ICs generating a force of about 30% of MVC of three different durations: brief (<1 s), long (5 s) and very long (10 s). They were asked to hold their respiration throughout the contraction. We ended the session when we obtained 8 trials for each requested duration of IC, with a total of 24 trials.

The third session was done in order to analyze the possibility of generating SSR by action imagery. Instructions to subjects were to imagine that they performed a brief IC of about 30% MVC, beginning when the baseline of their EMG activity reached a vertical cursor placed in the middle of the computer's screen. If any activity was observed in the triceps, the recording was rejected and the trial was repeated.

The fourth session was intended to analyze the differences between mSSR and eSSR characteristics. Subjects were requested to perform 8 consecutive ICs of 30% of their maximum force. After a break of 15 min subjects were submitted to 8 consecutive electrical stimuli to the right brachial plexus at the axillae.

In the first three experimental sessions, we measured the onset latency, peak-to-peak amplitude and duration of SSR responses obtained after onset of real or imagined IC. Responses were considered when there was a change in the baseline of an amplitude larger than 2 SD above background. Onset latency of mSSR was measured from the beginning of the EMG activity in the triceps. Duration was measured from the first significant deviation from the baseline to the last crossing of the baseline. Normality of distribution of the data was assessed using Kolmogorov–Smirnoff. We used the Spearman's correlation coefficients and repeated measures ANOVA as needed. We excluded trials showing unsteady IC and unwanted respiratory or synkinetic movements of the left hand during IC.

In the fourth experimental session, apart from the abovementioned variables, we also measured the habituation index (HI) of mSSRs and eSSRs. The HI of the SSRs was calculated as the number of recordings out of the 8 repeated stimuli in which the amplitude of the SSR was lower than 50% of the amplitude of the response to the first stimulus in the same series. Therefore, reduced habituation corresponded to low SSR-HI values. The Student's *t*-test was used for comparison between mSSR and eSSR variables. We additionally noted the SSR waveform [15] and determined whether there was a predominantly negative oscillation (N type) or a predominantly positive oscillation (P type). Mixed SSR potentials (M type) were not considered for the statistical analysis. Fig. 3 shows examples of different wave shapes. These data were analyzed by using χ^2 test. A p value <0.05 was considered to indicate statistical significance.

Clear and well defined single mSSRs were obtained in all trials in which IC was above 8% of subject's MVC, regardless of the duration of the contraction (Fig. 1). In compliance with the instructions given in the first experimental session, data tend to be distributed in

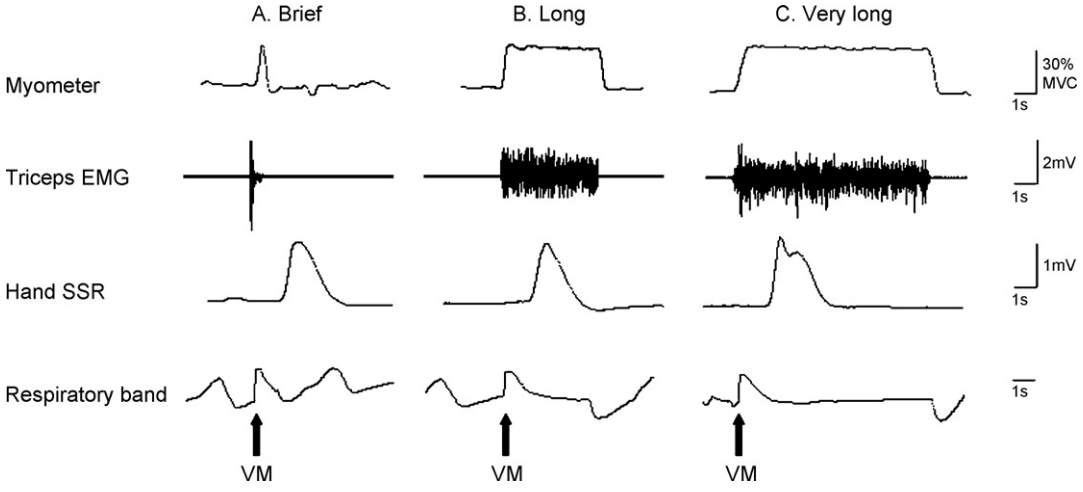

Fig. 1. Illustrative examples of SSR potentials elicited by isometric contractions (IC) of 30% MVC in: (A) brief; (B) long and (C) very long ICs. The black arrow indicates the beginning of the Valsalva maneuver (VM) that lasted the entire IC.

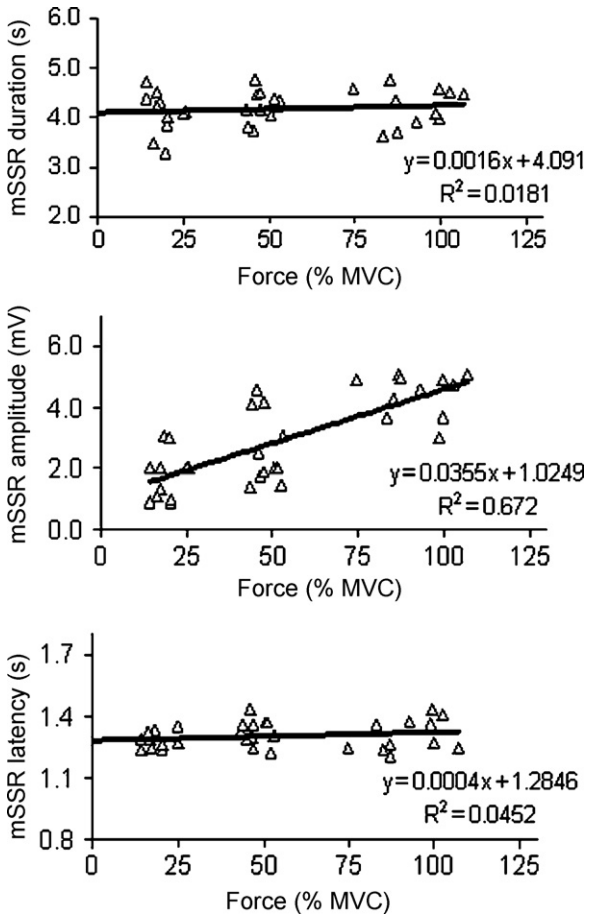

Fig. 2. Correlation graphics offorce of isometric contraction (% MVC) and SSR: (A) duration; (B) amplitude and (C) latency.

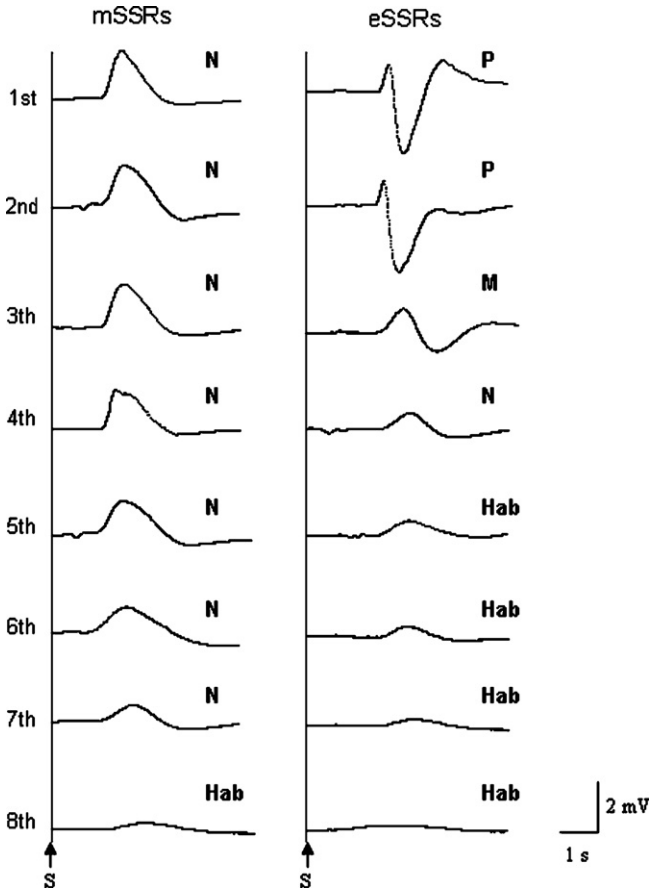

Fig. 3. Eight consecutive SSRs elicited by isometric muscle contractions (mSSRs) of 30% MVC (A) and supramaximal electrical nerve stimuli (eSSRs) (B). Note the higher prevalence of N type wave morphology and lower of habituation (Hab) in mSSRs, in comparison with eSSRs.

three force levels, albeit with a large variability within and between subjects. Mean duration of the burst of EMG activity in the triceps was 498 ± 108 ms. The percentage of MVC for low, medium and high forces were 19.0 ± 3.4%, 47.8 ± 3.4% and 96.38 ± 9.8%, respectively. There was a positive correlation between intensity of IC and amplitude of the mSSR (Spearman's coefficient = 0.67; $p < 0.001$), but no other significant correlations were found (Fig. 2). In the second experimental session, no differences were found between ICs of different durations regarding amplitude, latency or duration of mSSR. No consistent time-locked SSRs were seen in the third experimental session, when subjects imagined ICs.

Data obtained from the comparison between mSSR and eSSR in the fourth session are summarized in Table 1. The mean latency was shorter and the mean amplitude was larger for the mSSRs than for the eSSR (*t*-test; $p < 0.05$). The HI was significantly lower for the mSSR than for eSSR (*t*-test: $p = 0.002$). The mSSR waveforms were predominantly N (Fig. 3A), with only occasional P waveforms. In contrast, the eSSRs had higher prevalence of P waveforms (χ^2 test; $p < 0.05$), especially in the first trial of the series (Fig. 3B).

Table 1
Averaged data on the SSR elicited by repeated isometric contraction and electrical stimuli.

SSR variables[a]		IC	ES	P
Duration (s)		5.9 (0.5)	4.3 (1.2)	NS
Mean latency (s)		1.34(0.5)	1.58 (0.3)	0.001
Amplitude 1st (mV)		2.9(0.1)	3.9(1.0)	NS
Mean amplitude (mV)		2.0 (0.5)	1.4 (0.2)	0.03
Habituation index[b]		2.1(0.2)	5.3 (0.1)	0.02
Waveform	N (%)	85.1	56.6	0.02
	P (%)	5.2	35.4	<0.001

IC, isometric contraction; ES, electrical stimulation; NS, not significant.
[a] All statistical analysis were done using Student's *t*-test, except for waveform (χ^2 test).
[b] Possible HI values ranges from 0 to 8.

The main findings of our study are: (1) voluntary ICs are accompanied by the generation of a SSR in sites distant from the activated muscles; (2) the characteristics of the SSR suggest that it is endogenously generated and issued together with the motor commands at onset of IC; (3) the mSSR is less prone to habituation than the eSSR, which can be of interest for clinical practice.

There are several lines of evidence suggesting that the central command is likely the major generator of SSNA responses during IC in humans, and not the mechanoreceptors coming from the activated muscle voluntarily [21,23,28,24,25]. During exercise, central command volleys descend from rostral brain and radiates to autonomic centers in the brainstem, leading to concomitant activation of motor and sympathetic neurons [5]. Changes in EDA are obtained with direct electrical stimulation of frontoparietal cortex of cats [22] or ventrolateral brainstem [3], suggesting that autonomic centers involved in sudomotor activity receive cortical inputs during movements. In our study, the fact that the latency of the mSSR was significantly shorter than the latency of the eSSRs is in line with the hypothesis of a major role of central motor commands in the generation of the mSSRs. Therefore, we believe that the onset of the mSSR does not depend on muscle afferents. This could have applicability in clinical practice for the assessment of sympathetic activity in patients with afferent nerve problems, as it can be seen in the SSRs induced by TMS in patients with sensory neuronopathy [18].

However, in some situations such as during pain stimuli or spontaneous respiration the central command is maybe not required and autonomic brainstem nuclei have major role in eliciting SSRs.

We found a strong correlation between muscle force and mSSR amplitude, which is in accordance with the intensity-dependent increase in SSNA reported by other authors during exercise [27,28]. This correlation is also seen with respiratory maneuvers, a more complex type of muscle activation in which the volume of volitional inspiration reflects strength of the number of activated brain areas [7]. There is no objective method to measure the strength of the central command. Several authors have tried to establish experimentally a "subjective index of central command" [28] by asking the subjects to rate their perceived effort on a scale at the end of each exercise period. If, according to our findings, the mSSR is mainly generated at the central nervous system, its amplitude could be used as a measurable index of central command.

Although central efferent projections appear to modulate sudomotor activity [24,14], it was not possible to elicit consistent SSR by means of imagery exercises. Although motor imagery shares similar mechanisms underlying movement execution [4], a real descendent motor volley is probably required in order to stimulate autonomic nuclei along this pathway and generate recordable SSRs. Rossini et al. [18], for example, observed SSRs only when the TMS was applied to motor cortical sites. In short, although imagery facilitates larger MEPs during TMS [6], such task probably has different efferent volleys to brainstem autonomic centers in comparison with known cortico-bulbar efferent volleys coming from primary motor cortex during voluntary real movements.

Apart from the central commands, afferent activity induced by IC also contributes to the generation of sympathetic nerve activity during exercise [20,21]. The mSSR was of longer duration than the eSSR, reflecting the effect of a less synchronized volley. This points that, in addition to the endogenously generated volley, we believe that subsequent inputs to the autonomic centers, such as those generated by a Valsalva maneuver or a synchronized discharge from muscle afferents, could have contributed to the longer duration of mSSRs. This is in accordance with the findings reported by Kaufman et al. [9], who demonstrated a combined influence of mechanoreceptors activity and cortical efferent projections on the generation of autonomic responses during long lasting motor activity. Interestingly, in some cases, we observed a bimodal SSR when subjects performed long ICs (Fig. 1C), which could reflect the response to a second (afferent) volley.

We observed a higher prevalence of N waveforms in mSSRs than in eSSRs. According to Mitani et al. [15], the N phase of the SSR corresponds to the generation of an electrical dipole at sweat gland ductus, whereas the P phase indicates the spread of Na^+ outside the skin, the latter frequently observed with stimuli carrying high levels of arousal [26]. Therefore, our results of predominantly N waveforms may indicate low arousal levels during IC and provide an explanation for unchanged sweat rates during isometric handgrip reported by Crandall et al. [2].

In our study, habituation was lower in mSSR than in eSSR. This observation can be explained by two different mechanisms. First, the mSSR involves a circuit with less synapses than the eSSR and it is known that habituation is more marked in polysynaptic reflex responses [19]. Second, the mSSR is in its most part generated by an endogenous source, which are known to occur with a reduced level of arousal with respect to exogenous sources. The control of arousal may be an important part of response habituation with repeated stimuli [28]. This is agreement with the lack of habituation observed with SSRs induced by deep breathing [23,11]. Indeed, habituation is one of the main drawbacks of the eSSRs and the reduced habitation of the mSSR would make it appropriate for certain studies.

It could be argued that the mSSR could have been elicited before the triceps IC by movements of other non-monitored muscles during motor preparation. However there is substantial evidence showing that a small motor activity such as low hand grip force [13] or slow key press in a computer keyboard [12] are not strong enough to activate sweat glands. Accordingly, some of the trials from low IC stimuli, especially in those with less than 8% MVC did not induce any SSRs at all.

In conclusion, the IC-evoked SSR, although far from the accuracy of microneurography and skin biopsy techniques, it provides a simple non-invasive means of assessment of sympathetic autonomic function that, in the same way as TMS and inspiratory-evoked SSR, does not depend on afferent input. Therefore, this type of maneuver could be used for the analysis of autonomic function in patients with disordered afferent input (i.e., sensory neuronopathy). Studies using other experimental conditions such as modulation of muscle mechanoreceptor inputs or other type of movements would be adequate to further delineate the relationship between motor commands and sympathetic outflow.

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