Anesthesiology 2005; 102:509–14

Increased Sensitivity to Thermal Pain and Reduced Subcutaneous Lidocaine Efficacy in Redheads

Edwin B. Liem, M.D., Teresa V. Joiner, B.S.N.,† Kentaro Tsueda, M.D.,‡ Daniel I. Sessler, M.D.§*

Background: **Anesthetic requirement in redheads is exaggerated, suggesting that redheads may be especially sensitive to pain. Therefore, the authors tested the hypotheses that women with natural red hair are more sensitive to pain and that redheads are resistant to topical and subcutaneous lidocaine.**

Methods: **The authors evaluated pain sensitivity in red-haired (n = 30) or dark-haired (n = 30) women by determining the electrical current perception threshold, pain perception, and maximum pain tolerance with a Neurometer CPT/C (Neurotron, Inc., Baltimore, MD). They evaluated the analogous warm and cold temperature thresholds with the TSA-II Neurosensory Analyzer (Medoc Ltd., Minneapolis, MN). Volunteers were tested with both devices at baseline and with the Neurometer after 1-h exposure to 4% liposomal lidocaine and after subcutaneous injection of 1% lidocaine. Data are presented as medians (interquartile ranges).**

Results: **Current perception, pain perception, and pain tolerance thresholds were similar in the red-haired and dark-haired women at 2,000, 250, and 5 Hz. In contrast, redheads were more sensitive to cold pain perception (22.6 [15.1–26.1] *vs.* 12.6 [0–20]°C; *P* = 0.004), cold pain tolerance (6.0 [0–9.7] *vs.* 0.0 [0.0–2.0]°C; *P* = 0.001), and heat pain (46.3 [45.7–47.5] *vs.* 47.7 [46.6–48.7]°C; *P* = 0.009). Subcutaneous lidocaine was significantly less effective in redheads (*e.g.*, pain tolerance threshold at 2,000-Hz stimulation in redheads was 11.0 [8.5–16.5] *vs.* > 20.0 (14.5 to > 20) mA in others; *P* = 0.005).**

Conclusion: **Red hair is the phenotype for mutations of the melanocortin-1 receptor. Results indicate that redheads are more sensitive to thermal pain and are resistant to the analgesic effects of subcutaneous lidocaine. Mutations of the melanocortin-1 receptor, or a consequence thereof, thus modulate pain sensitivity.**

RED hair nearly always results from mutations of the melanocortin-1 receptor gene (*MC1R*).[1–3] The human melanocortin-1 receptor (MC1R) is expressed on the surface of melanocytes and is a key regulator of intracellular signaling to the melanin biosynthetic pathway governing pigment formation. In general, the balance of pheomelanin (yellow-red) and eumelanin (dark brown) pigments determines hair and skin color in the white population.[4] The red hair phenotype results from excess pheomelanin production due to dysfunctional MC1Rs.[5,6] In contrast, when a normal (consensus) MC1R is expressed, the predominant pigment produced by melanocytes is eumelanin, resulting in a high eumelanin-to-pheomelanin ratio.

In a previous study, we found that women with red hair required 19% more desflurane to suppress movement in response to noxious electrical stimulation than women with dark hair, making red hair a distinct phenotype associated with anesthetic requirement in humans.[7] The effects of human MC1R dysfunction on anesthetic requirement were further supported by the finding that anesthetic requirement is slightly, but significantly, increased in melanocortin-1 receptor knockout mice.[8] And finally, the recent work of Mogil *et al.*[9] also suggests involvement of MC1R in pain modulation.

MC1R expression has been identified in human pituitary tissue, glial cells, and in cells of the human periaqueductal gray matter.[10,11] However, the central nervous system is not a major site of *MC1R* expression.[6] Therefore, it remains unclear why *MC1R* mutation should alter anesthetic requirement. Because anesthetic requirement in previous studies was measured in the context of a response to a noxious stimulus, these results suggest that MC1R dysfunction could possibly modulate a response to any stimulus that might be perceived as painful. A possible explanation is that *MC1R* mutation up-regulates production of the receptor's primary ligands, melanocortins including α-melanocyte-stimulating hormone, which also stimulates other melanocortin receptors—including the melanocortin-4 receptor that modulates cold and mechanical allodynia in a rat neuropathic pain model.[12]

To the extent that this theory is correct, one might expect baseline pain sensitivity to be exaggerated in redheads. Anecdotal reports support this theory: After reports of our previous study[7] were published in the lay press, we received more than a hundred communications from redheads who claimed that anesthesia often failed or that unusually large doses of local anesthetics were required to achieve adequate analgesia. Therefore, we tested the hypotheses that natural redheads are more sensitive to pain than women with dark hair and that redheads are resistant to topical and subcutaneous lidocaine.

Materials and Methods

With institutional approval (University of Louisville, Louisville, Kentucky) and informed written consent, we

* Assistant Professor, Outcomes Research™ Institute and Department of Anesthesiology and Perioperative Medicine, † Research Coordinator, Outcomes Research™ Institute, § Vice Dean for Research and Associate Vice President for Health Affairs, Director Outcomes Research™ Institute, Lolita & Samuel Weakley Distinguished University Research Chair, and Interim Chair and Professor of Anesthesiology. ‡ Deceased. Formerly Associate Professor, Department of Anesthesiology and Perioperative Medicine.

Received from the Outcomes Research™ Institute and the Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, Kentucky. Submitted for publication July 26, 2004. Accepted for publication October 21, 2004. Supported by grant No. GM 061655 from the National Institutes of Health, Bethesda, Maryland; the Gheens Foundation, Louisville, Kentucky; the Joseph Drown Foundation, Los Angeles, California; and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, Kentucky. None of the authors have any personal financial interest related to this research.

Address reprint requests to Dr. Sessler: Outcomes Research™ Institute, 501 East Broadway, Louisville, Kentucky 40202. Address electronic mail to: sessler@louisville.edu. On the World Wide Web: www.or.org. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

studied healthy (American Society of Anesthesiologists physical status I) white female volunteers aged 18–40 yr who had natural bright red, black, or dark brown hair. We considered volunteers to be white if they reported being primarily of northern European descent. Volunteers were monetarily reimbursed for their time.

Other studies indicate that women report different pain experiences and more negative responses to pain than men,[13–16] as well different responses to analgesics.[17] Therefore, we restricted our study population to women. A higher sensitivity to pain stimuli has been observed during the luteal phase of the menstrual cycle.[18,19] We therefore also restricted studies to the first 10 days of the participants' menstrual cycles unless they were using hormonal contraceptives.

Exclusion criteria included chemical hair treatment, any history of medical or psychiatric problems, history of current or past chronic pain conditions, skin abrasions or lesions on testing sites, pregnancy, body mass index greater than 30 kg/m^2, recreational drug use, or use of medications other than oral contraceptives. Based on the means and SDs obtained from preliminary test results on the Neurometer CPT/C device (Neurotron, Inc., Baltimore, MD),[20] an *a priori* sample-size estimate suggested that 18 subjects in each group would provide a 90% power for detecting a 40% reduction in pain tolerance thresholds at a two-tailed, unpaired α level of 0.05. Therefore, we enrolled 30 volunteers with red hair and 30 with dark hair.

All studies were started at 8:00 AM. Volunteers fasted and refrained from smoking for at least 8 h before the start of the protocol. Studies were conducted in a quiet room that was maintained at a comfortable ambient temperature. Each volunteer's height, weight, and age were recorded. Sensory and pain thresholds for each volunteer were tested with two devices: the Neurometer CPT/C and the TSA-II Neurosensory Analyzer (Medoc Ltd., Minneapolis, MN).

The Neurometer CPT/C produces a biphasic sinusoid alternating current waveform stimulus at frequencies of 2,000, 250, and 5 Hz.[20,21] Sine waves at 2,000, 250, and 5 Hz correspond to depolarization periods of 0.25, 2, and 100 ms, respectively. The large-diameter fibers can respond to the rapid 2,000-Hz stimulus, whereas the small unmyelinated fibers require several milliseconds of a continuous depolarization period to respond. However, large fibers repolarize faster than the slow increase of the 5-Hz stimulus can depolarize them and therefore do not achieve threshold potential with that stimulation. Together, these factors result in the 2,000, 250 and 5-Hz sine wave depolarizations selectively evoking responses from the large myelinated A-β, the small myelinated A-δ, and the small unmyelinated C fibers, respectively.[22,23] The Neurometer automatically compensates for alterations in skin resistance by adjusting the voltage to maintain a constant current.[21] Our Neurometer was modified to deliver currents from 0 to a maximum of 20 mA.

For determination of the baseline sensory, pain perception, and pain tolerance thresholds, pairs of gold electrodes were positioned on glabrous skin of both the right and left ring fingers. For each specific threshold measurement, both sides (dominant and nondominant hand) were tested sequentially, with the order determined by random assignment. The skin was prepared for testing with a gentle abrasive cleaning preparation. A pair of gold electrodes (1-cm diameter) separated by a 1.7-cm Mylar spreader was coated with a thin layer of chloride-free electroconductive gel and taped to the finger. Volunteers were instructed as to how to respond to each stimulus according to a standardized script and were blinded at all times to the threshold measurement results displayed on the Neurometer device.

The baseline current perception (sensory) thresholds were tested first at 2,000, 250, and 5 Hz. The operator slowly increased the stimulus until the volunteer consistently reported detecting the stimulus at 0.02 mA and not detecting the stimulus 0.2 mA below this value. The manual intensity alignment was followed by auto test cycles controlled by the device. Auto test cycles with true or false testing confirmed that the volunteer responses were within $\pm$0.04 mA. After repeated and consistent crossovers occurred, the device determined the exact milliampere current value.

After completing the baseline current perception threshold measurements on both hands, baseline pain perception thresholds and then pain tolerance thresholds were measured on both hands. For pain perception and pain tolerance threshold measurements, the volunteer initiated the stimulation by pushing a button on the device. As long as the volunteer depressed the button, the amount of stimulation slowly increased automatically. We asked volunteers to release the button when they perceived the stimulus as painful (for pain perception thresholds) or when it became intolerable (for pain tolerance thresholds). We allowed at least 2 min, or until sensation in the finger had returned to baseline, between successive stimuli. In summary, three different frequencies of stimulation (2,000, 250, and 5 Hz) were used to obtain three different threshold measurements (current perception, pain perception, and maximum pain tolerance). These baseline sensory and pain thresholds in response to electrical stimulation were normally distributed.

To determine baseline thermal sensory, pain perception, and pain tolerance thresholds, contact heat stimuli were delivered using a computer-controlled thermal sensory analyzer (TSA-II Neurosensory Analyzer). This device has been used extensively for quantitative assessment of thermal sensory and pain thresholds.[18,24] The maximum delivered temperature was 50°C, and the minimum temperature was 0°C.

For temperature threshold testing, a 3 × 3-cm square thermode was positioned on the volar area of the volunteer's forearm. Both the dominant and nondominant arms were tested sequentially, with the order determined randomly. From a baseline of 32°C, probe temperature was increased or decreased at a rate of 0.5°C/s until the volunteer responded. The slow increase presumably evokes mainly stimulation of C-nociceptive afferents.[25] Volunteers were instructed as to how to respond to each stimulus according to a standardized script and were always blinded to results. Four trials of warm and cold sensory thresholds were given to each volunteer, followed by four trials of heat pain and cold pain (perception) thresholds and then four trials of heat pain and cold pain tolerance thresholds. Volunteers were instructed to press a button to interrupt the stimulus whenever they thought that the appropriate threshold had been reached. The four trials were averaged to determine the thresholds. A few volunteers reported mild tenderness at the testing site after maximum intensity stimulation; in these volunteers, the position of the thermode was altered slightly between trials to avoid either sensitization or habituation of cutaneous receptors. In addition, we allowed at least 60 s between successive stimuli. Subjects were blinded at all times to the temperature threshold values obtained with the TSA-II Neurosensory Analyzer.

In addition to the baseline current and thermal threshold measurements, we also investigated how the pain tolerance thresholds were affected by local anesthetic. The methodology to evaluate the sensitivity to different local anesthetics using the Neurometer has been described in previous studies.[17,26] Briefly, the volar surface of the nondominant forearm of the volunteer was divided into three areas, each measuring approximately 2 × 4 cm. One area functioned as control; the second area was covered with a 6-mm-thick layer of 4% liposomal lidocaine (ELA-Max; Ferndale laboratories, Ferndale, MI), which was wiped clean after 60 min. In a previous study,[26] the average onset time for this formulation of lidocaine was 7 min; the application time of 60 min in this study should therefore be sufficient to provide cutaneous anesthesia. In the third area, we injected 2 ml lidocaine, 1.0%, subcutaneously and allowed an onset time of at least 5 min.

Pain tolerance threshold values were determined at frequencies of 2,000, 250, and 5 Hz as described above for all three areas. Subjects were blinded to the pain tolerance threshold values generated for each area. Pain tolerance thresholds of areas tested for local anesthetic sensitivity were found to have a censored outcome, *i.e.*, many volunteers reached maximum pain tolerance thresholds and could go no higher.

Table 1. Demographic and Morphometric Characteristics, Baseline Current Perception, Pain Perception, and Pain Tolerance Thresholds

	Red Hair	Dark Hair	*P* Value
Height, cm	163 ± 8	161 ± 6	0.25
Weight, kg	65 ± 11	62 ± 10	0.35
Age, yr	27 ± 5	27 ± 6	0.86
Current threshold perception, mA			
2,000 Hz	2.16 ± 0.44	2.02 ± 0.38	0.20
250 Hz	0.78 ± 0.18	0.74 ± 0.20	0.40
5 Hz	0.44 ± 0.18	0.46 ± 0.22	0.75
Pain perception threshold, mA			
2,000 Hz	6.8 ± 2.8	7.2 ± 3.3	0.60
250 Hz	2.8 ± 1.3	3.2 ± 2.1	0.33
5 Hz	1.9 ± 1.1	2.2 ± 1.1	0.35
Pain tolerance threshold, mA			
2,000 Hz	10.5 ± 3.8	10.9 ± 4.0	0.68
250 Hz	4.2 ± 1.7	4.7 ± 2.9	0.42
5 Hz	2.8 ± 1.4	3.3 ± 1.9	0.27

Data are presented as mean ± SD. Comparisons are made with unpaired, two-tailed *t* tests.

Data Analysis

We compared the demographics and other volunteer characteristics with unpaired, two-sided *t* tests for continuous variables and chi-square or Fisher exact tests for categorical variables. The analysis of perception and threshold outcomes and all continuous outcomes depended on the distribution of the data and whether any of the values were censored. Values were considered censored when the maximum possible pain threshold values were not reached, *i.e.*, the maximum possible pain threshold values in these volunteers were a function of the limits of the Neurometer device (maximum output is 20 mA) and not a physical limitation. That is, the actual pain threshold values were not known because the values were truncated or "right censored" at 20 mA. Outcomes that were normally distributed were compared with unpaired, two-sided *t* tests. If the values were skewed, the Mann–Whitney rank sum test was used for comparing the groups. If some of the data were censored, we used Kaplan–Meier survival curves and log rank tests. $P < 0.05$ was considered statistically significant.

Results

Demographic and morphometric characteristics of the red-haired and dark-haired volunteers were similar (table 1). Baseline thresholds for the dominant and nondominant arms were also similar; values from each arm were thus averaged. None of the baseline responses to electrical stimulation (Neurometer; current perception, pain perception, or pain tolerance thresholds) differed significantly between the two groups (table 1).

Table 2. Thermal Perception, Pain Perception, and Pain Tolerance Thresholds

	Red Hair	Dark Hair	*P* Value
Cold sensory perception threshold, °C	30.7 (30.3–31.0)	30.5 (29.9–31.2)	0.596
Cold pain perception threshold, °C	22.6 (15.1–26.1)	12.6 (0.0–20.0)	0.004
Cold pain tolerance threshold, °C	6.0 (0.0–9.7)	0.0 (0.0–2.0)	0.001
Heat sensory perception threshold, °C	33.8 (33.5–34.0)	33.5 (33.4–33.8)	0.015
Heat pain perception threshold, °C	41.4 (39.7–43.1)	42.4 (41.3–44.6)	0.059
Heat pain tolerance threshold, °C	46.3 (45.7–47.5)	47.7 (46.6–48.7)	0.009

Data are presented as median (interquartile range). Comparisons are made with Mann–Whitney rank sum tests.

In contrast, baseline threshold responses to thermal stimuli were different between the groups: Redheads were more sensitive to cold pain, both in terms of cold pain perception and cold pain tolerance (table 2). Although the difference in heat pain perception between the two groups did not reach statistical significance, redheads had a lower threshold for heat pain tolerance (table 2).

Liposomal lidocaine was slightly, but not significantly, less effective in redheads (table 3). In contrast, subcutaneous lidocaine was significantly less effective in redheads than in subjects with dark hair: Median survival thresholds for pain tolerance (table 3) were lower in red-haired than in dark-haired volunteers (fig. 1).

Discussion

The range of the baseline current perception, pain perception and pain tolerance thresholds in this study was consistent with those reported in earlier studies using test sites on the fingers[27] or the volar surface of the forearm.[26] Although we measured considerably lower pain tolerance thresholds on the forearm test sites compared with the finger test sites, this difference is consistent with the difference observed in other studies when different test sites were used.[26,27] This merely seems to indicate that the absolute range of the threshold measurements depends on the location of a particular test site. The highest values for each threshold were obtained with electrical stimulation at 2,000 Hz, and the lowest values were obtained with 5-Hz stimulation, consistent with previous observations.[26] Nonetheless, we were unable to detect any differences in baseline sensory, pain perception, or pain tolerance thresholds in response to electrical stimuli between women with red or dark hair.

Table 3. Effect of Topical and Subcutaneous Lidocaine on Pain Tolerance Thresholds (mA)

	Red Hair	Dark Hair	*P* Value
Control			
2,000 Hz	5.5 (4.5–6.5)	6.0 (4.5–7.5)	0.187
250 Hz	2.8 (2.4–3.2)	2.8 (1.6–4.0)	0.292
5 Hz	2.0 (1.5–2.4)	2.1 (1.5–2.8)	0.708
Liposomal lidocaine			
2,000 Hz	7.5 (5.5–8.5)	9.0 (6.5–11.5)	0.460
250 Hz	3.6 (3.2–6.0)	5.0 (3.2–6.0)	0.114
5 Hz	3.2 (2.8–4.0)	4.5 (3.2–5.0)	0.106
Subcutaneous lidocaine			
2,000 Hz	11.0 (8.5–16.5)	> 20 (14.5 to > 20)	0.005
250 Hz	5.0 (4.0–9.0)	11.6 (8.0–13.0)	0.003
5 Hz	6.3 (3.2–10.2)	8.5 (7.0–14.2)	0.013

Data are presented as median survival threshold (95% confidence interval). Comparisons are made with log rank tests.

Baseline heat pain perception and heat pain tolerance threshold values in this study corresponded well to those reported in previous studies.[16,18,24] We found that redheads were significantly more sensitive to cold pain perception, cold pain tolerance, and heat pain tolerance. Heat pain perception threshold was also lower, but not significantly so, in redheads. In contrast to the pain tolerance thresholds, the heat sensory perception threshold was actually higher in redheads.

Interestingly, our baseline responses to thermal stimuli contrast with those reported by Mogil *et al.*,[9] in which no group differences were reported in ischemic pain perception thresholds, ischemic pain tolerance thresholds, or thermal pain intensity ratings as a function of hair color.[9] Methodologic differences are a possible explanation: In the study of Mogil *et al.*, a series of suprathreshold thermal stimuli consisting of 10 heat pulses at 52°C were applied, and the subjects rated the intensity of each pulse on a scale of 0–100. The ratings were then combined to obtain a score for thermal pain intensity. Despite the fact that such scales have fixed endpoints, a limitation in the use of this and other such scales is the fact that these endpoints are entirely based on a subject's previous subjective experiences. The use of rating scales possibly leads to a more variable measurement range compared with the determination of specific threshold values.

We therefore observed differences between the hair color groups in baseline thermal sensitivity, but not in baseline electrical pain. That responses differed with electrical and thermal stimuli is perhaps unsurprising: It is well established that sensitivity to one type of pain poorly predicts sensitivity to other types of pain as various mechanisms underlie different types of pain.[28] An alternative explanation is that electrical stimulation bypasses peripheral transduction mechanism whereas thermal stimulation does not. The observed differences in thermal thresholds could therefore also be due to differences in peripheral transduction rather than (central) processing of pain signals beyond the nociceptors. Despite the fact that the differences in thermal thresholds were statistically significant, the clinical significance re-

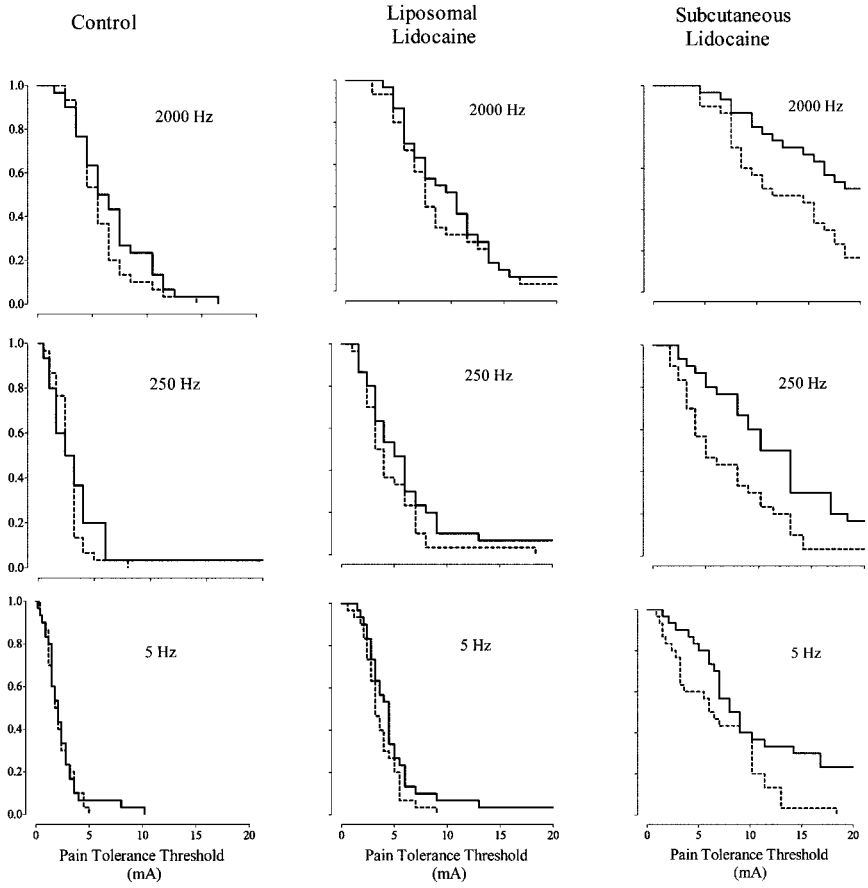

Fig. 1. Pain tolerance thresholds to 2,000-, 250-, or 5-Hz stimulation on the forearm of volunteers with dark hair (*dark, solid lines*) or red hair (*pale, dashed lines*). Three areas of the arm were tested: an untreated control area, an area treated with 4% liposomal lidocaine, and an area injected with 1 ml lidocaine, 1%. Data were plotted as Kaplan–Meier survival curves, and the curves were compared with log rank tests. The *y-axis* represents the fraction of the study population still able to reach a particular threshold. The curves for the two groups were significantly different for all three frequencies on the area treated subcutaneously with lidocaine.

mains unclear because the absolute temperature differences between the two groups were quite small.

The pain threshold changes to liposomal lidocaine in this study were comparable to those found in previous studies,[26,29] but despite a trend toward higher threshold values in the red-haired group, none of the comparisons between the two groups reached statistical significance for liposomal lidocaine. Our most striking finding, though, was that redheads were resistant to anesthesia produced by subcutaneous lidocaine as measured by the pain perception and tolerance thresholds. This outcome is consistent with the anecdotal observations that prompted our study and makes red hair a distinct phenotype associated with local anesthetic sensitivity. However, without a dose–response relation, it remains unclear whether this represents absolute failure of local anesthetic action or merely a shift of the dose–response curve to the right.[30] That is, redheads may simply require more local anesthetic but ultimately obtain adequate analgesia.

Local anesthetics such as lidocaine prevent transmission of nerve impulses by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes.[31–33] However, the peripheral nervous system is not a known site of MC1R expression.[6] Therefore, there is no known direct association between MC1R function and peripheral local anesthetic action. In the study by Mogil *et al.*,[9] women with two variant *MC1R* alleles displayed significantly greater analgesia in response to the κ opioid pentazocine compared to those with one or zero variant *MC1R* variant alleles. The authors suggested that involvement of MC1Rs in analgesia could be mediated through MC1Rs expressed in brain glial cells[11] and the neurons of the periaqueductal gray,[34] a brain area that critically modulates nociception.[35] Another possibility is that dysfunctional peripheral *MC1R* mutations produce compensatory up-regulation of central melanocortins that in turn increase baseline pain sensitivity *via* stimulation of melanocortin-4 receptors. Numerous other explanations might be postulated, and currently available information does not provide the basis for identifying a specific mechanism by which *MC1R* mutations might influence pain sensitivity or anesthetic requirement. Whether resistance to local anesthesia is therefore due to central up-regulation of melanocortin receptor ligands or some other mechanism remains unknown.

It is well established that women are more sensitive to painful stimuli and require more analgesic medication than men.[13–15] To reduce variability, we restricted this study and a previous one in redheads to women.[7] Mogil *et al.*[9] found significant effects of the *MC1R* genotype on pentazocine analgesia, but this effect only emerged in women, which suggests that the effects of MC1R dys-

function might be sex specific. Whether our results can be extrapolated to men thus remains unknown.

Another limitation of our study is that we did not perform DNA analysis on our volunteers. However, DNA analysis in our previous study[7] confirmed that all of the red-haired volunteers carried at least one variant *MC1R* allele and that 9 of 10 carried two such alleles, which is consistent with previous reports.[1–3,36] In contrast, 5 of 10 dark-haired volunteers carried a single mutant allele, and the remaining 5 showed consensus *MC1R* alleles.[7] Therefore, it is reasonable to assume that virtually all our redheaded volunteers have MC1 receptor dysfunction, and it is equally reasonable to assume that the receptor functions normally in our dark-haired volunteers.

A final limitation is that we were unable to blind investigators (or the subjects) to hair color. Therefore, we cannot fully rule out bias on the part of the investigators or evaluate the extent to which our bias may have influenced participants' responses. However, the volunteers were not informed of our hypothesis. They were also fully blinded to temperature readings of the Neurosensory Analyzer thermode and Neurometer current intensity readings. It therefore seems unlikely that bias was the primary explanation for differences we identified between redheads and volunteers with dark hair, especially as differences were only identified under certain conditions.

In summary, redheads are more sensitive to thermal pain than women with dark hair but do not show differences in baseline electrical pain thresholds. Furthermore, redheads are more resistant to the analgesic effects of subcutaneous lidocaine. These results extend the previous observation that redheads are more resistant to volatile anesthetics. Mutations of the melanocortin-1 receptor, or as a consequence thereof, therefore seem to modulate pain sensitivity. It remains unclear whether this modulation occurs at a central or a peripheral level or both. An apparent genetic association may not necessarily mean that a straightforward mechanism for the phenotypic effect will be forthcoming. Thus far, these differences seem to be most clearly defined in the presence of drugs (local anesthetic, volatile anesthetic) that suppress responses to noxious stimuli.

References

1. Schiöth HB, Phillips SR, Rudzish R, Brich-Machin MA, Wikberg JES, Rees JL: Loss of function mutations of the human melanocortin receptor are common and are associated with red hair. Biochem Biophys Res Commun 1999; 260:488–91
2. Healy E, Jordan S, Budd P, Suffolk R, Rees J, Jackson I: Functional variation of MC1R alleles from red-haired individuals. Hum Mol Genet 2001; 10:2397–402
3. Rees JL, Flanagan N: Pigmentation, melanocortins and red hair. QJM 1999; 92:125–31
4. Rees JL: Genetics of hair and skin color. Annu Rev Genet 2003; 37:67–90
5. Sturm R, Duffy D, Box N, Newton R, Shepherd A, Chen W, Marks L, Leonard J, Martin N: Genetic association and cellular function of MC1R variant alleles in human pigmentation. Ann NY Acad Sci 2003; 994:348–58
6. Abdel-Malek Z: Melanocortin receptors: Their functions and regulation by physiological agonists and antagonists. Cell Mol Life Sci 2001; 58:434–41
7. Liem EB, Lin C-M, Suleman M-I, Doufas AG, Gregg RG, Veauthier JM, Loyd G, Sessler DI: Increased anesthetic requirement in redheads. ANESTHESIOLOGY 2004; 101:279–83
8. Xing Y, Sonner JM, Eger EI, II, Cascio M, Sessler DI: Mice with a melanocortin 1 receptor mutation have a slightly greater MAC than control mice. ANESTHESIOLOGY 2004; 101:544–6
9. Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV, Lariviere WR, Groce MK, Wallace MR, Kaplan L, Staud R, Ness TJ, Glover TL, Stankova M, Mayorov A, Hruby VJ, Grisel JE, Fillingim RB: The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci U S A 2003; 100:4867–72
10. Chhajlani V: Distribution of cDNA for melanocortin receptor subtypes in human tissues. Biochem Mol Biol Int 1996; 38:73–80
11. Wikberg JE: Melanocortin receptors: Perspectives for novel drugs. Eur J Pharmacol 1999; 375:295–310
12. Vrinten DH, Gispen WH, Groen GJ, Adan RA: Antagonism of the melanocortin system reduces cold and mechanical allodynia in mononeuropathic rats. J Neurosci 2000; 20:8131–7
13. Fillingham R, Ness T: Sex-related hormonal influences on pain and analgesic responses. Neurosciences Biobehav Rev 2000; 24:485–501
14. Keogh E, Herdenfeldt M: Gender, coping and the perception of pain. Pain 2002; 97:195–201
15. Sarlani E, Greenspan JD: Gender differences in temporal summation of mechanically evoked pain. Pain 2002; 97:163–9
16. Fillingim R, Ness T, Glover T, Campbell C, Price D, Staud R: Experimental pain models reveal no sex differences in pentazocine analgesia in humans. ANESTHESIOLOGY 2004; 100:1263–70
17. Sarton E, Olofsen E, Romberg R, den Hartigh J, Kest B, Nieuwenhuijs D, Burm A, Teppema L, Dahan A: Sex differences in morphine analgesia: An experimental study in healthy volunteers. ANESTHESIOLOGY 2000; 93:1245–54
18. Fillingim RB, Maixner W, Girdler SS, Light KC, Harris MB, Sheps DS, Mason GA: Ischemic but not thermal pain sensitivity varies across the menstrual cycle. Psychosom Med 1997; 59:512–20
19. Tassorelli C, Sandrini G, Cecchini AP, Nappi RE, Sances G, Martignoni E: Changes in nociceptive flexion reflex threshold across the menstrual cycle in healthy women. Psychosom Med 2002; 64:621–6
20. Raj P, Chado HN, Angst M, Heavner J, Dotson R, Brandstater ME, Johnson B, Parris W, Finch P, Shahani B, Dhand U, Mekhail P, Daoud E, Hendler N, Somerville J, Wallace M, Panchal S: Painless electrodiagnostic current perception threshold and pain tolerance threshold values in CRPS subjects and healthy controls: A multicenter study. Pain Practice 2001; 1:53–60
21. Katims JJ: Neuroselective current perception threshold quantitative sensory test. Muscle Nerve 1997; 20:1468–9
22. Rendell MS, Katims JJ, Richter R, Rowland F: A comparison of nerve conduction velocities and current perception thresholds as correlates of clinical severity of diabetic sensory neuropathy. J Neurol Neurosurg Psychiatry 1989; 52:502–11
23. Liu S, Kopacz DJ, Carpenter RL: Quantitative assessment of differential sensory nerve block after lidocaine spinal anesthesia. ANESTHESIOLOGY 1995; 82:60–3
24. Fillingim RB, Edwards RR: The association of hormone replacement therapy with experimental pain responses in postmenopausal women. Pain 2001; 92:229–34
25. Yeomans DC, Proudfit HK: Nociceptive responses to high and low rates of noxious cutaneous heating are mediated by different nociceptors in the rat: Electrophysiological evidence. Pain 1996; 68:141–50
26. Finkel J, Yang C, Yarvitz J, Patel K: Neuroselective sensory electrodiagnostic evaluation of 4% liposomal topical lidocaine. Anesth Analg 2002; 94:1259–62
27. Skarke C, Darimont J, Schmidt H, Geisslinger G, Lotsch J: Analgesic effects or morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. Clin Pharmacol Ther 2003; 73:107–21
28. Janal M, Glusman M, Kuhl J, Clark W: On the absence of correlation between responses to noxious heat, cold, electrical and ischemic stimulation. Pain 1994; 58:403–11
29. Sakai T, Tomiyasu S, Yamada H, Ono T, Sumikawa K: Quantitative and selective evaluation of differential sensory nerve block after transdermal lidocaine. Anesth Analg 2004; 98:248–51
30. Nakamura T, Popitz-Bergez F, Birknes J, Strichartz G: The critical role of concentration for lidocaine block of peripheral nerve *in vivo*: Studies of function and drug uptake in the rat. ANESTHESIOLOGY 2003; 99:1189–97
31. Butterworth J, Strichartz G: Molecular mechanisms of local anesthesia: A review. ANESTHESIOLOGY 1990; 72:722–34
32. Ragsdale D, McPhee J, Scheuer T, Cattterall W: Molecular determinants of state-dependent block of Na^+ channels by local anesthetics. Science 1994; 265:1724–8
33. Brau M, Vogel W, Hempelmann G: Fundamental properties of local anesthetics: Half-maximal blocking concentrations for tonic block of Na^+ and K^+ channels in peripheral nerve. Anesth Analg 1998; 87:885–9
34. Xia Y, Wikberg J, Chhajlani V: Expression of melanocortin 1 receptor in periaqueductal gray matter. Neuroreport 1995; 6:2193–6
35. Basbaum AI, Fields HL: Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 1984; 7:309–38
36. Valverde P, Healy E, Jackson I, Rees JL, Thody AJ: Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. Nat Genet 1995; 11:328–30