Effects of ageing on spinal motor and autonomic pain responses

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\textbf{A B S T R A C T}

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.

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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 Aβ 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 Aβ 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-sinal influence on the latter [12].
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 Aβ 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 A6 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 the elderly of 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 means 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 Susse Medizintechnik (SUEmpathy100) was employed. For synchronized recording of both the NFR and SSR both devices were connected via an electronic interface (designed by Zentrales Entwicklungs labor 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, where the sural nerve was localized by the neurography in the individual patient with reversed 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 noxious 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 RII 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. Rela-tive 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 RII 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 RII 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 extra-segmental at the lower extremities (as in the present study) to evoke the SSR at the upper extremities. Amplitude and latency velocities of at least 40 m/s with amplitude of at least 5 μV were required for inclusion into the study.
of the SSR were measured. Amplitude was defined as voltage difference between the initial negative and the positive peak of the biphasic response. Latency was defined as time from stimulation to the onset of the negative deflection. Trials with initial positive deflection and responses with latencies below 600 ms were not considered for further evaluation. The mean values of amplitude and latency of the 10 (at least 5 valid SSR responses were required for computing mean values) SSR responses elicited by stimulation at 5 mA above NFR threshold were selected for further computations.

Pain report was assessed following each electrical stimulation concurrent to the determination of the NFR threshold and the assessment of the supra-threshold NFR and SSR responses by using a six-point categorical scale (no pain, slight pain, moderate pain, intense pain, very intense pain and unbearable pain). Only ratings of the supra-threshold stimuli were used for further calculations.

Prior to the experiment, a thorough neurological and neuropsychological examination was conducted in order to identify persons, who met the exclusion criteria. The electrophysiological tests followed. First, the sural neurography was performed as described. Then, the nociceptive flexion reflex threshold was assessed. Supra-threshold NFR and SSR responses were measured thereafter. Following each stimulus application, the subjects provided verbal pain ratings using the categorical scale. The next electrical stimulus for eliciting both the NFR and SSR was applied 5 s after the preceding stimulus. For computing mean values, SSR responses elicited by stimulation of the supra-threshold stimuli were used for further calculations.

For statistical analysis the Statistical Package for Social Science (SPSS version 11.0) was employed. Student’s t-tests were performed for the comparison of NFR thresholds and verbal pain ratings. Data are given as mean ± S.D. Significant results are marked as bold.

Table 1 Comparison of sural neurography, nociceptive flexion reflex (NFR) threshold and of SSR parameters, sympathetic skin response (SSR) and verbal pain ratings to supra-threshold electrical stimulation between the two age groups

<table>
<thead>
<tr>
<th></th>
<th>Young subjects (N=39)</th>
<th>Elderly subjects (N=52)</th>
<th>F(df) / F(85)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFR threshold (mA)</td>
<td>18.3 ± 9.7</td>
<td>20.9 ± 9.7</td>
<td>−0.0998(20)</td>
<td>0.321</td>
</tr>
<tr>
<td>NFR parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>98.2 ± 18.3</td>
<td>100.4 ± 22.1</td>
<td>0.241(85)</td>
<td>0.631</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>45.7 ± 37.8</td>
<td>55.7 ± 48.4</td>
<td>1.161(80)</td>
<td>0.282</td>
</tr>
<tr>
<td>Area (µVms)</td>
<td>2210.7 ± 1411.9</td>
<td>2012.5 ± 2181.0</td>
<td>0.250(85)</td>
<td>0.616</td>
</tr>
<tr>
<td>SSR parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (s)</td>
<td>1.49 ± 0.2</td>
<td>1.48 ± 0.3</td>
<td>0.061(85)</td>
<td>0.805</td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>280.4 ± 236.9</td>
<td>162.6 ± 122.3</td>
<td>9.173(85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>3.52 ± 0.8</td>
<td>3.61 ± 0.9</td>
<td>−0.439(85)</td>
<td>0.668</td>
</tr>
<tr>
<td>Sural neurography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>32.3 ± 14.6</td>
<td>16.2 ± 7.9</td>
<td>45.098(85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Velocity (m/s)</td>
<td>50.4 ± 3.9</td>
<td>48.4 ± 4.9</td>
<td>4.420(85)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

The results of the ANOVAs with the group factor ‘age’ are given. Student’s t-tests were performed for the comparison of NFR thresholds and verbal pain ratings. Data are given as mean ± S.D. Significant results are marked as bold.

No significant differences in the NFR threshold between the groups of younger and elderly subjects were found (see Table 1). A MANOVA with the group factor ‘age’ and the three parameters of the NFR for supra-threshold stimulation as dependent variables also showed no influence of age \( F(3, 86) = 0.863, p = 0.464 \). No significant age effect on verbal ratings of supra-threshold stimuli could be observed (see Table 1). A MANOVA with the group factor ‘age’ and the two parameters of the SSR as dependent variables showed a significant main effect of ‘age’ \( F(2, 85) = 4.606, p = 0.013 \) with significantly smaller amplitudes in the elderly group (see Table 1). Latency was not changed significantly (see Table 1). Furthermore, a MANOVA revealed a significant age effect with regard to the parameters of the sural neurography \( F(2, 87) = 22.694, p < 0.001 \), with lower amplitudes and slowed conduction velocity (see Table 1) in the group of the elderly.

The study was designed to investigate a putative influence of ageing on experimentally induced nociceptive autonomic and motor reflexes. The NFR and the SSR were recorded following noxious electrical stimulation. Our data revealed a significant age-related difference of the SSR amplitudes in two groups of healthy individuals with an average age around 25 years and around 70 years, respectively. In contrast, no ageing effects on the NFR thresholds, on the supra-threshold NFR parameters and on the verbal ratings of pain were observed.

To our knowledge, this is the first examination of the influence that ageing exerts on the NFR in adults. The preserved NFR response in the elderly of the present study suggests sufficiently intact Aβ sensory fiber function as well as unchanged nociceptive motor responses in the elderly. This finding of functionally preserved primary afferent function seems to be at variance with earlier observations. A decreased somatosensitivity caused by axonopathy is often an early sign of age-related deterioration of predominately Aβ- but also of Aδ- and C fiber sensory functions, which has been shown to be associated with a clearly reduced amplitude of the sural nerve (sural neurography, Aβ fibers) [23,25]. Chakour et al. [1] deduced from studies on the functionality of Aδ- and C fibers that the nociceptive system of the elderly predominantly utilizes C fiber-mediated noxious input, whereas in younger subjects also information from Aδ fiber-mediated input is used. According to these findings, a deterioration of Aδ fiber sensory functions in the elderly has been assumed. However, the NFR response, being primarily mediated by Aδ fibers in its afferent branch, is not altered in our study. The most likely explanation is that the intensity of the electrical stimulus in the present study – which was tailored to the individual reflex threshold and mainly rated as being painful – was strong enough to excite a sufficient number of intact afferents necessary for evoking the reflex response, in spite of a putative age-related decline in nociceptive fiber density. Furthermore, our very thorough examination of the subjects for excluding neuro-
pathic changes by clinical and electrophysiological tools prevented major neuropathology from influencing results. The finding of an unchanged subjective pain report in the elderly is in line with previous studies that have mostly not provided evidence for age-related changes in subjective report to electrically induced pain (for a comprehensive review see [11]).

The age-related decline of the SSR amplitude is in accordance with a previous study that demonstrated a significant negative correlation between SSR amplitude and age [3]. Furthermore, Drory and Korczyn [3] as well as Watanabe et al. [27] reported a clearly reduced frequency of occurrence of SSR responses in elderly subjects. However, all these authors used innocuous electrical stimuli, whereas we used noxious stimuli that are additionally conveyed by Aδ fibers. Nevertheless, it seems justifiable to compare our findings to these previous studies since it has been shown that SSR responses to noxious stimuli mainly differ from responses to innocuous stimuli by producing higher SSR amplitudes and shorter latencies [2].

Our data clearly point out that even more intense and noxious levels of stimulation do not retard the fact of an age-related decrease in the SSR amplitude that may either reflect axonal deterioration of the Aδ-mediated part of the sensory afferents or a deterioration of the efferent sympathetic branch. Centrally, a reduced sympathetic arousal at the hypothalamic level might be responsible. Peripherally, the efferent branch of the SSR might be affected by the process of ageing either at the preganglionic level, the level of the efferent fiber (C fiber) or at the level of sweat gland activity, whereas we used noxious stimuli that are additionally conveyed by Aδ fibers. Nevertheless, it seems justifiable to compare our findings to these previous studies since it has been shown that SSR responses to noxious stimuli mainly differ from responses to innocuous stimuli by producing higher SSR amplitudes and shorter latencies [2].

Our methodological approach does not allow for disenrollment of the potential central and peripheral neural as well as nociceptive mechanisms and regulating sudomotor activity, as are affected as a sequel of ageing.

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