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Anesthetic Requirement is Increased in Redheads

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Abstract

Background: Age and body temperature alter inhalational anesthetic requirement; however, no human genotype is associated with inhalational anesthetic requirement. There is an anecdotal impression that anesthetic requirement is increased in redheads. Furthermore, red hair results from distinct mutations of the melanocortin-1 receptor. We thus tested the hypothesis that the requirement for the volatile anesthetic desflurane is greater in natural redhead than in dark-haired women.

Methods: We studied healthy women with bright red (n=10) or dark (n=10) hair. Blood was sampled for subsequent analyses of melanocortin-1 receptor alleles. Anesthesia was induced with sevoflurane and maintained with desflurane randomly set at an end-tidal concentration between 5.5 and 7.5%. After an equilibration period, a noxious electrical stimulation (100 Hz, 70 mA) was transmitted through bilateral intradermal needles. If the volunteer moved in response to stimulation, desflurane was increased by 0.5%; otherwise it was decreased by 0.5%. This was continued until volunteers "crossed-over" from movement to non-movement (or vice versa) four times. Individual logistic regression curves were used to determine desflurane requirement (P_{50}). Desflurane requirements in the two groups were compared using Mann-Whitney nonparametric two-sample test; $P < 0.05$ was considered statistically significant.

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Results: The desflurane requirement in redheads (6.2 volume-percent [95% CI, 5.9 - 6.5]) was significantly greater than in dark-haired women (5.2 volume-percent [4.9 – 5.5], $P = 0.0004$). Nine of 10 redheads were either homozygous or compound heterozygotes for mutations on the melanocortin-1 receptor gene.

Conclusions: Red hair appears to be a distinct phenotype linked to anesthetic requirement in humans that can also be traced to a specific genotype.

Introduction

Inhalational anesthetic requirements are remarkably uniform in humans, mainly being affected by age and body temperature.[1,2] However, some anesthesiologists share an anecdotal impression that patients with natural red hair require more anesthesia than patients with other hair colors. The phenotype of nearly all red haired individuals can be traced to distinct mutations of the melanocortin-1 receptor gene (*MC1R*).[3-5]

The human MC1R is expressed on the surface of melanocytes and is a key regulator of intracellular signaling to the melanin biosynthetic pathway governing pigment formation. The red hair phenotype results from excess pheomelanin production. Production of this yellow-red pigment results from well-described mutations of the *MC1R*.[3-6] In contrast, when a normal (consensus) MC1R is expressed, the predominant pigment produced by melanocytes is eumelanin (dark brown) and the typical eumelanin to pheomelanin ratio is high.

An easily identifiable human phenotype that can be traced to a distinct genotype presents an opportunity to identify a genetic influence on anesthetic sensitivity in humans. Distinct genetic factors have been shown to contribute to anesthetic requirements in various animal species including mice,[7] nematodes (*Caenorhabditis Elegans*),[8] and fruit flies (*Drosophila Melanogaster*).[9] However, a similar association has yet to be established in humans. We, therefore, tested the hypothesis that women with natural red hair have a greater desflurane requirement than women with dark hair.

Methods

With institutional approval and written informed consent, we recruited 20 Caucasian women between 18-40 years, with natural bright red or dark (black or dark brown) hair. The study subjects were regarded as Caucasian if they were mainly of northern European descent as indicated by self-report. The subjects were drawn from Greater Louisville, Kentucky, an urban area with a population exceeding 1,000,000. The number of subjects was based on an a priori estimate that 10 subjects in each group would provide 90% power for detecting a 0.8% difference in desflurane requirement (*e.g.*, 5.8% to 5.0%) between the two groups using a two-tailed, unpaired *t* test with an alpha of 0.05 and an estimate of the standard deviation of 0.55.

As it remains unclear whether gender could cause significant differences in anesthetic requirement,[10,11] only women were included. Exclusion criteria included chemical hair treatment, any history of medical or psychiatric problems, any history of chronic pain problems, possible pregnancy, body mass index >30 kg/m^2, recreational drug usage, and medication usage other than oral contraceptives.

Protocol

Studies were started in the morning each day, because circadian rhythms slightly influence anesthetic requirement.[12] The effect of the menstrual cycle on anesthetic requirement is unclear; however, pain threshold varies as a function of the menstrual cycle.[13] Studies were,

therefore, restricted to the first ten days of the participants' menstrual cycles unless they took oral contraceptives.

The subjects fasted and refrained from smoking for at least eight hours before arriving at the laboratory. No premedication was given or allowed. Routine anesthetic safety monitors were applied in an operating room setting. Core body temperature was measured from the tympanic membrane using Mon-a-Therm® thermocouples (Tyco-Mallinckrodt, Inc. St. Louis, MO). General anesthesia was induced with sevoflurane in 100% oxygen; five minutes later, a laryngeal mask airway (Laryngeal Airway Mask, Co. Henley-on-Thames, UK) was inserted and sevoflurane was discontinued. Anesthesia was then subsequently maintained solely with desflurane and ventilation was assisted until spontaneous breathing was re-established. A forced-air warming cover positioned over the trunk (Bair Hugger, Augustine Medical, Inc. Eden Prairie, MN) was used to maintain normothermia.

There was a 45-min equilibration period after induction of anesthesia. Based on pharmacokinetic data,[14] this allowed sufficient time for sevoflurane concentrations to decrease to insignificant levels. It also gave time for the desflurane levels to equilibrate, such that the ratio of inspired (F_I) to end-tidal concentrations (F_A) closely approached 1.0.

After the equilibration period, a noxious electrical stimulation (100 Hz, 60-70 mA) was applied bilaterally for 10 seconds through needles inserted intradermally into the anterior thighs. A tetanic stimulus even 20% of this intensity is unbearable to unanesthetized subjects, but is not consciously sensed during anesthesia.

An independent investigator (one out of a group of four investigators was selected for each study session) was brought into the study room just before each stimulation period to evaluate movement in response to the noxious electrical stimulation and left within a few minutes after each stimulus. A positive response was defined as gross purposeful movement of the legs or arms within the first minute following stimulation. Grimacing and head movement were not considered purposeful responses.

The independent investigator was not blinded to the hair color and skin complexion of each volunteer because of the practical and technical difficulties involved with the latter, but the independent investigator was blinded to the desflurane concentration on the vaporizer dial and those from the gas analyzer readings. In addition, the initial concentration of desflurane was randomly set between 4.5 and 7.5 end-tidal volume-percent (%) to prevent the blinded investigator from guessing the actual desflurane concentration based on a uniform starting concentration.

The desflurane concentration was increased by 0.5 end-tidal volume-percent (*e.g.*, from 5.5 to 6%) when the volunteer moved in response to electrical stimulation, or decreased by 0.5% when the volunteer did not move. The new end-tidal concentration was maintained for at least 15 minutes to allow full equilibration between alveolar and brain concentrations before repeating electrical stimulation. To prevent desensitization at the needle insertion sites, the stimulating needles were moved cranially by one cm after each stimulation period. The up-and-down sequence was continued until participants “crossed-over” from movement to non-movement (or *vice versa*) four times. This procedure, known as the “Dixon up-and-down method,” is a standard technique for evaluating anesthetic potency.[15]

Anesthetic concentration was continuously determined from end-expired gas with a monitor accurate to within 0.1% (Datex-Engstrom, Helsinki, Finland). At equilibrium, end-expired desflurane values are essentially equal to brain concentration.[16]

For verification of hair color, hair samples were obtained from the nape of the volunteers' necks, and the ratio of eumelanin to total melanin in the hair was determined spectrophotometrically as described by Ozeki.[17] The total amount of eumelanin and pheomelanin was determined by the absorbance at 500 nm (A_{500}) and the amount of eumelanin alone by absorbance at 650 nm (A_{650}). Red hair has an A_{650}/A_{500} ratio near 0.13, while black hair has an A_{650}/A_{500} ratio near 0.30; the ratios for blond and brown hair are in between. Blood was sampled for subsequent analyses of *MC1R* alleles (see appendix: details of genetic analysis).

Data Analysis

Demographic, morphometric, and spectrophotometric hair analysis data for the volunteers with red or dark hair were compared using unpaired, two-tailed *t* tests. In each individual, anesthetic requirement was determined by correlation of responses to noxious electrical stimulation (movement or no movement) with end-expired desflurane concentration using logistic regression. The desflurane requirement for each group was defined as the average of the individual concentrations. Desflurane requirements in the two groups were compared using the Mann-Whitney nonparametric two-sample test. Results are presented as means [95% confidence intervals]; $P < 0.05$ was considered statistically significant.

Results

Demographic and morphometric data were similar in the groups (Table 1). Average core temperatures were similar for both groups (Table 1) Hair analysis confirmed that volunteers had typical ratios of eumelanin to total melanin for red or dark hair color (Table 1).

The volunteers with red hair required significantly more desflurane (mean 6.2 [95% CI, 5.9 - 6.5]) than those with dark hair (mean 5.2 [95% CI, 4.9 - 5.5]), $P = 0.0004$ (Fig. 1). This represents an increase of 19% in the desflurane partial pressure.

The single nucleotide polymorphism (SNP) analysis revealed that 9 of the 10 redheads had the following variant *MC1R* alleles (compared to consensus protein): R151C/Y152X, R151C/D294H, R151C/R160W (2 subjects), D294H/D294H, Y152X/R160W, R151C/29insA, R151C/V60L, R160W/D84E. One remaining redhead volunteer carried the R151C mutation on a single allele. In the dark haired volunteers, 5 of 10 carried a single mutant allele (D294H, R160W, R151C [3 subjects]) and the remaining 5 showed consensus *MC1R* alleles at the tested locations.

Discussion

Anesthetic requirement in red heads was increased 19%, a difference that was highly statistically significant ($P = 0.0004$). The results confirm anecdotal clinical impressions that anesthetic requirement is greater in redheads.

Inhalational anesthetic requirement is typically quantified in terms of the minimum alveolar requirement (MAC), the anesthetic concentration that prevents movement in response to skin incision in half of the population[18] The reported desflurane MAC in the literature for this age group is 7.25%.[19] We used an analogue of MAC in this study by applying repeated noxious electrical stimulation.[20] The mean values for desflurane requirement in both our study groups (6.2% for red hair and 5.2% for dark hair) are lower than the reported MAC, but expected with this model because anesthetic requirement depends on the type and intensity of the applied stimulation.[21] Skin incision is a supra-maximal stimulus that fully activates pain receptors and pathways. Electrical stimulation is not, and it therefore provides graded activation of pain pathways. Movement in response to electrical stimulation can thus be blocked by lower partial pressures than those required to prevent movement in response to skin incision.[20]

Chemical hair analysis also indicated that the volunteers had in fact been correctly assigned to each hair color group. Results of the DNA analysis in our volunteers were consistent with previously reports.[3-6] Three particular mutations of the *MC1R* alleles (R151C, R160W, and D294H) are present in the majority of redheads, with at least one of these three alleles found in 93% of those with red hair.[22] These variant *MC1R* alleles behave as recessive mutations.[6] Although many other discovered allele variants do not affect function, it has been shown that *MC1R* variants V60L, R142H, R151C, R160W, D294H lead to melanocortin-1 receptors that are unable to stimulate intracellular cyclic AMP production as efficiently as the wild type receptor when activated.[23] Presumably, early single nucleotide insertions (*e.g.*, ins29) will also result in loss of function because the frame shift will lead to many other different amino acid substitutions. Our DNA analysis showed that all 10 red haired volunteers in this study carried at least one dysfunctional or diminished function *MC1R* allele, and 8 carried two such alleles. The functional significance of mutation D84E, carried by one of the remaining two red haired subjects, remains unknown but this mutation is also strongly associated with red hair, having an odds ratio of 63 for red hair relative to the consensus *MC1R* allele.[22] In the dark haired group there was no clear evidence for the effect of heterozygosity on anesthetic requirement.

In addition to its expression on melanocytes, the presence of *MC1R* also has been identified in human pituitary tissue, glial cells, and in cells of the human periaqueductal gray matter.[24,25] The essential qualities produced by inhaled anesthetics, namely amnesia and immobility, are mediated through actions on the central nervous system. However, the central nervous system is not a major site of *MC1R* expression.[26] Furthermore, studies suggest that immobility may in fact be mediated through the spinal cord rather than higher centers[27,28] and severing of higher centers from the cord does not change MAC.[28,29]

A recent study by Mogil *et al*. suggests a possible role for the *MC1R* gene in female specific pain modulation. Women with two variant *MC1R* alleles displayed significantly greater analgesia in response to the kappa-opioid pentazocine compared to those with one or zero variant *MC1R* variant alleles.[30] Whether this finding would translate into a greater underlying sensitivity to the dynorphin, the endogenous kappa receptor ligand, remains unclear. Interestingly, dynorphin peptides can also bind to melanocortin receptors (including *MC1R)* and act as antagonists.[31] But to the extent that the results of Mogil *et al*. suggest an increased underlying sensitivity to certain endogenous opioids in subjects with red hair, we might expect reduced anesthetic requirement in red heads if such a system was tonically active, this would be the opposite of what we observed in this study.

Modulation of analgesic mechanism could possibly also occur from interaction between the various melanocortin receptors. *MC1R* is part of a family of melanocortin receptors (*MC1R, MC2R, MC3R, MC4R and MC5R*)[32,33] that are all stimulated by the same ligands (melanocortins α-melanocyte-stimulating hormone [MSH], β-MSH, γ-MSH, and ACTH). The receptor subtypes have different physiological functions and tissue distributions.[26] In fact, *MC3R* and *MC4R* are much more abundant in the central nervous system than *MC1R*, but have similar affinities for α-MSH and ACTH.[26] A functional antagonism between the opioid and melanocortin systems has been suggested, as the receptors are co-localized throughout the CNS, including the locus coeruleus where their regulatory activities oppose each other.[34] Furthermore, acute intrathecal administration of the *MC4R* antagonist SHU9119 reduces cold and mechanical allodynia in a rat neuropathic pain model[35] and can be antagonized by low doses of naloxone.[36]

The mechanisms controlling production of α-MSH remain unclear, but most pituitary functions are controlled by negative feedback systems that increase hormone release with end-organ failure. The observation that α-MSH injection into the paraventricular hypothalamic nucleus

decreases POMC gene expression is consistent with this hypothesis.[37] It is thus not unreasonable to postulate that *MCR1* dysfunction could similarly activate a feedback system that increases central α-MSH concentration.

Gender is an additional phenotype that may be associated with anesthetic requirement. For example, Goto *et al*. report that xenon MAC for elderly Japanese women was 26% less than xenon MAC for elderly Japanese men.[10] In contrast, the results from another study suggested that women require more desflurane using a similar model of electrical stimulation as this study.[38] Most recently, though, prospective[11] and retrospective [39] studies failed to identify any gender difference in MAC. Gender therefore does not appear to have a consistent or clinically important effect on anesthetic requirement.

In summary, our results confirm anecdotal clinical impressions that anesthetic requirement is greater in redheads. The observed 19% difference between the two groups makes red hair a distinct phenotype that correlates with inhalational anesthetic requirement in humans and can be traced to a specific genotype.

Appendix: Details of genetic analysis

DNA was extracted from either clotted or unclotted blood using PureGene DNA isolation kits (Gentra Systems, Inc, Minneapolis, Minnesota). A 1238 bp fragment encompassing the coding region of *MCR1* was amplified by polymerase chain reaction (PCR) using primers described by Miller *et al*.[40] The PCR mix contained the following in 20 μL: 50–100ng DNA, 0.3μM of each primer (1F: 5'–AGATGGAAGGAGGCAGGCAT–3' and 1R: 5'–CCGCGCTTCAACACTTCAGAGATCA–3'), 0.2μM each dNTP, 1.5 μM MgSO4, 2.5% DMSO, 1x KOD PCR buffer, and 0.4U of KOD Hot Start Taq polymerase (Novagen Inc., Madison, Wisconsin). The DNA was amplified for 36 cycles (0.5 minute at 94°C, 0.5 minute at 67°C, 1.5 minutes at 72°C) after activating the polymerase by incubation for 2 minutes at 94°C. Amplified PCR products were analyzed by agarose gel electrophoresis. For single nucleotide polymorphism (SNP) analyses, the full-length PCR products were used as templates after a 1000-fold dilution. Fragments containing the region of variants of interest (R151C, D294H, R142H, R160W, and Y152X) were amplified using the following primer pairs and conditions described above, except the concentration of dNTPs was decreased 10 fold. SNPs were detected using the CEQ8000 SNP detection kit (Beckman-Coulter Inc., Fullerton, California). Amplification and SNP interrogation primers were: D294H (amplification: 5'–TCATCGTCCTCTGCCCCGAG–3', 5'–ACACTTAAAGCGCGTGCACCGC–3'; SNP detection: 5'–TTTCTCGCCCTCATCATCTGCAATGCCATCATC–3'), R142H, R151C, R160W and Y152X (amplification: 5'-GCAGCAGCTGGACAATGTCATT-3', 5'–TGGTCGTAGTAGGCGATGAA–3'; SNP interrogation: R142H, 5'–TCTGCTTCCTGGGCGCCATCGCCGTGGACC–3'; R151C, 5'–TCGCCGTGGACCGCTACATCTCCATCTTCTACGCACTG–3'; R160W, 5'–AGATGGCCGCAACGGCTCGCCGCGCCC–3'; Y152X, 5'–CTACATCTCCATCTTCTACGCACTGCGCTA–3').

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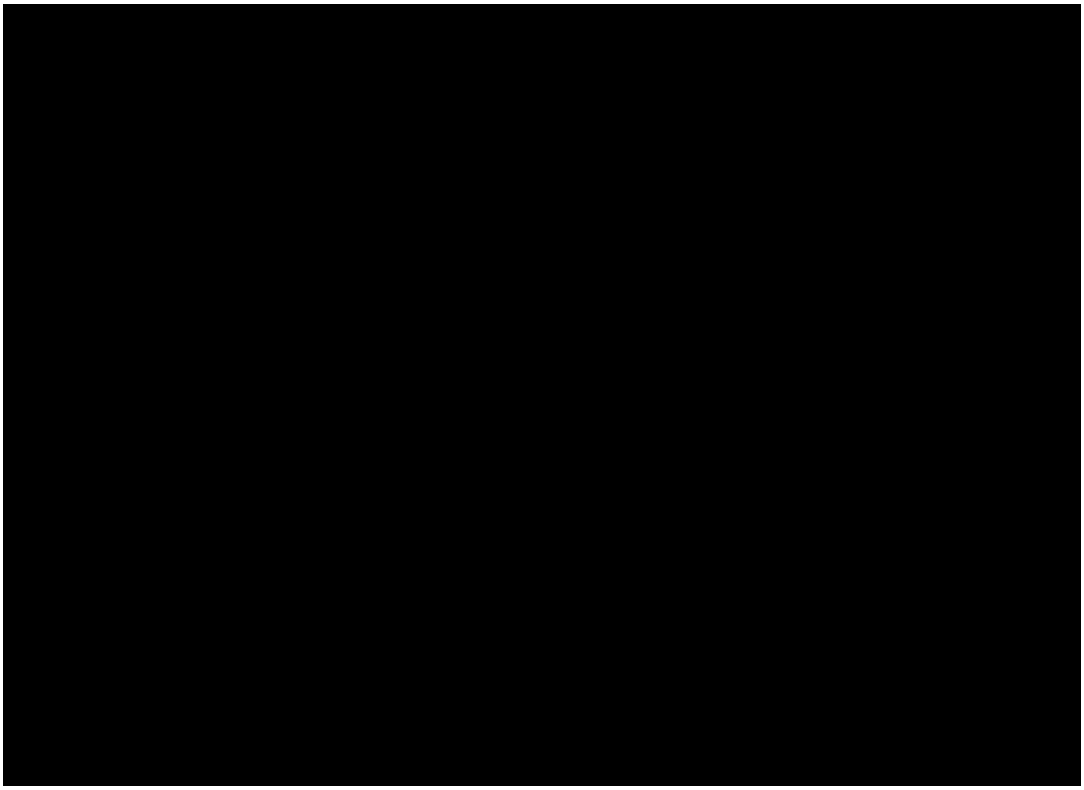

Fig. 1.
Anesthetic requirement for individual participants (circles) with group means (squares) and 95% confidence intervals.

Table 1

Patient Characteristics, Eumelanin/Total Melanin ratios (A_{650}/A_{500}), and Desflurane Requirements (means [95% confidence intervals])

	Red Hair	Dark Hair	P
Number of volunteers	10	10	—
Age (years)	24 [21-27]	24 [21 - 27]	1.0
Height (cm)	159 [155 -164]	162 [158 - 165]	0.42
Weight (kg)	60 [54 - 66]	61 [55 - 67]	0.89
Average Core Temp (°C)	36.52	36.45	0.63
A_{650}/A_{500} Ratio	0.13 [0.11 - 0.17]	0.27 [0.22 - 0.31]	0.0001
Desflurane Requirement (%)	6.2 [5.9 - 6.5]	5.2 [4.9 - 5.4]	0.0004

Results are presented as medians [95% confidence intervals].