Age-Associated Differences in Responses to Noxious Stimuli

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**Background.** Although population-based studies typically report age-associated increases in clinical pain, laboratory-based pain assessment procedures generally indicate diminished pain sensitivity with age. The majority of these studies have utilized noxious thermal stimuli as the method of pain induction. However, other pain assessment methodologies, including ischemic pain induction, may have a more meaningful relationship to clinical pain. The present study examined the effects of age on responses to a variety of experimental noxious stimuli. In addition, relationships between cardiovascular measures and pain responses were investigated in both older and younger subjects.

**Methods.** Responses to thermal, mechanical, and ischemic pain were assessed in 34 younger (mean age, 22.4 years) and 34 older adults (mean age, 62.2 years). In addition, relationships between resting blood pressure and pain responses were assessed separately for older and younger participants.

**Results.** Although group differences in thermal and mechanical pain responses did not achieve statistical significance, older individuals demonstrated substantially lower ischemic pain thresholds and tolerances assessed via the modified submaximal effort tourniquet procedure ($p < .01$). Overall, higher resting arterial blood pressures were associated with increased pain thresholds and tolerances, although relationships between blood pressure and ischemic pain variables were evident only for the younger group.

**Conclusions.** These findings indicate that age-related differences in responses to experimental noxious stimuli vary as a function of the pain induction task, with older individuals showing greater sensitivity to clinically relevant stimuli. In addition, the absence of a relationship between blood pressure and ischemic pain responses in older adults may suggest potential functional decrements in at least one endogenous pain-modulatory system.

The results of these investigations, however, are quite variable. One source of variability is the chosen method of pain induction. Experimental pain stimuli differ along a variety of dimensions including location of nociceptors, pain duration, quality of the noxious sensation, and type of afferent fibers stimulated. Historically, most studies investigating age effects have examined cutaneous thermal or electrical pain thresholds, and many have reported age-related increases in these thresholds.

However, studies assessing deeper, more tonic forms of pain (i.e., pressure pain tolerances and cold pressor tolerances) have reported decreased pain tolerance in elderly subjects (7,8). In addition, indirect evidence for an age-related enhancement in sensitivity to tourniquet ischemia has previously been reported in surgical patients (9). Collectively, these findings suggest that the effects of age on responses to noxious stimuli may depend on the pain induction task, with elderly individuals demonstrating elevated pain thresholds for brief, superficial, highly localized stimulation (such as thermal or electrical pain induction procedures), but enhanced sensitivity to tonic, deep, diffuse, clinically relevant noxious stimuli.

The purpose of the present study was to assess age-associated differences in responses to various forms of experimental noxious stimulation. Responses to noxious heat, pressure, and arm ischemia were evaluated in both old and young subjects. Although age-related differences in experimental ischemic pain in skeletal muscle have not previously...
been reported, we hypothesized that group differences in pain responses would be more prominent for ischemia than for other noxious stimulation modalities because it produces the most clinically relevant pain of any laboratory pain induction task (10). Induction of ischemic pain in skeletal muscle is typically cited as a clinically relevant laboratory pain task on the basis of its phenomenological similarity to most clinical pain (tonic, aching, deep muscle pain), its sensitivity to manipulations of the endogenous opioid system (11–14), its primacy of C-fiber input over A-delta fibers (15), and its substantial affective component (16). In addition to evaluating multiple noxious stimuli, we assessed the relationship of blood pressure to pain responses in both age groups, as systolic blood pressure has been demonstrated to play a role in pain modulation (17,18).

METHODS

Participants

A total of 72 subjects (34 younger, 38 older) were recruited via posted advertisements; all were paid $10.00 per hour. Participants were screened by phone for the presence of the following: ongoing pain problems, hypertension, circulatory disorders, cardiac problems, metabolic disease (e.g., diabetes), other significant health risks, and use of centrally acting agents. Four older women were taking anti-hypertensive medications; consequently, these individuals were not included in the analyses. The younger (mean age, 22.4 years, SD = 2.2; range, 18 to 27 years) and older subject groups (mean age, 62.2 years, SD = 3.4; range, 55 to 67 years) were each comprised of 21 women and 13 men. All experimental procedures described later were approved by the University of Alabama at Birmingham’s Human Subjects Committee.

Session Protocol

Each subject participated in a single experimental session lasting approximately 2 hours. Prior to conducting experimental procedures, subjects provided written informed consent and completed several questionnaires. Next, a 15-minute semi-reclined rest period was followed by a 5-minute baseline period during which systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were sampled each minute using a Dinamap 1846 SX blood pressure monitor (Critikon, Tampa, FL). During this procedure, subjects were instructed to relax quietly with their eyes closed. Upon completion of cardiovascular sampling, subjects underwent the thermal, mechanical, and ischemic pain tasks described later. The order of thermal and pressure pain assessment was randomized. Ischemic pain responses were assessed last in all subjects to prevent carry-over effects.

Rating Scales

During pain assessment procedures for which subjects were instructed to rate the intensity and unpleasantness of noxious stimuli (pressure and ischemic pain assessments), joint numerical and verbal descriptor box scales were employed (19). These scales provide ratio-level scaling of both the sensory (intensity) and affective (unpleasantness) dimensions of pain on 0–20-point rating scales. All subjects were instructed in the conceptual distinction between pain unpleasantness and intensity using standard instructions (20). For pressure and ischemic pain assessments, the order of intensity and unpleasantness ratings was varied across subjects.

Thermal Pain Procedures

Thermal procedures involved assessment of warmth threshold, heat pain threshold, and heat pain tolerance. Contact heat stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001: Ramat Yishai, Israel), a peltier-element-based stimulator. Temperature levels were monitored by a contactor-contained thermistor and returned to a preset baseline of 32°C by active cooling at a rate of 10°C per second. The 9-cm² contact probe was applied to the left volar forearm. Warmth thresholds, heat pain thresholds, and heat pain tolerances were assessed using an ascending method of limits. From a baseline of 32°C, probe temperature increased at a rate of 0.5°C per second until the subject responded by pressing a button. Four trials of warmth threshold, heat threshold, and heat pain tolerance were presented. Within each block of trials, the position of the thermode was altered slightly between individual trials (resulting in a total of four stimulation sites on the volar forearm), and interstimulus intervals of at least 30 seconds were maintained between successive stimuli.

Pressure Pain Procedures

A Somedic algometer (Sollentuna, Sweden) was used to assess responses to noxious mechanical pressure. Mechanical pressure was applied using a 0.503-cm² probe covered with a 1-mm polypropylene material (21). Pressure was increased steadily at an application rate of 30 kPa per second until the subject responded by pressing a button, at which point stimulation was terminated. Pressure pain thresholds were assessed at two sites: the left upper trapezius and left masseter muscles. Pressure pain thresholds were assessed four consecutive times at each site, and the order of sites was randomized. Following threshold assessment, pressure pain “tolerance” was operationalized as the pressure that the subject matched to a rating of 15 on the unpleasantness rating scale, as the verbal descriptor associated with this point is “intolerable.” Tolerance was averaged across two trials at each site.

Modified Submaximal Effort Tourniquet Procedure

Following completion of thermal and mechanical pain assessment procedures, a second baseline blood pressure assessment was performed. Next, subjects underwent the modified submaximal effort tourniquet procedure, which involves exercising the hand as blood flow to the arm is occluded, evoking ischemic pain (22). Maximum grip strength of the right hand was determined using a Lafayette handheld dynamometer (Lafayette Instrument Co., Lafayette, IN). Next, the right arm was exsanguinated by elevating it above heart level for 30 seconds, after which the arm was occluded with a standard blood pressure cuff positioned proximal to the elbow and inflated to 240 mm Hg using a
Hokanson E20 rapid cuff inflator (D.E. Hokanson, Inc., Bellevue, WA). Subjects then performed 20 handgrip exercises of 2-second duration at 4-second intervals at 50% of their maximum grip strength. Cuff inflation was maintained until the perceived pain became intolerable; the procedure was terminated by the experimenter if pain tolerance had not been achieved at 15 minutes following initiation of the handgrip exercises. Every 30 seconds, subjects alternately rated either the intensity or unpleasantness of their pain using the rating scales described previously. In addition to these ratings, the time to ischemic pain threshold and time to ischemic pain tolerance were assessed.

Data Analysis

Data are presented as means and standard errors. Warmth thresholds, thermal pain thresholds, thermal pain tolerances, and pressure pain thresholds were determined by calculating the mean of the second, third, and fourth trials. Pressure pain tolerances for each site were entered as mean values obtained at a rating of 15 on the unpleasantness rating scale, as the verbal descriptor associated with this point is “intolerable.”

Generally, mixed factorial analyses of variance (ANOVAs) were used to test for interactions between age and other variables. Initially, for the purposes of the overall analysis, all pain-response variables were standardized to distributions with a mean of 1 and a standard deviation of 1. A 2 × 8 (age group × pain variable) mixed factorial ANOVA revealed a nonsignificant overall effect of age group (p = .08) and a significant age group by pain variable interaction (p < .001), suggesting that the effect of age on pain responses varied across pain assessment procedures. These results are depicted graphically in Figure 1. Follow-up analyses for each noxious stimulus modality are presented below.

RESULTS

Global Analyses

No group differences were noted in gender or racial (83% Caucasian for the younger group; 88% for the older group) composition (p > .1). In addition, no significant order effects were observed for: pain task order, rating scale order, or order of pressure pain sites (all p > .1). Finally, analysis of individual trials for thermal and pressure pain responses yielded no significant effects of trial or age group by trial interactions for thermal and pressure pain responses (p > .05), suggesting that responses to these stimuli remained consistent across trials for both older and younger subjects.

Data for heat pain threshold and tolerance, ischemic pain threshold, and ischemic pain tolerance, and pressure pain threshold and tolerance at both sites were individually standardized to distributions with a mean and standard deviation of 1. A 2 × 8 (age group × pain variable) mixed factorial ANOVA revealed a nonsignificant overall effect of age group (p = .08) and a significant age group by pain variable interaction (p < .001), suggesting that the effect of age on pain responses varied across pain assessment procedures. These results are depicted graphically in Figure 1. Follow-up analyses for each noxious stimulus modality are presented below.

Figure 1. Group comparison of responses to noxious heat, pressure, and ischemia. Group means are presented as standardized scores; error bars represent SEM. HPTH = heat pain threshold; HPTO = heat pain tolerance; MPPTH = pressure pain threshold on the masseter; MPPTO = pressure pain tolerance on the masseter; TPPTH = pressure pain threshold on the trapezius; TPPTO = pressure pain tolerance on the trapezius; IPTH = ischemic pain threshold; IPTO = ischemic pain tolerance. *p < .01.

<table>
<thead>
<tr>
<th></th>
<th>Younger (n = 34)</th>
<th>Older (n = 34)</th>
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<tbody>
<tr>
<td>Warmth threshold (°C)</td>
<td>34.2 (0.2)</td>
<td>34.7 (0.4)</td>
</tr>
<tr>
<td>Heat pain threshold (°C)</td>
<td>43.9 (0.9)†</td>
<td>45.6 (0.9)</td>
</tr>
<tr>
<td>Heat pain tolerance (°C)</td>
<td>48.3 (0.6)</td>
<td>48.8 (0.6)</td>
</tr>
<tr>
<td>PPTH-masseter (kPa)</td>
<td>239.6 (25.5)</td>
<td>196.6 (19.9)</td>
</tr>
<tr>
<td>PPTO-masseter (kPa)</td>
<td>310.3 (30.9)†</td>
<td>241.7 (27.4)</td>
</tr>
<tr>
<td>PPTH-trapezius (kPa)</td>
<td>662.5 (97.2)</td>
<td>569.6 (59.9)</td>
</tr>
<tr>
<td>PPTO-trapezius (kPa)</td>
<td>966.5 (129.3)†</td>
<td>696.2 (86.7)</td>
</tr>
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Notes: Values are means (SE). PPTH = pressure pain threshold. PPTO = pressure pain tolerance. †p < .10.
To examine the relationships between cardiovascular activity and responses to noxious stimuli in both older and younger subjects, correlation coefficients were computed separately for each age group. For both age groups, resting SBP and MAP were generally positively correlated with thermal pain thresholds and tolerances. However, although higher SBP and MAP were associated with increased ischemic pain thresholds and tolerances among the younger participants, these relationships did not emerge among older subjects, although this difference achieved statistical significance only for the relationship between SBP and ischemic pain tolerance (see Table 3).

**Effect Sizes**

To determine the relative magnitude of effects for each of the pain response variables, Cohen’s $d$ was computed for each measure of pain responses. Briefly, $d$ is calculated by dividing the difference in group means by the pooled standard deviation. Effect sizes were as follows: heat pain threshold = .40; heat pain tolerance = .15; masseter pain threshold = .34; trapezius pain threshold = .22; masseter pain tolerance = .43; trapezius pain tolerance = .45; ischemic pain threshold = .98; ischemic pain tolerance = 1.40.

**DISCUSSION**

The results of the present study suggest stimulus-specific age effects on responses to noxious stimuli. Several recently published comprehensive reviews of the literature regarding laboratory studies of pain in older adults have noted the difficulty of interpreting a diverse set of empirical findings (2–4). Specifically, these reviewers note that although approximately half of the extant studies examining cutaneous pain thresholds using radiant or contact heat suggest increases in pain thresholds in elderly subjects, the remaining studies report no significant age effects. In the present study, the mean thermal pain threshold for the older subject group was 1.7 degrees higher than that for the younger group. However, this difference did not achieve statistical significance. Thus, we concur with Harkins (3,4), who suggests that age-associated effects on cutaneous pain thresholds are likely minimal. In addition, the present results are somewhat consistent with those of Woodrow and colleagues (8), who found decreased pressure pain tolerance in elderly subjects. Even though the present findings relating to pressure pain tolerance did not achieve statistical significance, a trend toward lower pressure pain tolerance in the older group was noted. Finally, older individuals in the present study demonstrated significantly lower ischemic pain thresholds and tolerances than younger subjects. To our knowledge, this is the first report of age-associated differences in responses to ischemic arm pain. Overall, although small to moderate age-related effect sizes were observed for thermal and mechanical pain, large effects were evident on ischemic pain measures. In addition, the directions of the thermal and ischemic effects differed, with older participants demonstrating a (non-significant) 1.7-degree increase in thermal pain thresholds.
and substantially decreased thresholds and tolerances for ischemic pain.

One potential explanation for this differential effect may depend on age-associated changes in central nervous system pain-modulatory systems. Bodnar (25) reviewed evidence from a variety of sources suggesting that aging produces decrements in nearly all identified neural and hormonal endogenous pain-modulatory systems, particularly in opioid-mediated antinociception (10). However, putative decrements in these systems in elderly individuals may not be universally evident during noxious stimulation. Mense (26) and Yu and Mense (27) have reported that descending inhibitory pain-control systems function primarily to modulate deep pain, such as the ischemic pain produced by the tourniquet procedure. Moreover, the selective opioid antagonist naloxone has been found to increase ischemic (11–14), but not thermal pain sensitivity (28,29), suggesting greater endogenous opioid influence over ischemic than thermal pain. Thus, age-related decrements in pain inhibition may be most evident for the ischemic task.

Preliminary findings have recently suggested that elderly individuals may be less able to activate endogenous pain-modulatory systems than are younger individuals (30). The present results also hint at the possibility that at least one pain-modulatory system may begin to show decreasing efficacy with advancing age. Increased arterial blood pressure is associated with reduced responses to noxious stimuli (17), and endogenous opioids may mediate this inverse relationship between blood pressure and pain sensitivity (18,31,32). Our results indicate that although increased arterial blood pressure was generally associated with increased pain thresholds and tolerances, these relationships appeared somewhat stronger among younger subjects, especially with respect to the ischemic pain data. Although higher resting SBP and MAP were associated with decreased sensitivity to ischemic pain among younger subjects, this effect was not present within the older group. However, given that only 1 of 32 correlations differed significantly in magnitude between older and younger subjects, interpretations of these data must remain cautious.

An alternative explanation for the present findings may be related to stimulus-specific age-associated differences in response bias. Several previous studies by Harkins and Chapman (33,34), employing Sensory Decision Theory (SDT) methodology in the context of electrical stimulation of tooth pulp, suggested that aging had differential effects on willingness to report sensations as painful at varying levels of stimulation. At lower levels of actual and perceived stimulus intensity, elderly subjects were less willing to report sensations as painful; however, at greater shock intensities, older individuals were significantly more willing than their younger counterparts to label the stimuli as painful. Although the methodology of the present study did not incorporate SDT-based techniques, the finding that older subjects demonstrated significantly lower thresholds and tolerances only for the ischemic task (which may be more intensely noxious than other stimulation modalities) may be construed as consistent with these earlier findings. Thus, it may be that stimulus-specific age differences in response bias, rather than pain sensitivity, underpin our findings.

It may also be necessary to consider differences among stimulus modalities in the spectrum of activated nociceptive fibers (A-delta and C fibers), as well as selective age-related changes in those fibers. For example, several recent studies have suggested that aging may have differential effects on responses to A-delta- and C-fiber-dependent noxious stimuli (35,36). Specifically, older subjects may employ C-fiber-mediated sensations more than those mediated by A-delta fibers in generating responses to noxious stimuli, perhaps as a consequence of differential physiological effects of senescence on these fibers. Thus, differences among experimental noxious stimuli in the relative proportion of C- to A-delta-fiber stimulation may produce different response profiles in the two age groups, with older subjects being most sensitive to ischemic pain, which selectively activates C fibers (15).

The present study includes several limitations, which may restrict the generalizability of the results. First, these findings are concerned entirely with responses to acute experimental pain, while many other studies examining age-associated variations in pain experience have investigated chronic pain. Second, it is unclear whether the results of the present study might remain applicable outside of the relatively healthy population studied here. Finally, the older subjects in the present study had a mean age in their early 60s and a relatively limited age range (55–67 years), which did not permit examination of age-associated changes in pain responses across the full life span. Nonetheless, the present results may represent a first step toward a more thorough characterization of the complex relationships between normal aging and the experience of pain.

In sum, the results of the present study suggest substantially increased sensitivity to ischemic pain among older adults. The present findings also provide preliminary evidence for an age-associated uncoupling of the inverse relationship between blood pressure and ischemic pain sensitivity. Although the clinical implications of the present study remain unclear, recent evidence suggests that elderly adults have inadequate access to multidisciplinary pain rehabilitation programs (37). If older adults do indeed experience increases in sensitivity to clinically relevant noxious stimuli, they may require enhanced, not reduced, treatment options. Such a conclusion, however, awaits a reconciliation of the literatures relating clinical to experimental pain in the elderly population.

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