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Effects of ageing on spinal motor and autonomic pain responses

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ABSTRACT

The course of ageing leads to various changes in the nervous system, which can affect pain processing in the elderly. However, the affection of different components of the nociceptive system remains unclear. To investigate basic nocifensive responses, we compared age-related changes of autonomic and motor reflex responses to noxious electrical stimulation. In 39 healthy young subjects (mean ± S.D.; 24.1 ± 3.3 years) and 52 healthy elderly subjects (mean ± S.D.; 71.9 ± 5.3 years) the nociceptive flexion reflex (NFR) and the sympathetic skin response (SSR) were determined using noxious electrical stimulation of the sural nerve. Verbal pain ratings were assessed in addition. No ageing effects on the NFR and on verbal pain ratings were found, whereas the SSR amplitude declined significantly with ageing. Since both SSR and NFR share comparable primary afferent pathways and the motor as well as the subjective responses to noxious stimulation were preserved, our data seem to suggest that central or peripheral efferent sympathetic functions are altered by age.

Pain sensitivity seems to be altered with increasing age, which might compromise the warning function of pain and leads to under- or over-reporting of pain symptoms. In which way pain sensitivity is affected by the process of ageing is currently under debate. The methods of stimulation seem to be crucial when looking at age-related changes in pain. Higher pain thresholds for thermal stimulation were found in the elderly, whereas almost no ageing effect has been shown for stimulation with electrical current (for review see [11]). Using ischemia and pressure stimuli, even lower pain thresholds have been reported in the elderly [4,15].

These differences between various physical stressors suggest that afferents, namely nociceptors and nociceptive pathways are differently vulnerable to age-related changes. Thermal pain of a type, which is dependent on Aδ fiber functions, appeared to be particularly vulnerable to ageing whereas C fiber sensory functions remained relatively preserved [1]. In contrast, morphological studies found a reduction of innervation by sensory afferents with preponderance of unmyelinated fibers with advancing age [24]. Accordingly, there is evidence of an impairment of nociceptive small-fiber functions, the exact kind of which is still under debate.

While there has been at least some interest in the ageing of the afferent parts of nociceptive circuits in humans, the different branches of the efferent response system have been almost completely neglected. The nocifensive efferent response system typically includes autonomic and motor response branches. The aim of the present study was to investigate the influence of age on the efferent response system to noxious stimulation. For this reason, we compared age-related changes in autonomic and motor responses to noxious electrical stimulation, namely the sympathetic skin response (SSR) and the nociceptive flexion reflex (NFR), which share comparable primary afferent pathways but differ in central processing and efferent transmission.

The NFR constitutes a nocifensive motor response. Cutaneous noxious stimuli capable of eliciting the reflex activate Aδ fibers connecting with neurons in the dorsal horn of the spinal cord, the activation of which leads to an ipsilateral contraction of flexion muscles. The electrophysiological response consists of two parts. The first response with a latency of 40–70 ms (RII) is mediated by Aβ fibers and the second response with a latency of 80–150 ms (RIII) is the nociceptive reflex and is mediated mainly by Aδ fibers [5,6,29]. At the spinal level the peripheral input is processed and subject to segmental and descending control in a polysynaptic pathway before it triggers the motor response. Since the NFR has appeared to correlate well with subjective pain perception, it has been widely used in experimental pain research (for review see [21]). However, there is increasing evidence that a dissociation between reflex activity and pain sensation can occur, which suggests stronger supra-spinal influence on the latter [12].

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The SSR is part of the autonomic defensive response system and consists of a change in the electrical potential of the skin after arousing stimuli, which can be elicited (amongst others) by activation of nociceptive Aδ fibers. After central activation of the anterior cingulate cortex (ACC), neural activity descends to the anterior hypothalamus, which controls efferent sudomotor functions [26]. The descending pathways synapse first with spinal neurons of the intermediolateral cell column and finally with neurons in the sympathetic ganglia before inducing cholinergic sudomotor responses via postganglionic C fibers. Besides the supra-spinal regulation of these sympathetic neurons there is presumably also a control by intra-spinal circuits [19,26]. Although the activation of Aβ fibers is sufficient to induce a sudomotor response, activation of Aδ fibers has been found to induce SSR responses with shorter latencies and higher amplitudes [2].

When activated by identical noxious electrical stimulation both NFR and SSR are likely mediated by similar afferent pathways, namely Aβ and Aδ primary afferents but differ in their central and efferent components. Therefore, we assume that potential differences between age-related changes in NFR and SSR (elicited by electrical stimulation) are more likely due to an alteration of central and peripheral efferent mechanisms than to afferent pathways.

Thirty-nine young subjects between the ages of 20 and 38 years (mean ± S.D.; 24.1 ± 3.3 years) and 52 elderly subjects between the ages of 65 and 83 years (mean ± S.D.; 71.9 ± 5.3 years) participated in the study. Young subjects were recruited by advertisement on campus. The elderly subjects were recruited amongst students of the Senior University of Marburg and from participants of the Marburg Adult Education Program. The group of the young consisted of 20 female and 19 male subjects and the group of the elderly of 40 female and 12 male subjects. Participants were screened and examined for conditions that could affect pain sensitivity or cause pain such as diabetes, arterial hypertension, and neurological, neuropsychological and psychiatric disorders. Neuropathies were excluded by means of neurography (see below). Inclusion of patients with small-fiber neuropathy was made unlikely by examining the medical history and excluding participants with symptoms of polyneuropathy. The elderly individuals were screened for potential dementia by us of the Mini Mental Status Examination (MMSE), which allows for a maximum score of 30 for non-demented individuals (mean = 29.6; S.D. = 0.75 for the resulting sample of elderly subjects). None of the subjects had taken any analgesic medication for at least 24 h prior to the test sessions. The study protocol was approved by the local Ethics Committee of the University of Marburg. Informed consent was obtained from all subjects before participation of the study. Subjects were reimbursed for their participation.

Electrical stimulation and EMG recording were performed using a standard electro-diagnostic device (Viking IV D, VIASYS Healthcare) with modified software. For recording of the SSR an electro-diagnostic device designed by Suess Medizintechnik (SUEmpathy100) was employed. For synchronized recording of both the NFR and SSR both devices were connected via an electronic interface (designed by Zentrales Entwicklungslabor für Elektronik, Marburg, Germany).

In order to localize the sural nerve for reflex stimulation and to exclude patients with sensory polyneuropathy, we performed a sural neurography. For stimulation, a bar electrode was attached on the left calf in a proximal–distal orientation (cathode distal; distance anode–cathode: 2.54 cm) with a distance of about 10 cm from the recording electrodes. For recording, surface electrodes were fixed to the left leg over the retromalleolar course of the sural nerve. Following localization of the sural nerve, 20 consecutive recordings after supra-threshold stimulation were averaged. Nerve conduction velocities of at least 40 m/s with amplitude of at least 5 μV were required for inclusion into the study.

For reflex recording, the volunteers were seated upright in a comfortable armchair with knees flexed at 130°. The stimulating electrode was attached on the left calf, where the sural nerve was localized by the neurography in the individual patient with inversed electrode direction to avoid anodal block. This individualized procedure – in contrast to standardized retromalleolar stimulation as in previous studies (for review see [20]) – allows for definite stimulation of the sural nerve. For recording, the differential surface electrode was attached ipsilaterally over the short head of the biceps femoris muscle with the reference electrode fixed near the tendon of the biceps femoris muscle at the head of the fibula bone. We inspected, cleaned and abraded skin before to avoid electrode contact with skin abnormalities and to keep the impedance at the lowest level possible.

A time window of 80–150 ms was selected for the onset of the reflex in order to exclude early RII responses and voluntary limb movements according to the results of previous studies [8,28]. Furthermore, amplitude of at least 40 μV (corresponding to a level of 150% of the usual baseline fluctuations) within 100 ms after the reflex onset was required to reliably distinguish reflex responses from baseline fluctuations. As in previous investigations, a train of five impulses with 1 ms duration at a frequency of 250 Hz was used for stimulation [18,20,22]. Between each stimulus a variable interval from 20 to 30 s was used in order to avoid habituation.

The nociceptive flexion reflex threshold was assessed using the up–down staircase method [8,16]. Stimulation intensity was increased in 3 mA increments until the flexion reflex RIII component was detected the first time or a maximum stimulus intensity of 40 mA was reached. Next, we lowered stimulus intensity in 2 mA steps until the reflex disappeared. After that, steps of 1 mA were used and the procedure was repeated until the reflex appeared and subsided two more times. Mean values of three peaks (current intensity that just elicited a reflex) and three troughs (current intensity that just no longer elicited a reflex) determined the reflex threshold. Thereafter, a supra-threshold reflex recording was performed. Many different selection criteria for supra-threshold stimulation have been reported and no standard has yet been established [9,10,22]. Absolute increase of 5 mA above threshold was chosen to definitely reach noxious stimulation levels. Relative criteria may have resulted in too low supra-threshold stimulus intensities in case of low NFR thresholds. Ten supra-threshold stimuli were applied. The evoked motor responses were rectified and averaged. Averaged reflex responses were used because of very inhomogeneous single reflex responses observed in previous studies [9,10,22]. Reflex latency was measured from stimulation onset to the onset of the RIII component within the time window of 80–150 ms; amplitude and area under the reflex curve were measured within 100 ms from onset of the reflex [30]. In case of an unstable or/and elevated baseline before the time window of the RIII component, the voltage level just at reflex onset was defined as baseline for calculation of amplitude and area under the reflex curve.

Sympathetic skin responses to electrical stimuli were measured concurrently to the assessment of the supra-threshold NFR responses. For recording the differential surface electrode was fixed at the palm of the left hand with the reference electrode fixed on the proximal third of the left forearm. We measured the SSR at the upper extremities, because these responses have been shown to be more reliable than those of the lower extremities, particularly in the elderly [3,27]. Since the SSR is not solely dependent on segmental spinal circuits it is possible to apply a stimulus extrasegmental at the lower extremities (as in the present study) to evoke the SSR at the upper extremities. Amplitude and latency