


ANESTHESIA REQUIREMENTS FOR REDHEADS

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OBJECTIVES

- Identify at risk populations
- Review current literature, both supporting and disputing the claim that several aspects of anesthesia are altered in redheads
- Discuss current and future anesthetic implications
- Raise awareness for Student Registered Nurse Anesthetists attending Adventist University

CASE SCENARIO

In the midst of a pediatric specialty rotation, the first case of the day was a 6 month old infant scheduled for an inguinal hernia repair.
After an uneventful inhalational induction and subsequent intubation, the patient was prepped and draped.

After approximately 15 minutes, the surgeon began the procedure.
Despite an end tidal sevoflurane concentration of 3.1% and adequate narcotic administration, the patient moved significantly to initial incision.

After increasing the anesthetic gas to nearly 4%, and waiting approximately 5 minutes for equilibration, the surgeon continued the procedure uneventfully.

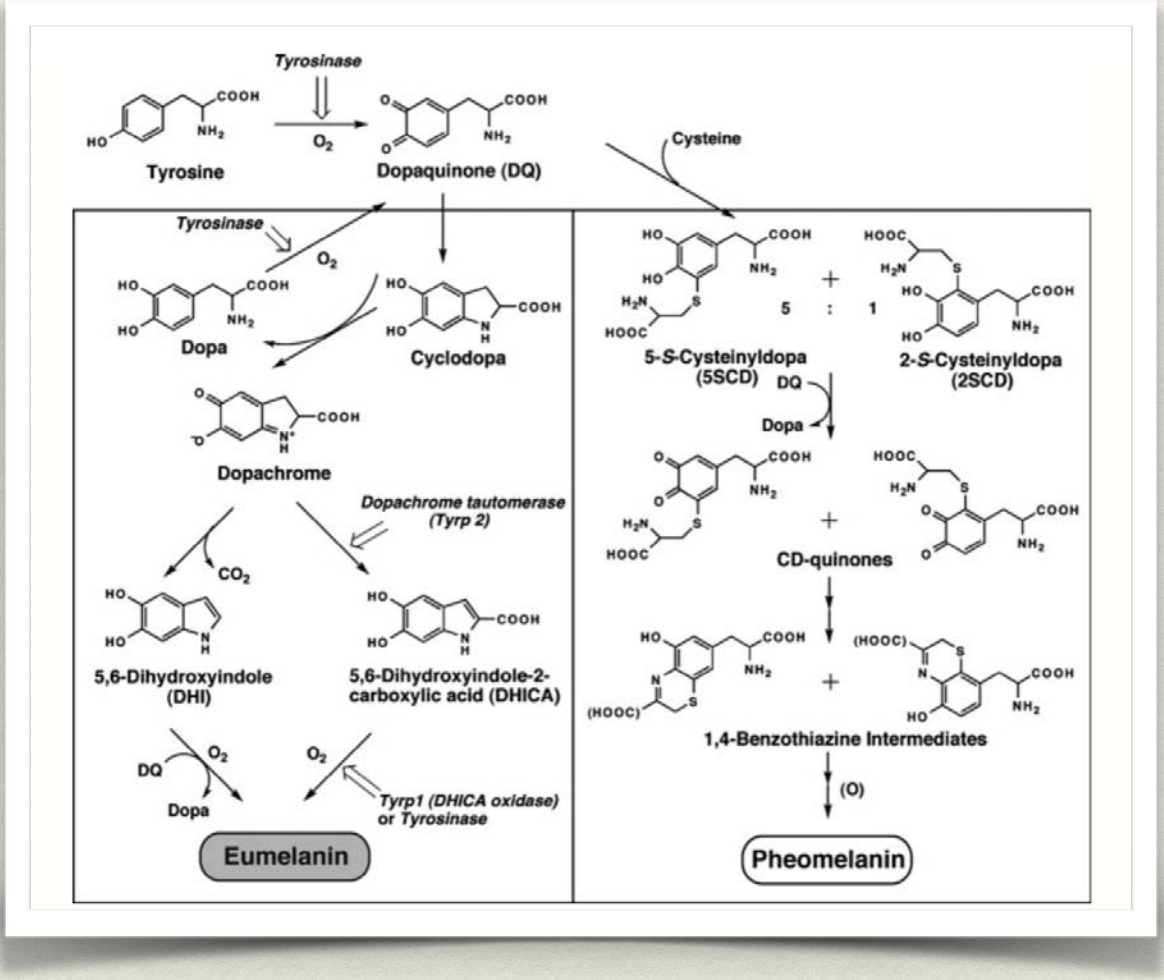
TO WHICH TYPE OF REDHEADS DO I REFER??

IMPACT OF HAIR COLOR

- Hair color is one of the most conspicuous phenotypes of humans
- Hair color ranges from black, dark brown, brown, light brown, and blonde to red, with a myriad of hues in each category
- Hair color has tremendous societal and cosmetic impact
- Diversity of hair color arises primarily from the quantity and ratio of two types of pigment: black to brown eumelanin, and reddish brown to yellow pheomelanin

THE SCIENCE BEHIND RED HAIR

Melanin is synthesized in follicular melanocytes within membrane-bound organelles called melanosomes, which are transferred to the keratinocytes that form the hair shaft. Melanosomes contain tyrosinase, which catalyzes L-tyrosine to L-dopaquinone, the initial step in melanogenesis.



"On the other hand, when L-cysteine is present at a sufficient level in melanosomes, it interacts with dopaquinone to give exclusively the isomers 5-S- and 2-S-cysteinyldopa in a ratio of 5 : 1. The oxidation of these cysteinyldopa isomers with dopaquinone (hence dependent on tyrosinase) leads eventually to the production of reddish brown pigment pheomelanin via benzothiazine intermediates."

Image from: Ito, S., Wakamatsu, K. (2011). Diversity of human hair pigmentation as studied by chemical analysis of eumelanin and pheomelanin. *Journal of the European Academy of Dermatology and Venereology, 25,* 1369-1380.

THE SCIENCE BEHIND RED HAIR

Another picture interpreting the interaction of a functional and non-functional MC1R (also called melanocyte-stimulating hormone receptor (MSHR)...

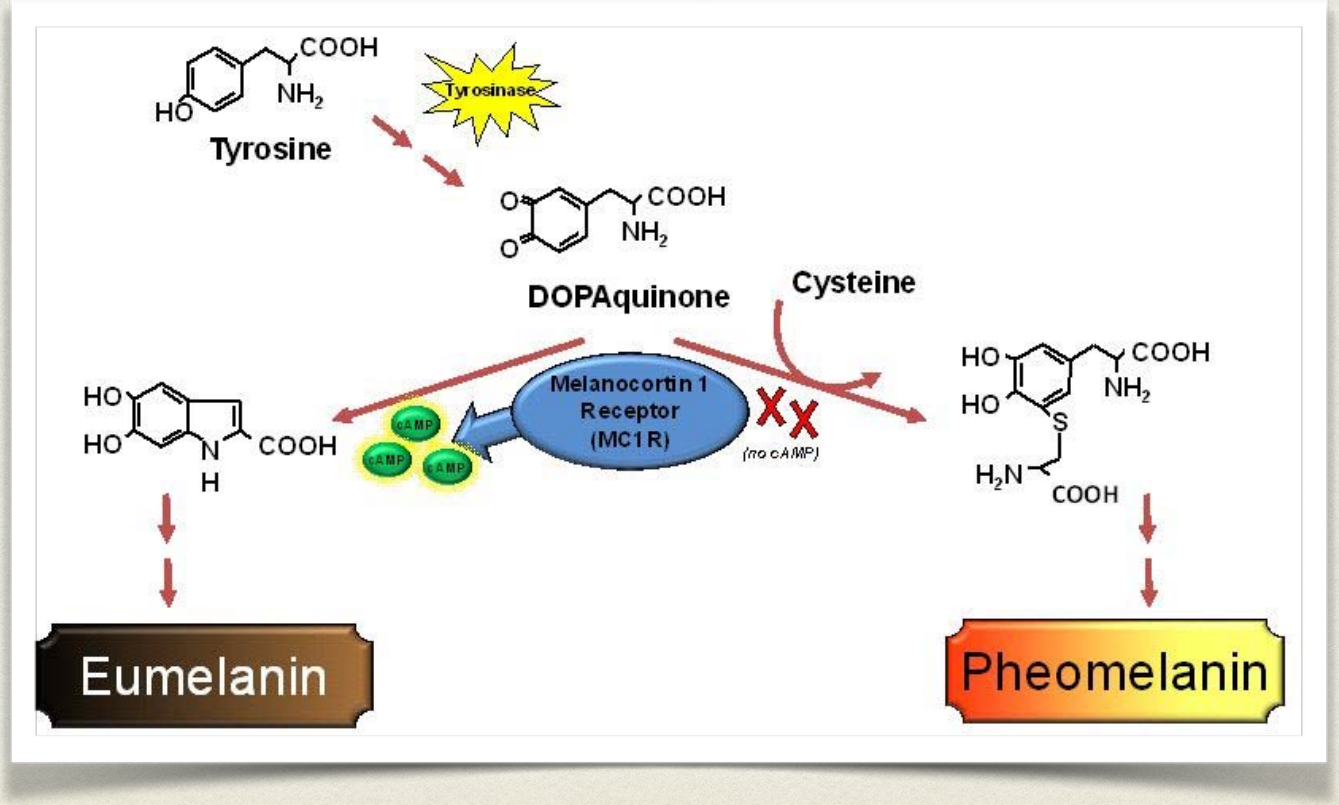


Image from: http://www.intechopen.com/books/melanoma-current-clinical-management-and-future-therapeutics/melanoma-epidemiology-risk-factors-and-the-role-of-adaptive-pigmentation

THE SCIENCE BEHIND RED HAIR

And another…

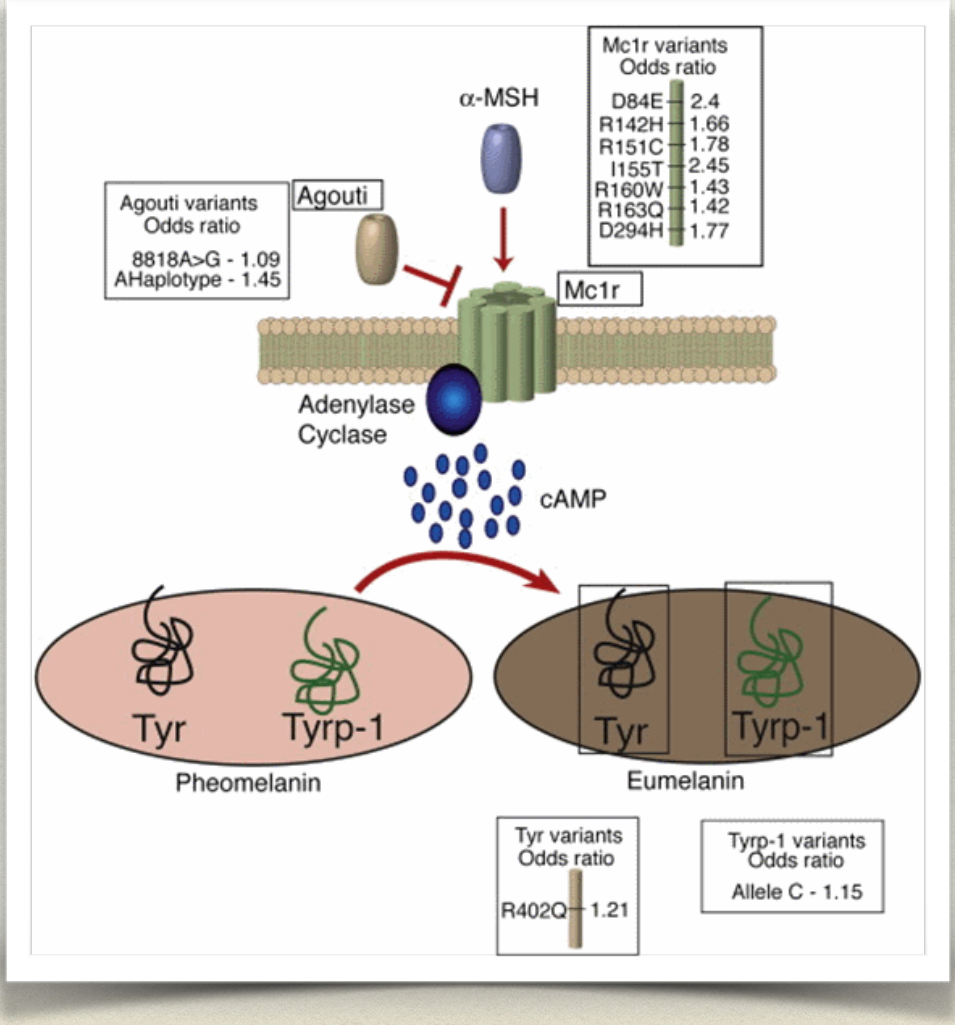


Image from: http://cancerlink.ru/enmelgenetics.html

THE SCIENCE BEHIND RED HAIR

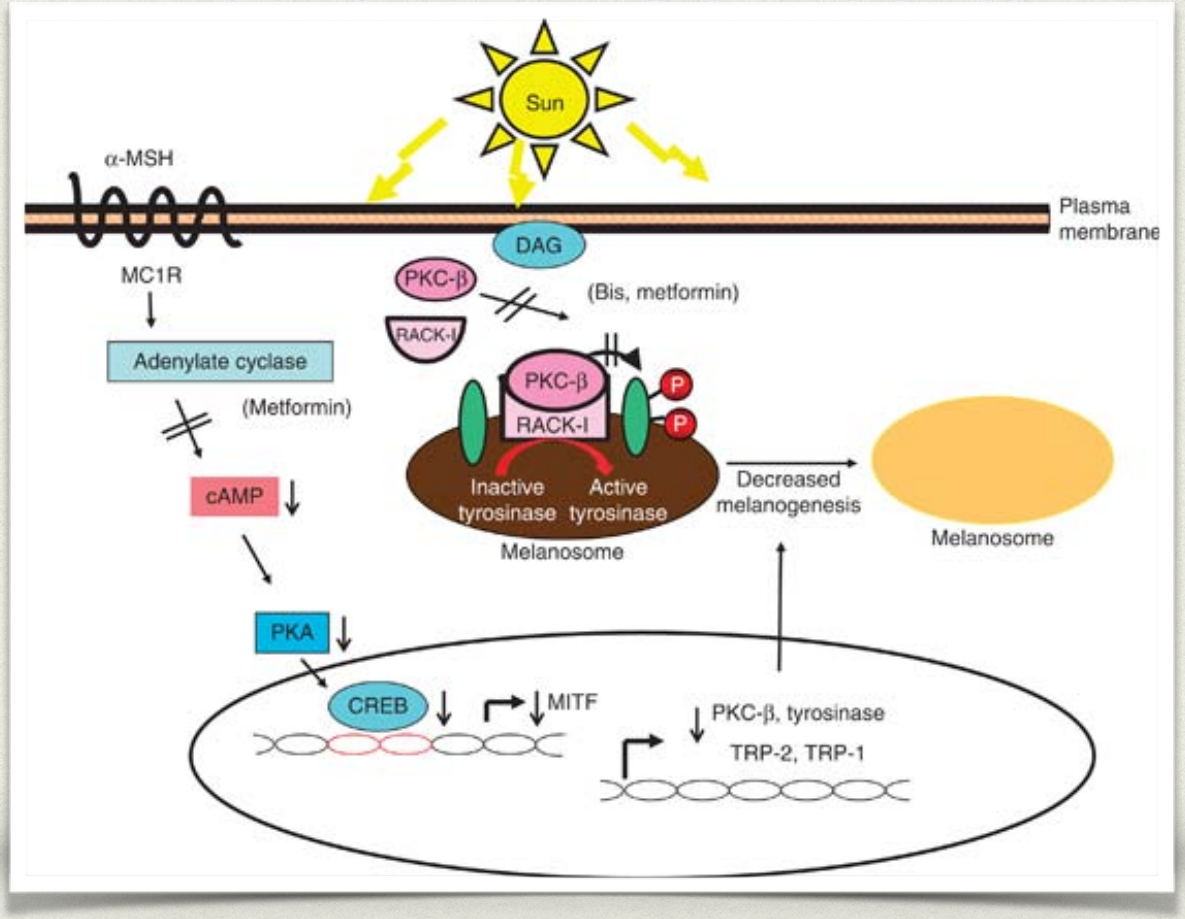


Image from: http://www.nature.com/jid/journal/v134/n10/fig_tab/jid2014245f1.html

THE SCIENCE BEHIND RED HAIR

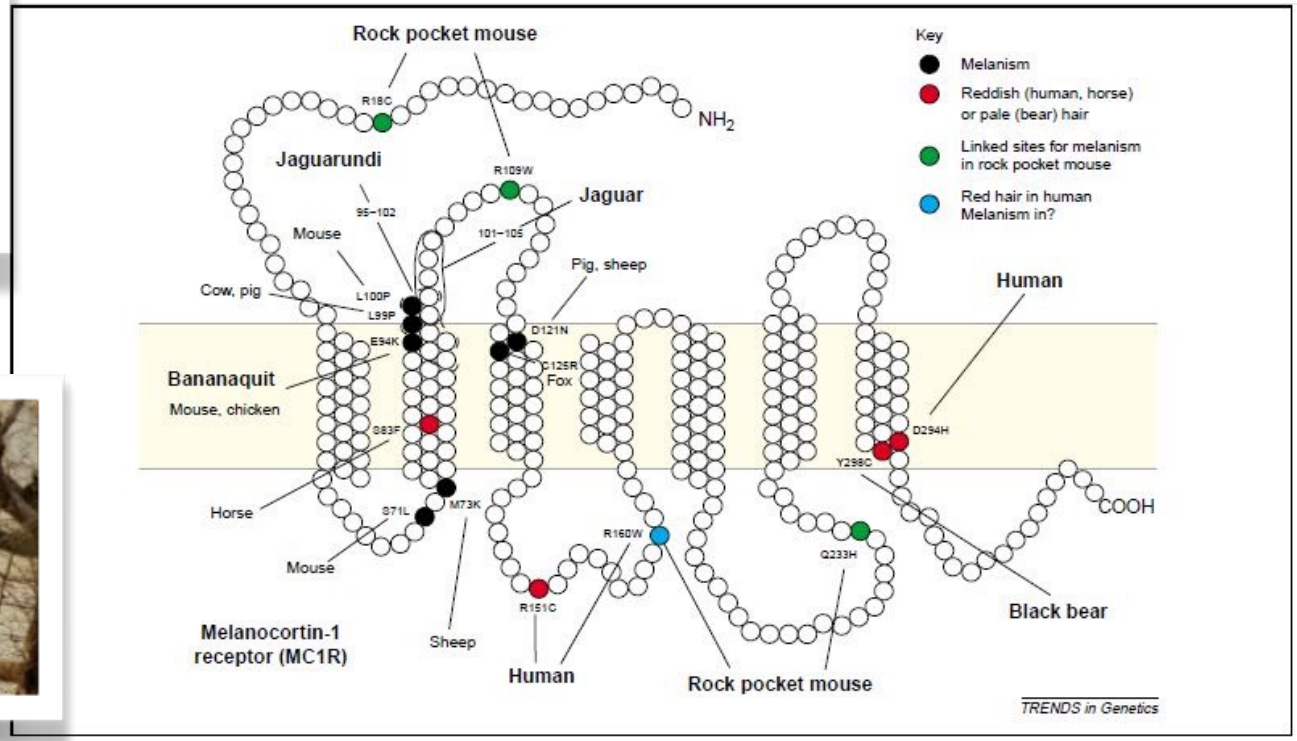


Figure 3. Melanocortin-1 receptor (*MC1R*) variants associated with coat colour changes in mammals and birds. The *MC1R* gene is depicted in the cell membrane of a melanocyte, with the extracellular surface facing up. The six species for which naturally occurring *MC1R* associations have been described are shown in bold. Residue numbering follows human *MC1R*. The broken black loop shows the eight amino acid deletion in jaguarundis and the solid black loop shows the five amino acid deletion in jaguar. Three further amino acid changes are possibly associated with melanism in jaguarundis: *P22L, 163V, Q310R* [14]. See Ref. [14] for references to other studies.

(this is a Jaguarundi…)

Image from:https://afarensis99.wordpress.com/2012/11/23/mutations-that-affect-phenotype/

THE SCIENCE BEHIND RED HAIR

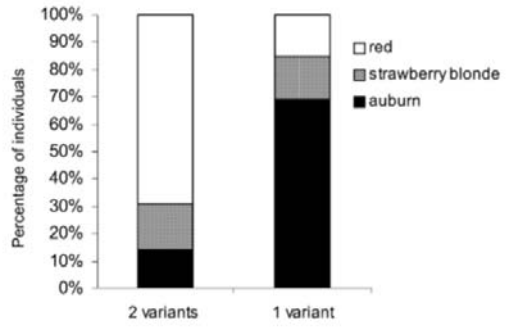


Figure 3. Shade of red hair in unrelated redheaded individuals with two (n = 84) or a single (n = 13) *MC1R* variant alleles (D84E, R142H, R151C, I155T, R160W, D294H, 86insA and 537insC) or no variants (n = 2).

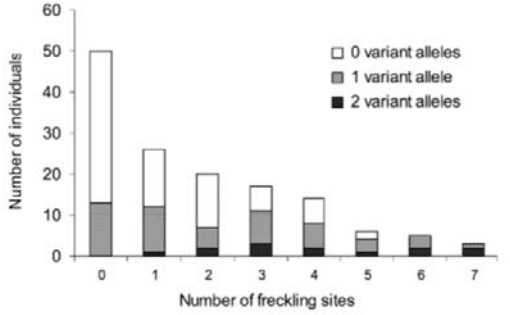


Figure 4. Relation between number of freckling sites and number of *MC1R* variants (D84E, R142H, R151C, I155T, R160W, D294H, 86insA and 537insC) in 141 controls.

From Flanagan et al...

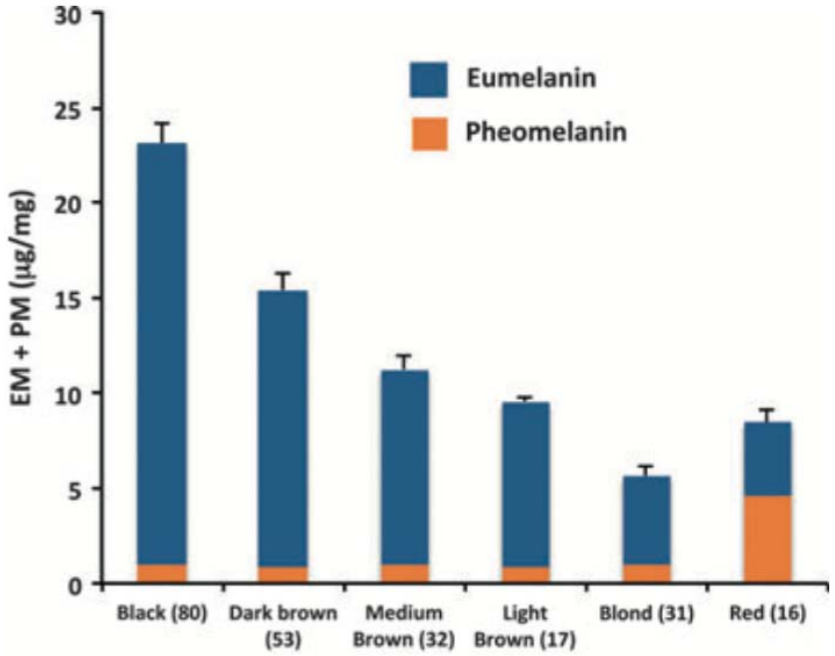


Figure 4 Contents of eumelanin and pheomelanin (the 'chemical' phenotype) in human hair samples (n = 228) of various colours (the 'visual' phenotype). PTCA and TTCA are used as markers for eumelanin and pheomelanin, respectively. Note that if we use 4-AHP as a marker for pheomelanin, its contents in eumelanic hairs (black to blond) become several-fold smaller than those shown in this figure. (Taken from ref. 38).

From Ito and Wakamatsu...

THE SCIENCE BEHIND RED HAIR

That's nice, but...
What do the melanocortin receptors do?

Melanocortin receptors are actively involved in adrenocortical steroidogenesis, immune and inflammatory responses, hypothalamic regulation of food intake, body weight, exocrine gland function and thermoregulation.

THE SCIENCE BEHIND RED HAIR

Receptor	Main sites of expression	Physiological functions	Disease phenotype of patients with loss-of-function mutations	OMIM
MC1R	Melanocytes, macrophage	Pigmentation, inflammation	Increased risk of skin cancers	155555
MC2R	Adrenal cortex	Adrenal steroidogenesis	Familial glucocorticoid deficiency	202200
MC3R	Central nervous system (CNS), gastrointestinal (GI) tract, Kidney	Energy homeostasis, inflammation	Obesity	155540
MC4R	CNS, spinal cord	Energy homeostasis, appetite regulation, erectile function	Obesity	155541
MC5R	Lymphocytes, exocrine cells	Exocrine function, regulation of sebaceous glands	Decreased production of sebaceous lipids in mice	600042

Image from: http://journal.frontiersin.org/article/10.3389/fendo.2013.00009/full

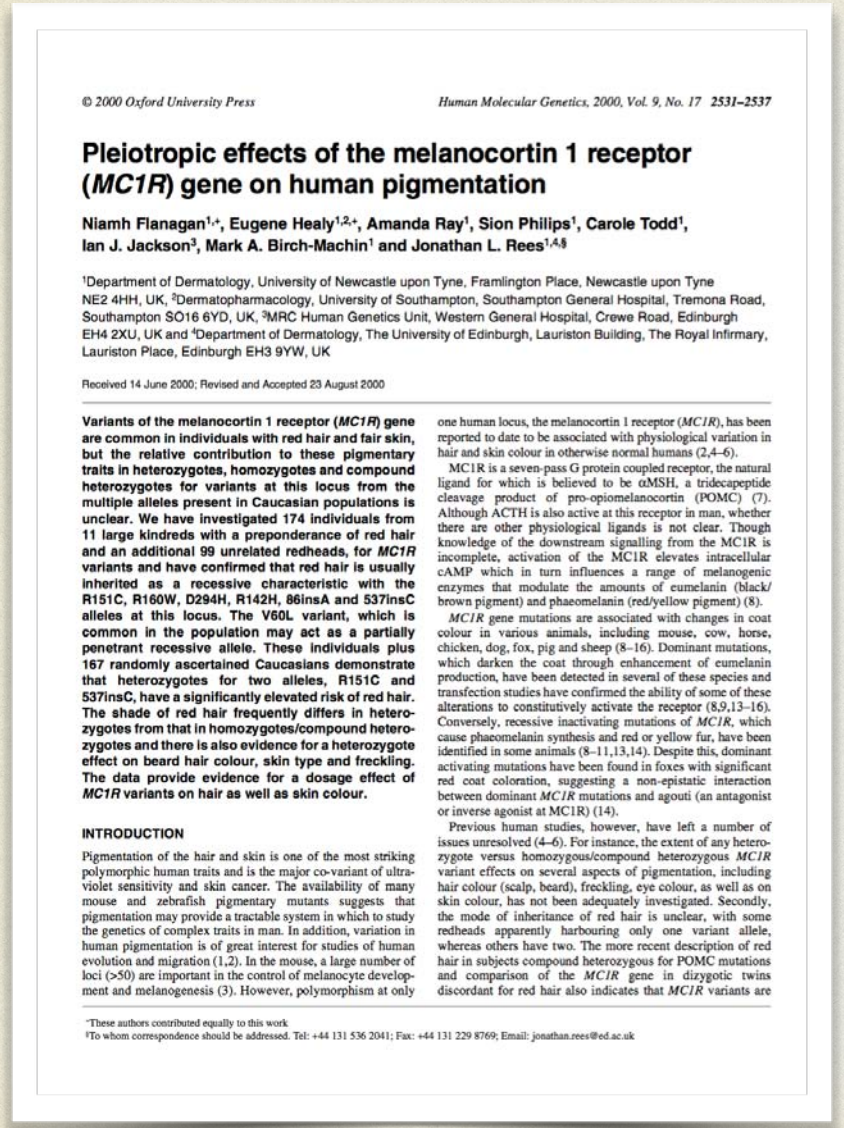
THE SCIENCE BEHIND RED HAIR

Also nice, but...

What DON'T the melanocortin receptors do??

Melanocortin receptors have nothing to do with beta agonists, beta antagonists, or acetylcholinesterase inhibitors...

REVIEW OF LITERATURE



Human Molecular Genetics, 2000, Vol. 9, No. 17 2531–2537

Pleiotropic effects of the melanocortin 1 receptor (*MC1R*) gene on human pigmentation

Niamh Flanagan[1,+], Eugene Healy[1,2,+], Amanda Ray[1], Sion Philips[1], Carole Todd[1], Ian J. Jackson[3], Mark A. Birch-Machin[1] and Jonathan L. Rees[1,4,§]

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Variants of the melanocortin 1 receptor (*MC1R*) gene are common in individuals with red hair and fair skin, but the relative contribution to these pigmentary traits in heterozygotes, homozygotes and compound heterozygotes for variants at this locus from the multiple alleles present in Caucasian populations is unclear. We have investigated 174 individuals from 11 large kindreds with a preponderance of red hair and an additional 99 unrelated redheads, for *MC1R* variants and have confirmed that red hair is usually inherited as a recessive characteristic with the R151C, R160W, D294H, R142H, 86insA and 537insC alleles at this locus. The V60L variant, which is common in the population may act as a partially penetrant recessive allele. These individuals plus 167 randomly ascertained Caucasians demonstrate that heterozygotes for two alleles, R151C and 537insC, have a significantly elevated risk of red hair. The shade of red hair frequently differs in heterozygotes from that in homozygotes/compound heterozygotes and there is also evidence for a heterozygote effect on beard hair colour, skin type and freckling. The data provide evidence for a dosage effect of *MC1R* variants on hair as well as skin colour.

INTRODUCTION

Pigmentation of the hair and skin is one of the most striking polymorphic human traits and is the major co-variant of ultraviolet sensitivity and skin cancer. The availability of many mouse and zebrafish pigmentary mutants suggests that pigmentation may provide a tractable system in which to study the genetics of complex traits in man. In addition, variation in human pigmentation is of great interest for studies of human evolution and migration (1,2). In the mouse, a large number of loci (>50) are important in the control of melanocyte development and melanogenesis (3). However, polymorphism at only one human locus, the melanocortin 1 receptor (*MC1R*), has been reported to date to be associated with physiological variation in hair and skin colour in otherwise normal humans (2,4–6).

MC1R is a seven-pass G protein coupled receptor, the natural ligand for which is believed to be αMSH, a tridecapeptide cleavage product of pro-opiomelanocortin (POMC) (7). Although ACTH is also active at this receptor in man, whether there are other physiological ligands is not clear. Though knowledge of the downstream signalling from the MC1R is incomplete, activation of the MC1R elevates intracellular cAMP which in turn influences a range of melanogenic enzymes that modulate the amounts of eumelanin (black/brown pigment) and phaeomelanin (red/yellow pigment) (8).

MC1R gene mutations are associated with changes in coat colour in various animals, including mouse, cow, horse, chicken, dog, fox, pig and sheep (8–16). Dominant mutations, which darken the coat through enhancement of eumelanin production, have been detected in several of these species and transfection studies have confirmed the ability of some of these alterations to constitutively activate the receptor (8,9,13–16). Conversely, recessive inactivating mutations of *MC1R*, which cause phaeomelanin synthesis and red or yellow fur, have been identified in some animals (8–11,13,14). Despite this, dominant activating mutations have been found in foxes with significant red coat coloration, suggesting a non-epistatic interaction between dominant *MC1R* mutations and agouti (an antagonist or inverse agonist at MC1R) (14).

Previous human studies, however, have left a number of issues unresolved (4–6). For instance, the extent of any heterozygote versus homozygous/compound heterozygous *MC1R* variant effects on several aspects of pigmentation, including hair colour (scalp, beard), freckling, eye colour, as well as on skin colour, has not been adequately investigated. Secondly, the mode of inheritance of red hair is unclear, with some redheads apparently harbouring only one variant allele, whereas others have two. The more recent description of red hair in subjects compound heterozygous for POMC mutations and comparison of the *MC1R* gene in dizygotic twins discordant for red hair also indicates that *MC1R* variants are

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Purpose

To ascertain the downstream effects of the MC1R gene on human pigmentation.

Sample Size

219 individuals from 11 families.

Key thoughts

Most redheads are homozygous or compound heterozygous for two variant MC1R alleles. The majority of the single variant redheads have auburn or strawberry blonde hair. Red hair is usually inherited as an autosomal recessive trait.

REVIEW OF LITERATURE

■ CLINICAL INVESTIGATIONS

Anesthesiology 2004; 101:279–83

Anesthetic Requirement Is Increased in Redheads

Edwin B. Liem, M.D., Chun-Ming Lin, M.D.,† Mohammad-Irfan Suleman, M.D.,‡ Anthony G. Doufas, M.D., Ph.D.,* Ronald G. Gregg, Ph.D.,§ Jacqueline M. Veauthier, Ph.D.,‖ Gary Loyd, M.D.,# Daniel I. Sessler, M.D.***

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. Therefore, the authors tested the hypothesis that the requirement for the volatile anesthetic desflurane is greater in natural redheaded than in dark-haired women.**

Methods: **The authors 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 nonmovement (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.**

Results: **The desflurane requirement in redheads (6.2 vol% [95% CI, 5.9–6.5]) was significantly greater than in dark-haired women (5.2 vol% [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 seems to be a distinct phenotype linked to anesthetic requirement in humans that can also be traced to a specific genotype.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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Received from the OUTCOMES RESEARCH™ Institute and the Departments of Anesthesiology, Biochemistry and Molecular Biology, and Pharmacology and Toxicology, University of Louisville, Louisville, Kentucky, and the Department of Chemistry, University of Texas, Austin, Texas. Submitted for publication September 9, 2003. Accepted for publication December 8, 2003. Supported by grant No. GM 061655 from the National Institutes of Health, Bethesda, Maryland; the Joseph Drown Foundation, Los Angeles, California; and the Commonwealth of Kentucky Research Challenge Trust Fund, Louisville, Kentucky. Dr. Veauthier is the recipient of an Postdoctoral Fellowship (5?32 GM20854) from the National Institutes of Health, Bethesda, Maryland. None of the authors have any financial interest in products related to this study. These data were presented in abstract form at the Annual Meeting of the American Society of Anesthesiologists, Orlando, Florida, October 12–16, 2002.

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.

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. Therefore, we tested the hypothesis that women with natural red hair have a greater desflurane requirement than women with dark hair.

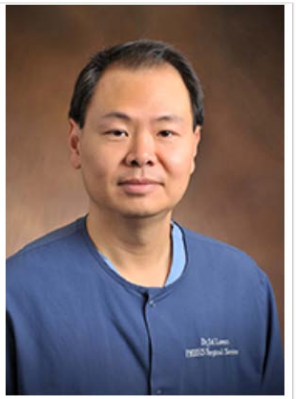
Materials and Methods

With approval of the University of Louisville Human Studies Committee and written informed consent, we recruited 20 white women aged between 18 and 40 yr, with natural bright red or dark (black or dark brown) hair. The study subjects were regarded as white 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 α of 0.05 and an estimate of the SD of 0.55.

Because it remains unclear whether sex could cause

Purpose

The authors tested the hypothesis that the requirement for the volatile anesthetic desflurane is greater in natural redheaded than in dark-haired women.



Sample Size

20 (10 redhead women, 10 dark-haired women).

Results

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.

	Red Hair	Dark Hair	*P* Value
No. of volunteers	10	10	—
Age, yr	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 temperature, °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

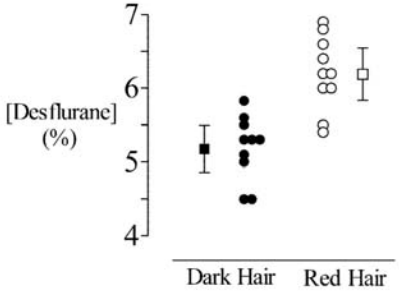
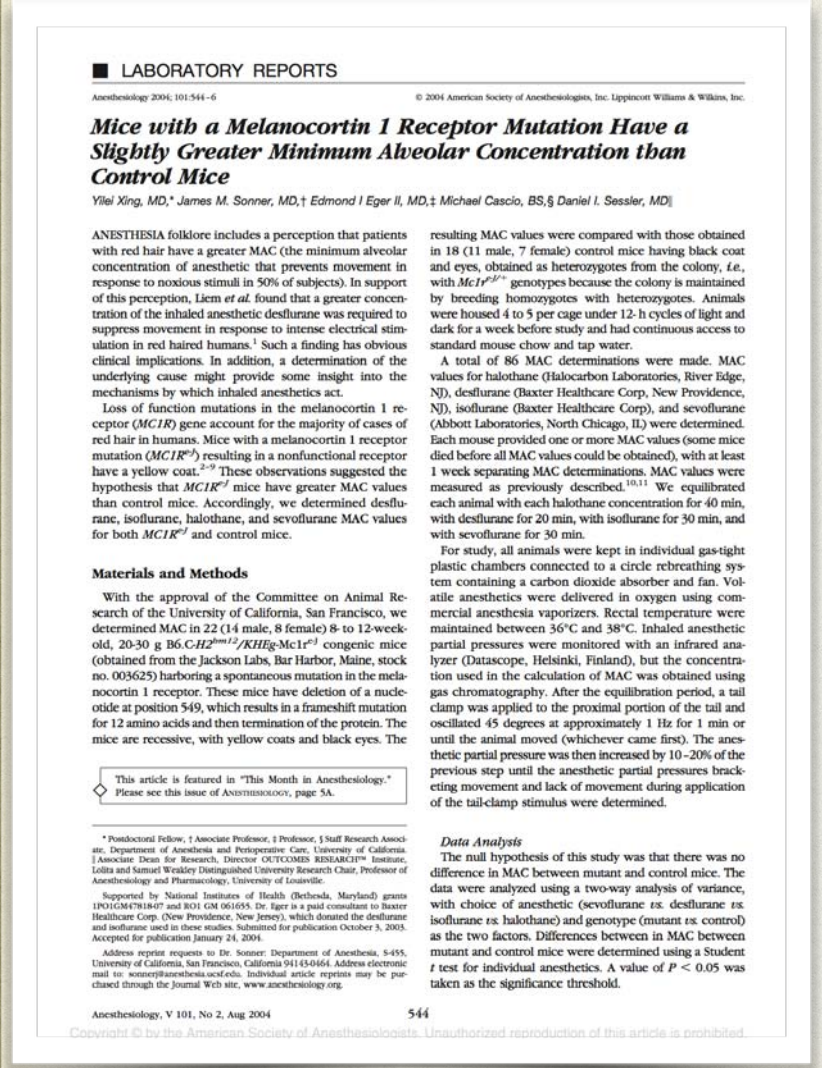


Fig. 1. Anesthetic requirement for individual participants (*circles*) with group means (*squares*) and 95% confidence intervals.

REVIEW OF LITERATURE



LABORATORY REPORTS

Anesthesiology 2004; 101:544–6

Mice with a Melanocortin 1 Receptor Mutation Have a Slightly Greater Minimum Alveolar Concentration than Control Mice

Yilei Xing, MD,* James M. Sonner, MD,† Edmond I Eger II, MD,‡ Michael Cascio, BS,§ Daniel I. Sessler, MD‖

ANESTHESIA folklore includes a perception that patients with red hair have a greater MAC (the minimum alveolar concentration of anesthetic that prevents movement in response to noxious stimuli in 50% of subjects). In support of this perception, Liem *et al.* found that a greater concentration of the inhaled anesthetic desflurane was required to suppress movement in response to intense electrical stimulation in red haired humans.[1] Such a finding has obvious clinical implications. In addition, a determination of the underlying cause might provide some insight into the mechanisms by which inhaled anesthetics act.

Loss of function mutations in the melanocortin 1 receptor (*MC1R*) gene account for the majority of cases of red hair in humans. Mice with a melanocortin 1 receptor mutation ($MC1R^{e/e}$) resulting in a nonfunctional receptor have a yellow coat.[2–9] These observations suggested the hypothesis that $MC1R^{e/e}$ mice have greater MAC values than control mice. Accordingly, we determined desflurane, isoflurane, halothane, and sevoflurane MAC values for both $MC1R^{e/e}$ and control mice.

Materials and Methods

With the approval of the Committee on Animal Research of the University of California, San Francisco, we determined MAC in 22 (14 male, 8 female) 8- to 12-week-old, 20–30 g B6.C-*H2*^{bm12}/*KhEg*-Mc1r$^{e/e}$ congenic mice (obtained from the Jackson Labs, Bar Harbor, Maine, stock no. 003625) harboring a spontaneous mutation in the melanocortin 1 receptor. These mice have deletion of a nucleotide at position 549, which results in a frameshift mutation for 12 amino acids and then termination of the protein. The mice are recessive, with yellow coats and black eyes. The resulting MAC values were compared with those obtained in 18 (11 male, 7 female) control mice having black coat and eyes, obtained as heterozygotes from the colony, i.e., with $Mc1r^{e/+}$ genotypes because the colony is maintained by breeding homozygotes with heterozygotes. Animals were housed 4 to 5 per cage under 12-h cycles of light and dark for a week before study and had continuous access to standard mouse chow and tap water.

A total of 86 MAC determinations were made. MAC values for halothane (Halocarbon Laboratories, River Edge, NJ), desflurane (Baxter Healthcare Corp, New Providence, NJ), isoflurane (Baxter Healthcare Corp), and sevoflurane (Abbott Laboratories, North Chicago, IL) were determined. Each mouse provided one or more MAC values (some mice died before all MAC values could be obtained), with at least 1 week separating MAC determinations. MAC values were measured as previously described.[10,11] We equilibrated each animal with each halothane concentration for 40 min, with desflurane for 20 min, with isoflurane for 30 min, and with sevoflurane for 30 min.

For study, all animals were kept in individual gas-tight plastic chambers connected to a circle rebreathing system containing a carbon dioxide absorber and fan. Volatile anesthetics were delivered in oxygen using commercial anesthesia vaporizers. Rectal temperature were maintained between 36°C and 38°C. Inhaled anesthetic partial pressures were monitored with an infrared analyzer (Datascope, Helsinki, Finland), but the concentration used in the calculation of MAC was obtained using gas chromatography. After the equilibration period, a tail clamp was applied to the proximal portion of the tail and oscillated 45 degrees at approximately 1 Hz for 1 min or until the animal moved (whichever came first). The anesthetic partial pressure was then increased by 10–20% of the previous step until the anesthetic partial pressures bracketing movement and lack of movement during application of the tail-clamp stimulus were determined.

Data Analysis

The null hypothesis of this study was that there was no difference in MAC between mutant and control mice. The data were analyzed using a two-way analysis of variance, with choice of anesthetic (sevoflurane *vs.* desflurane *vs.* isoflurane *vs.* halothane) and genotype (mutant *vs.* control) as the two factors. Differences between in MAC between mutant and control mice were determined using a Student *t* test for individual anesthetics. A value of $P < 0.05$ was taken as the significance threshold.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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Address reprint requests to Dr. Sonner: Department of Anesthesia, S-455, University of California, San Francisco, California 941 43-0464. Address electronic mail to: sonnerj@anesthesia.ucsf.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Sample Size

40 mice (22 mice with spontaneous MC1R mutation, with yellow coats and black eyes, 18 control mice with black coats and black eyes).

MC4R are mainly expressed in the nervous system and may influence nociception, hyperalgesia, and pain. The melanocortins, including adrenocorticotropic hormone (ACTH), α-melanocyte stimulating hormone (α-MSH), β-MSH, and γ-MSH, are a family of bioactive peptides that share similar structures and bind to the melanocortins receptors to conduct their biologic functions. Whereas all the melanocortins (ACTH, α-MSH, β-MSH, and γ-MSH) bind to MC1R, MC3R, MC4R, and MC5R to conduct their functions, ACTH binds only to MC2R.[18–20] Among the five melanocortin receptors in humans, MC1R has the highest affinity for α-MSH.[21] Phenotypic changes (*e.g.*,

Major Findings

There was a significant difference between recessive mice that were homozygous for the MC1R mutation and control mice. This effect was, however, small with only on average a 5.5% increase in MAC in mutant compared to control mice. There was no significant genotype/anesthetic interaction (*P* 0.200).

Key thoughts

MC1Rs are mainly found in the periphery, but they also are expressed in brain glial cells and in neurons of the ventral periaqueductal gray, a region known to modulate nociception A change in central a-MSH concentrations in *MC1R* mutant mice may be responsible for the increased MAC.

Discussion

We observed a significant ($P = 0.023$) difference in anesthetic requirement between recessive homozygous mice harboring two nonfunctional genes for the melanocortin 1 receptor, and control heterozygous mice with one functional and one nonfunctional gene for the melanocortin 1 receptor. Anesthetic requirement was studied for four clinical anesthetics (isoflurane, desflurane, sevoflurane, and halothane). Taken in aggregate for all MAC determinations and agents, mutant mice had, on average, a 5.5% increase in MAC. This result is consistent with the observation that red-headed people require more desflurane to produce immobility, but is smaller than the difference reported in humans.[1]

REVIEW OF LITERATURE

GENERAL ANESTHESIA 25

Midazolam causes less sedation in volunteers with red hair

[Le midazolam cause moins de sédation chez des volontaires aux cheveux roux]

Marlene V. Chua MD, Kentaro Tsueda MD, Anthony G. Doufas MD PhD

Purpose: We studied sedation, cognition, and mood during midazolam infusion in volunteers with red and non-red (blond or brown) hair, to test the hypothesis that patients with red hair may require more drugs to attain desired levels of sedation.

Methods: Twenty red and 19 non-red hair subjects were studied in a randomized, placebo-controlled cross-over design. Subjects were studied during placebo and midazolam at 30 ng·mL^{-1} target effect site concentration. Sedation was assessed using the observer's assessment of alertness/sedation (OAA/S) scale, the drowsiness visual analogue scale (VAS), and the bispectral index; cognition was assessed using the Repeatable Battery for Assessment of Neuropsychological Status; and mood was assessed using the bipolar form of the Profile of Mood States (POMS).

Results: Red hair volunteers showed significantly higher OAA/S ($P < 0.01$) and lower drowsiness VAS ($P < 0.05$) scores compared to non-red hair subjects during midazolam infusion. Visuospatial score was significantly higher in subjects with red compared to non-red hair during placebo and midazolam trials. Delayed memory score was significantly higher during midazolam infusion in subjects with red compared to non-red hair. There were no group differences in POMS during either trials.

Conclusion: Midazolam appears to cause significantly less sedation and cognitive impairment in red haired subjects.

Objectif : *Étudier la sédation, la fonction cognitive et l'humeur pendant une perfusion de midazolam chez des volontaires aux cheveux roux et non roux (blonds ou châtains) pour tester l'hypothèse voulant que chez les patients aux cheveux roux, il faut de plus grandes quantités de médicaments pour obtenir les niveaux de sédation désirés.*

Méthode : *Vingt sujets roux et 19 non roux ont participé à l'étude randomisée, croisée et contrôlée contre placebo. L'expérimentation a eu lieu pendant que la concentration cible au site effecteur était de 30 ng·mL^{-1} de midazolam ou de placebo. La sédation a été notée avec l'évaluation par un observateur de l'échelle d'attention/sédation (EOA/S), l'échelle visuelle analogique de somnolence (EVA) et l'index bispectral ; la fonction cognitive par la Batterie de tests répétables de l'évaluation de l'état neuropsychologique et l'humeur par la forme bipolaire du Profile of Mood States (POMS).*

Résultats : *Avec le midazolam, les volontaires roux, comparés aux non roux, ont présenté des scores significativement plus élevés à l'échelle d'EOA/S ($P < 0,01$) et moins de somnolence à l'EVA ($P < 0,05$). Le score visuospatial a été significativement plus élevé chez les sujets roux sous placebo ou midazolam. Le score de mémoire différée a été significativement plus élevé avec le midazolam chez les sujets roux. Les scores au POMS n'ont présenté aucune différence intergroupe pendant une épreuve ou l'autre.*

Conclusion : *Le midazolam semble causer moins de sédation et d'altération de la fonction cognitive chez les sujets aux cheveux roux.*

ANECDOTAL descriptions exist that subjects with red hair may faint easily and are difficult to anesthetize.[1] A mail survey of anesthesiologists[A] has shown that red-haired patients are perceived to have a propensity for drug hypersensitivity, airway difficulties, hemodynamic instability, dysrrhythmias, combativeness and confusion at anesthesia emergence, nausea/vomiting, and bleeding. Our clinical observations suggest that patients with red hair may also require more drugs to attain desired levels of sedation.

A *Algarra NN, Foust JA, Green SM, Hardy AE, Hendrix SR.* Perception of certified registered nurse anesthetists in Georgia regarding anesthesia morbidity in patients with red hair. Houston: University of Texas Health Science Center, School of Nursing, 1994: 1–5.

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CAN J ANESTH 2004 / 51: 1 / pp 25–30

Observer's assessment of alertness/sedation scale

The results of the study suggest that red haired subjects appear to be less sedated than are those with non-red hair for a given plasma concentration of midazolam. Change in the melanocortin system may be a part of the mechanism for the apparent resistance to the sedative effect of midazolam observed in red-haired subjects.

Purpose

We studied sedation, cognition, and mood during midazolam infusion in volunteers with red and non-red (blonde or brown) hair, to test the hypothesis that patients with red hair may require more drugs to attain desired levels of sedation.

Discussion

We found that the OAA/S score was significantly higher and the VAS score for drowsiness was significantly lower in subjects with red compared to non-red hair during midazolam infusion. The midazolam concentration used in this study was equivalent to that expected approximately 30 min after a bolus injection of 2 mg midazolam in a 70-kg subject.[4] Sedation in

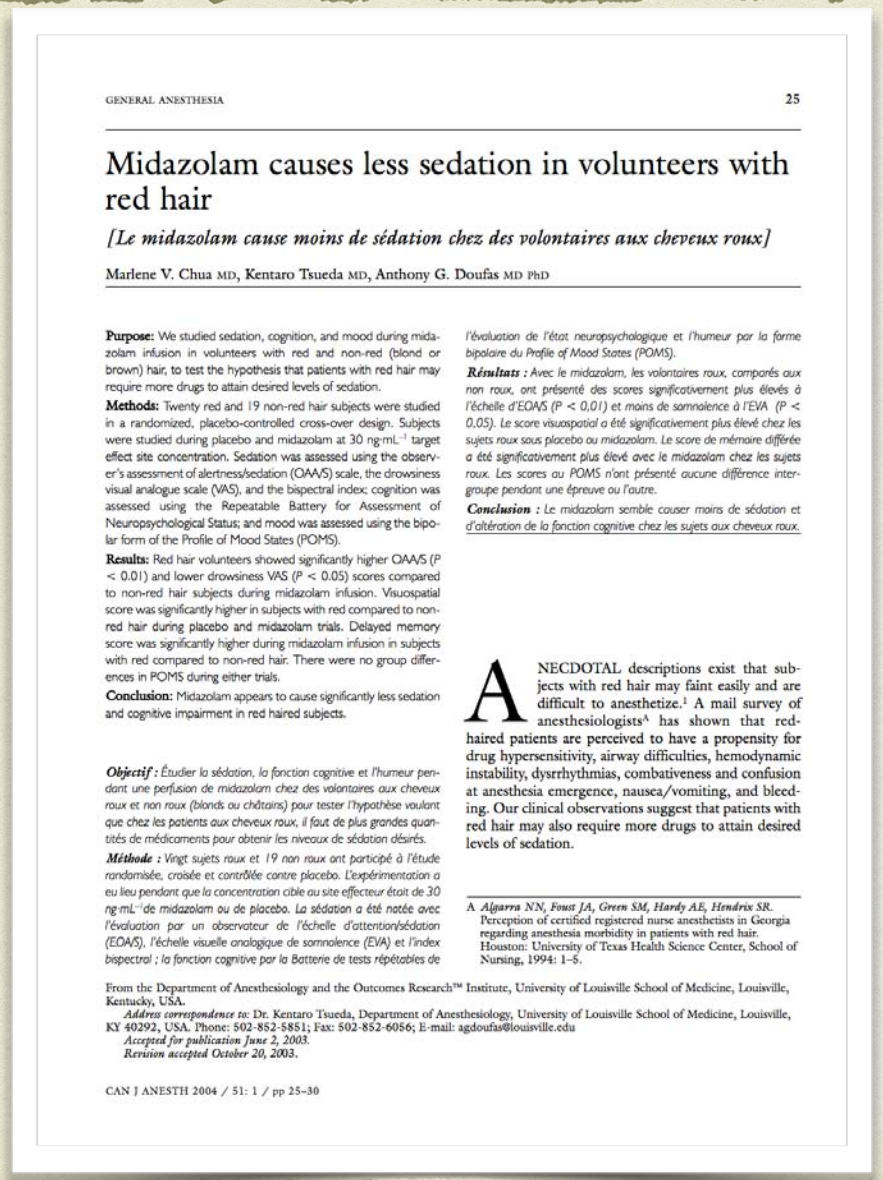
Sample Size

39 (20 red and 19 non-red hair subjects).

Key thoughts

15 red-haired volunteers had 28 previous surgical procedures. Ten of these subjects had 18 general anesthetics, and ten subjects had 11 maxillary and/or mandibular nerve blocks for dental procedures. Three red-haired subjects experienced intraoperative awareness, and four other subjects required repeated injections of local anesthetics for dental extraction (resistance to loco-regional anesthesia)… none in the control group experienced any unusual event.

REVIEW OF LITERATURE



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Proopiomelanocortin (POMC) is synthesized and cleaved into peptides that include α-melanocyte-stimulating hormone (α-MSH), adrenal corticotrophic hormone (ACTH), and ß-endorphine in the pituitary gland, gastrointestinal tract, gonads, placenta, and skin.[9] Neuropeptides, ACTH and α-MSH, are potent modulators of cognitive function and neurobehavioural activities in animals and humans.[10,11] The peptides

The takeaway? Increased benzodiazepine requirement in patients with MC1R variant is primarily due to the effect of the **α**-melanocyte-stimulating hormone (**α**-MSH) and adrenal corticotrophic hormone (ACTH)…

REVIEW OF LITERATURE

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.

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MC1R expression has been identified in the pituitary, glial cells, and in the periaqueductal gray matter, but primarily exists peripherally.

As the central nervous system is NOT a major expression site of MC1R, it remains UNCLEAR why MC1R variance should alter anesthetic requirement.

A possible explanation?? "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."

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REVIEW OF LITERATURE

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REVIEW

Pharmacogenetics and anesthesiologists

Helen F Galley†, Amr Mahdy & Damon A Lowes

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Genetic variation contributes to an individual's sensitivity and response to a variety of drugs important to anesthetic practice. Early insights into the clinical impact of pharmacogenetics were provided by anesthesiology – investigations into prolonged apnea after succinylcholine administration, thiopental-induced porphyria and malignant hyperthermia contributed to the novel science of pharmacogenetics in the early 1960s. Genetic polymorphisms involved in pharmacokinetics (absorption, distribution, metabolism, and excretion of drugs) and pharmacodynamics (receptors, ion channels and enzymes) can affect an individual's response to the drugs used in anesthetic practice. In addition, genetic variation in proteins directly unrelated to drug action or metabolism can influence responses to environmental changes that occur during anesthesia. This review will summarize the current knowledge of genetic variation in response to drugs relevant to anesthesia, and how this impacts upon clinical practice.

There is much heterogeneity in the way individuals respond to anesthesia and surgery, in terms of both toxicity and therapeutic effects. These differences in response, which can ultimately be linked to patient outcome, can be attributed in part to a variety of factors. These factors include age, sex and race, the etiology and severity of pre-existing disease, the type of surgery, therapeutic interventions and drug interactions, hepatic and renal function, nutritional status and any co-morbidity (Figure 1), and, of course, genetics. Inherited differences in proteins involved in the pharmacokinetics and pharmacodynamics of drugs used in the practice of anesthesia, including anesthetic agents themselves, analgesics, antiemetics, inotropes, antiarrythmics, and muscle relaxants, influence the efficacy and toxicity of drugs, and hence influence outcome from surgery and anesthesia. Other inherited genetic factors seemingly unrelated to anesthetic metabolism or action can also influence interaction with anesthesia.

The history of pharmacogenetics & anesthesiology

During the Second World War, it was noted that some black soldiers who were given primaquine as prophylaxis against malaria developed hemolytic anemia, whilst others did not. Subsequently, interindividual differences in the activity of the enzyme glucose-6-phosphate dehydrogenase were found to be responsible for these variable reactions [1]. In the 1950s, clinical evidence of inherited differences in responses to drugs used in anesthesia continued to emerge. Prolonged muscle relaxation after suxamethonium administration was explained by an inherited deficiency of the enzyme cholinesterase [2]. In the late 1980s, the occurrence of diplopia and blurred vision following administration of the antiarrhythmic drug sparteine, and severe orthostatic hypotension following treatment with the antihypertensive agent debrisoquine in some individuals led to the discovery of a genetic polymorphism that affects the drug-metabolizing enzyme cytochrome P450 (CYP)2D6 [3]. This was a major breakthrough toward understanding the molecular genetic basis for inherited differences in drug disposition and metabolism, and the implications of this for the anesthesiologist.

Genetic polymorphisms may affect drug action via effects on pharmacokinetics or pharmacodynamics. Polymorphisms elsewhere can also affect responses to anesthesia. Not all polymorphisms that affect pharmaco-kinetics or -dynamics are clinically important. However, the likelihood of a clinically significant event is greater if:

- The drug is commonly used in clinical practice
- The drug has a narrow therapeutic range
- The defective metabolic pathway is quantitatively significant in determining the overall fate of the compound in the body
- Therapeutic alternatives are limited or absent

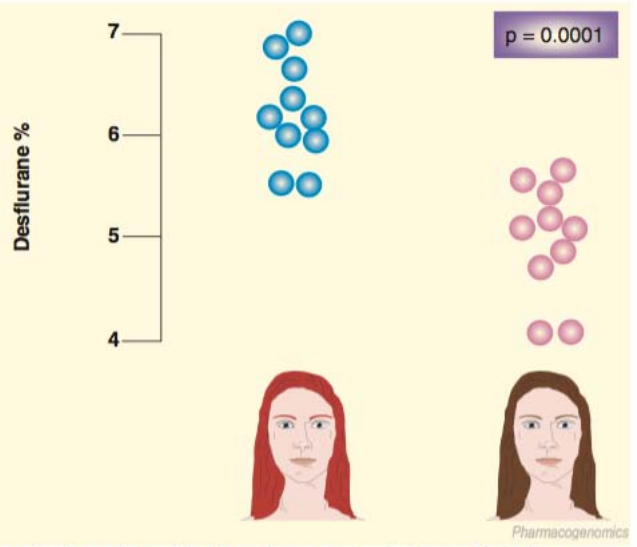
Pharmacokinetics

Drug-metabolizing enzymes

These enzymes are usually classified as either Phase I enzymes, which introduce a polar group into the drug molecule (oxidation, reduction or hydrolysis) or Phase II, which conjugate drugs to endogenous hydrophilic substances to make

Keywords: analgesia, anesthesia, anesthesiology, genetics, pharmacodynamics, pharmacokinetics, polymorphism

Figure 2. The difference in desflurane anesthetic requirements in ten naturally red-headed women and ten dark-haired women.



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 painful electrical stimulation 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.
Redrawn from data presented in [57].

REVIEW OF LITERATURE

DOI: 10.1111/j.1468-3083.2011.04278.x JEADV

INVITED ARTICLE

Diversity of human hair pigmentation as studied by chemical analysis of eumelanin and pheomelanin

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Abstract

Hair colour is one of the most conspicuous phenotypes in humans, ranging from black, brown, blond to red. This diversity arises mostly from the quantity and ratio of the black-dark brown eumelanin and the reddish-brown pheomelanin. To study the chemical basis underlying the diversity of hair colour, we have developed several chemical methods to quantify those two pigments. Alkaline H_2O_2 oxidation affords pyrrole-2,3,5-tricarboxylic acid (PTCA) as a eumelanin marker and thiazole-2,4,5-tricarboxylic acid (TTCA) as a pheomelanin marker. Pheomelanin can also be analysed as 4-amino-3-hydroxyphenylalanine (4-AHP) after hydroiodic acid hydrolysis. Using those methods, we evaluated the contents of eumelanin and pheomelanin (the 'chemical' phenotype) in human hairs of black, dark brown, brown, light brown, blond and red colour (the 'visual' phenotype). Eumelanin contents decrease in that order, with a trace but constant level of pheomelanin, except for red hair which contains about equal levels of pheomelanin and eumelanin. Thus, the chemical phenotype correlates well with the visual phenotype. The genotype of melanocortin-1 receptor (*MC1R*), a gene regulating the red hair phenotype, is predictive of hair melanin expressed as the log value of eumelanin to pheomelanin ratio, with a dosage effect evident. Hair melanin contents were also analysed in patients with various hypopigmentary disorders including Hermansky–Pudlak syndrome, Menkes disease, proopiomelanocortin deficiency, cystinosis, malnutrition and trace metal deficiency. The chemical phenotype helped evaluate the precise effects of each disease on pigmentation. In studies of human hair, the chemical phenotype will find more and more application as an objective measure of pigmentation.

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Conflict of interest

None declared.

Funding sources

This work was supported, in part, by a grant from the Japan Society for the Promotion of Science (JSPS) (No. 20591357).

Key points

- Diversity of hair colour arises mostly from the quantity and ratio of the black-dark brown eumelanin and the reddish-brown pheomelanin.
- 'Visual' inspection of hair colour is not only subjective but also qualitative. Therefore, we developed 'chemical' methods to analyse those two pigments objectively and quantitatively.
- Eumelanin can be analysed as a specific degradation product, pyrrole-2,3,5-tricarboxylic acid after alkaline H_2O_2 oxidation.
- Pheomelanin can be analysed as specific degradation products, thiazole-2,4,5-tricarboxylic acid (TTCA) after alkaline H_2O_2 oxidation or 4-amino-3-hydroxyphenylalanine (4-AHP) after hydroiodic acid hydrolysis.
- The 'chemical' phenotype of human hairs correlates well with the 'visual' phenotype. Thus, black, dark brown, brown, light brown and blond hairs are eumelanic with melanin content in this order, while only red hairs contain equal amounts of eumelanin and pheomelanin.
- Pathologically hypopigmented hairs can also be analysed with those methods to obtain a deeper understanding of the biochemical basis of the disease.
- The alkaline H_2O_2 oxidation method is simple and reproducible, and thus is suitable for broader use among researchers who do not have special expertise in analytical chemistry.

Introduction

Hair pigmentation is one of the most conspicuous phenotypes of humans. It ranges in colour from black, dark brown, brown, light brown and blond to red with subtle hues in each category. Hair colour has an enormous cosmetic and social impact as exemplified

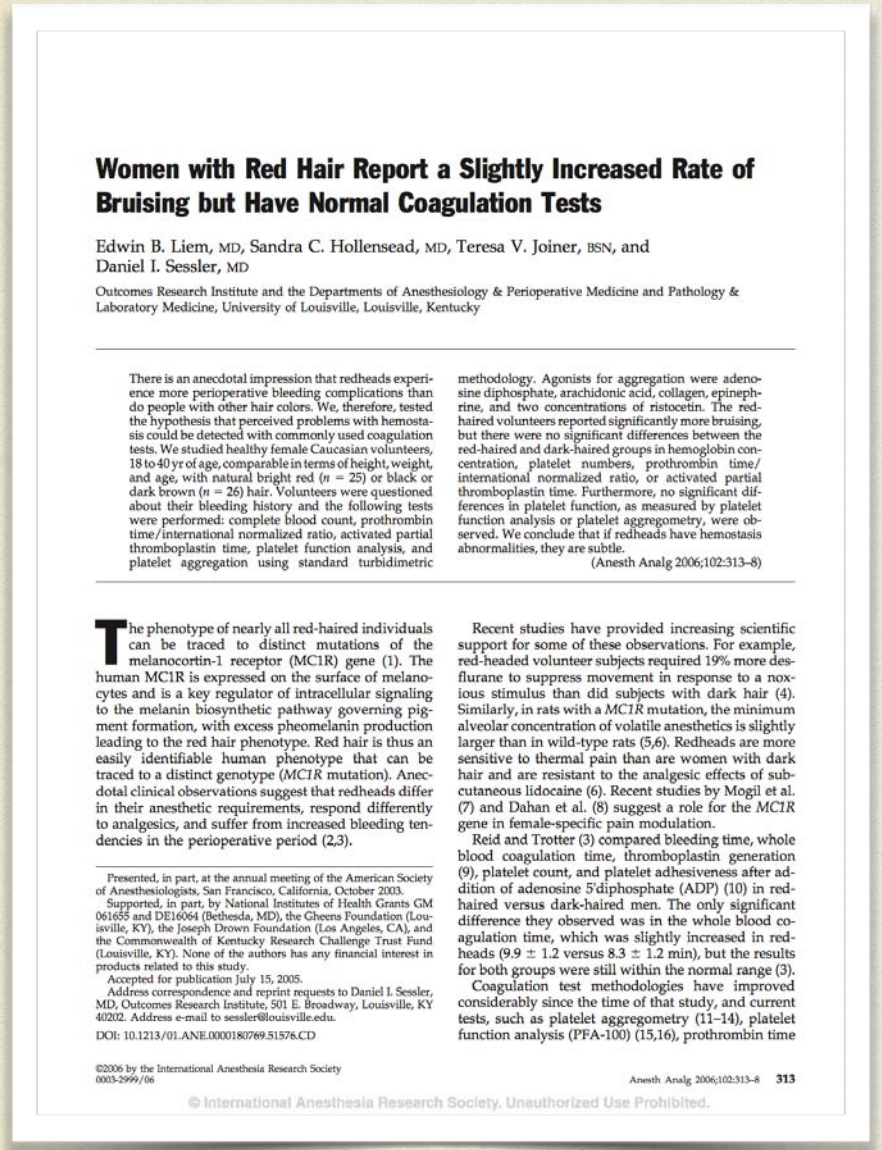
Purpose

We examined how the MC1R genotype affects the chemical phenotype by measuring the contents of eumelanin and pheomelanin in a Northern British population (n = 89).

Major Findings

The master regulator of pigment-type switching is the MC1R. When a-MSH binds to the MC1R on the plasma membrane of melanocytes, adenylate cyclase is activated through the stimulatory G-protein, raising levels of the second messenger cAMP, thereby activating the melanogenic transcription factor MITF.

REVIEW OF LITERATURE



Women with Red Hair Report a Slightly Increased Rate of Bruising but Have Normal Coagulation Tests

Edwin B. Liem, MD, Sandra C. Hollensead, MD, Teresa V. Joiner, BSN, and Daniel I. Sessler, MD

Outcomes Research Institute and the Departments of Anesthesiology & Perioperative Medicine and Pathology & Laboratory Medicine, University of Louisville, Louisville, Kentucky

There is an anecdotal impression that redheads experience more perioperative bleeding complications than do people with other hair colors. We, therefore, tested the hypothesis that perceived problems with hemostasis could be detected with commonly used coagulation tests. We studied healthy female Caucasian volunteers, 18 to 40 yr of age, comparable in terms of height, weight, and age, with natural bright red ($n = 25$) or black or dark brown ($n = 26$) hair. Volunteers were questioned about their bleeding history and the following tests were performed: complete blood count, prothrombin time/international normalized ratio, activated partial thromboplastin time, platelet function analysis, and platelet aggregation using standard turbidimetric methodology. Agonists for aggregation were adenosine diphosphate, arachidonic acid, collagen, epinephrine, and two concentrations of ristocetin. The red-haired volunteers reported significantly more bruising, but there were no significant differences between the red-haired and dark-haired groups in hemoglobin concentration, platelet numbers, prothrombin time/international normalized ratio, or activated partial thromboplastin time. Furthermore, no significant differences in platelet function, as measured by platelet function analysis or platelet aggregometry, were observed. We conclude that if redheads have hemostasis abnormalities, they are subtle.

(Anesth Analg 2006;102:313–8)

The phenotype of nearly all red-haired individuals can be traced to distinct mutations of the melanocortin-1 receptor (MC1R) gene (1). 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, with excess pheomelanin production leading to the red hair phenotype. Red hair is thus an easily identifiable human phenotype that can be traced to a distinct genotype (*MC1R* mutation). Anecdotal clinical observations suggest that redheads differ in their anesthetic requirements, respond differently to analgesics, and suffer from increased bleeding tendencies in the perioperative period (2,3).

Recent studies have provided increasing scientific support for some of these observations. For example, red-headed volunteer subjects required 19% more desflurane to suppress movement in response to a noxious stimulus than did subjects with dark hair (4). Similarly, in rats with a *MC1R* mutation, the minimum alveolar concentration of volatile anesthetics is slightly larger than in wild-type rats (5,6). Redheads are more sensitive to thermal pain than are women with dark hair and are resistant to the analgesic effects of subcutaneous lidocaine (6). Recent studies by Mogil et al. (7) and Dahan et al. (8) suggest a role for the *MC1R* gene in female-specific pain modulation.

Reid and Trotter (3) compared bleeding time, whole blood coagulation time, thromboplastin generation (9), platelet count, and platelet adhesiveness after addition of adenosine 5′diphosphate (ADP) (10) in red-haired versus dark-haired men. The only significant difference they observed was in the whole blood coagulation time, which was slightly increased in redheads (9.9 ± 1.2 versus 8.3 ± 1.2 min), but the results for both groups were still within the normal range (3).

Coagulation test methodologies have improved considerably since the time of that study, and current tests, such as platelet aggregometry (11–14), platelet function analysis (PFA-100) (15,16), prothrombin time

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0003-2999/06

Purpose

There is an anecdotal impression that redheads experience more perioperative bleeding complications than do people with other hair colors. We, therefore, tested the hypothesis that perceived problems with hemostasis could be detected with commonly used coagulation tests.

Sample Size

51 “healthy” Caucasian females, 25 redheads, 26 women with dark brown or black hair, 18-40 years old.

Key thoughts

Redhead women tended to report a history of easy bruising, however no change was noted in typical coagulation studies.

REVIEW OF LITERATURE

The presumed increased bleeding tendency in red-haired individuals is not associated with von Willebrand factor antigen levels in older individuals

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Red-haired individuals are known for their reputation of increased bleeding during surgical procedures and in women after childbirth [1]. However, only a few sound scientific studies have been performed to assess the association between red hair and bleeding. In a small study performed by Liem *et al.*, [2] women with red hair indeed reported a slightly increased rate of bruising. Reid *et al.* have investigated a limited number of coagulation parameters in red-haired vs. black-haired males. They found all laboratory results to be within the normal range [3]. Another previous study examined both primary and secondary hemostasis tests, including activated partial thromboplastin time (APTT), prothrombin time (PT), platelet aggregometry and platelet function analysis (PFA-100), in 25 healthy women with red hair and compared this with a control group of 26 dark-haired women [2]. Also in this study no differences were observed between the two groups for these global tests. However, it is known that the PFA-100 is not very sensitive to detect mildly decreased von Willebrand factor (VWF) levels. In addition, they observed a slightly lower high-dose, ristocetin-induced platelet aggregation (RIPA) in red-haired (87%) vs. in black-haired women (93%, $P = 0.06$). This observation led Favaloro [4] to propose that VWF may play a role in the red-hair associated bleeding phenotype, as the RIPA test is dependent on plasma VWF. In both the above-mentioned coagulation studies, VWF levels were not measured [2,3], whereas it is known that reduced levels of VWF may confer a risk factor for bleeding, even in individuals that have not been diagnosed with von Willebrand disease [5]. This led us to assess the association between hair color and VWF levels in a large cohort of nearly 4000 healthy individuals.

For this study, we included participants from the Rotterdam Study (RS), an ongoing, prospective, population-based cohort study among individuals of 55 years and older living in a suburb in the city of Rotterdam, the Netherlands, of whom > 90% are Caucasian [6]. Out of 3957 individuals, plasma was available for VWF determination and hair color (when young) was known for 97%.

Fasting venous blood samples were collected in citrated tubes and plasma was stored at −80 °C. VWF antigen (VWF:Ag) was determined with an in-house ELISA with polyclonal rabbit anti-human VWF antibodies and horseradish-peroxidase-conjugated anti-human VWF antibodies (DakoCytomation, Glostrup, Denmark) for catching and tagging, respectively. The intra-assay coefficient of variation was 5.8% and the inter-assay coefficient of variation was 7.8% [7]. Hair color when young was self-reported and classified as red, fair/blond, black or brown.

The characteristics of the study population are shown in the Table 1. The mean (standard deviation [SD]) age of the total study group was 65.7 (7.0). Of the included individuals 221 (57.8%) were female.

VWF:Ag levels for the different hair colors are given in the Table 1. No clear difference was observed between the groups. Red-haired individuals ($n = 104$) had VWF:Ag mean (range) levels of 1.39 IU dL^{-1} (0.4–3.3). VWF:Ag was 1.41 IU dL^{-1} (0.3–8.4) for fair hair ($n = 860$), 1.36 IU dL^{-1} (0.3–7.8) for brown hair ($n = 2511$) and 1.36 IU dL^{-1} (0.20–5.80) for black-haired individuals ($n = 369$). Using a linear regression model, VWF levels were significantly dependent upon age (beta = 0.02, SE 0.001, $P < 0.001$) and sex (beta = −0.06, SE 0.02, $P = 0.001$), but not of hair color (beta = 0.03, SE 0.06, $P = 0.65$). When blood group was included in the linear regression model the beta increased to 0.06, however, this was still not significant ($P = 0.323$). Low VWF levels, defined as a level < 5% of all individuals, were evenly distributed over all hair colors ($P = 0.49$, corrected for blood group). We observed a slightly higher frequency of blood group O in the

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Purpose

To assess the association between hair color and vWF levels in a large cohort of nearly 4000 healthy individuals.

Findings

Studies performed so far on the association between red hair and more pronounced bleeding have not yet revealed that this is caused by changes in coagulation parameters; no clear difference was observed between the groups.

Key thoughts

Other factors outside the coagulation mechanism may influence the bleeding risk in individuals undergoing surgery, including vascular factors. Several studies have reported an increased risk of hernia formation in red-haired individuals, which may be linked to collagen synthesis.

REVIEW OF LITERATURE

Anaesth Intensive Care 2012; 40: 683-689

The effect of hair colour on anaesthetic requirements and recovery time after surgery

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SUMMARY

Patients with red hair are much more likely to have a variant of the melanocortin-1 receptor gene and this may affect sensitivity to general anaesthetics and pain response. We did a prospective, matched cohort study of 468 healthy adult patients undergoing general anaesthesia for elective surgery. All patients received an inhalational general anaesthetic. Anaesthetic drugs and doses used, hypnotic depth, recovery times, pain scores and quality of recovery scores were recorded. More men than women had red hair, so we did subgroup and multivariable analyses to account for this imbalance. There was no significant difference in recovery times, pain scores or quality of recovery scores in those with red hair. After adjusting for age, sex, American Society of Anesthesiologists physical status and duration of surgery, the recovery ratio for time to eye-opening in redheads was comparable to those with black or brown hair, 0.82 (0.57-1.19), $P=0.30$. We found no evidence that patient hair colour affects anaesthetic requirements or recovery characteristics in a broad range of surgical procedures.

Key Words: redhead, gender, general anaesthesia

There is some evidence suggesting that redheads are less sensitive to general anaesthetics and this has been linked to variants of the melanocortin-1 receptor (MC1R) gene[1,2]. This implies that redheads may be more likely to awaken during or early after anaesthesia when compared with those with other hair colours receiving the same doses of anaesthetic agents.

Natural hair colour is genetically determined, due to variation in the amount, type, and packaging of melanin produced by melanocytes[4-7]. Melanin is the substance that gives skin, hair and eyes their colour, dependent on the relative amounts of the two forms of melanin, eumelanin and pheomelanin. People who produce mostly eumelanin tend to have brown or black hair; those who produce mostly pheomelanin tend to have red or blond hair[4,5]. There is a natural range of skin and hair colour, which is controlled by multiple pigmentation genes in a complex manner. Not all of these genes are as yet known, but several key genes have been characterised[4,8]. In humans the 'red hair colour' (RHC) phenotype is associated with allelic variants of the MC1R gene[5]. Mutations within this gene that reduce the function of the MC1R switch melanin synthesis to favour pheomelanin[4,8]. Valherde et al[5] found at least one variant allele in 82% of individuals with red hair, 33% of those with blond/fair hair, and less than 20% of those with brown/black hair; changes in both alleles were exclusively associated with RHC (29%). Subsequent association, familial and functional studies have supported the role of mutations that significantly impair the function of the MC1R in the RHC phenotype in caucasians[8-11].

The MC1R is a member of a group of melanocortin receptors that are active in cells involved in adrenocortical steroidogenesis, and the body's immune and inflammatory responses, hypothalamic regulation of food intake, body weight, exocrine gland function and thermoregulation[12,13]. A few previous studies have found that red hair may indicate a reduced sensitivity to general anaesthetics[1] and/or an altered pain response[13-16]. In view of the limited data available we set out to examine the effects of hair colour on requirements and response to general anaesthesia, and on recovery from anaesthesia, in a cohort study in adults undergoing general anaesthesia for elective surgery.

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Purpose

To examine the effects of hair colour on requirements and response to general anaesthesia, and on recovery from anaesthesia, in a cohort study in adults undergoing general anaesthesia for elective surgery.

Sample Size

Prospective, matched cohort study of 468 healthy adult patients (ASA I or II).

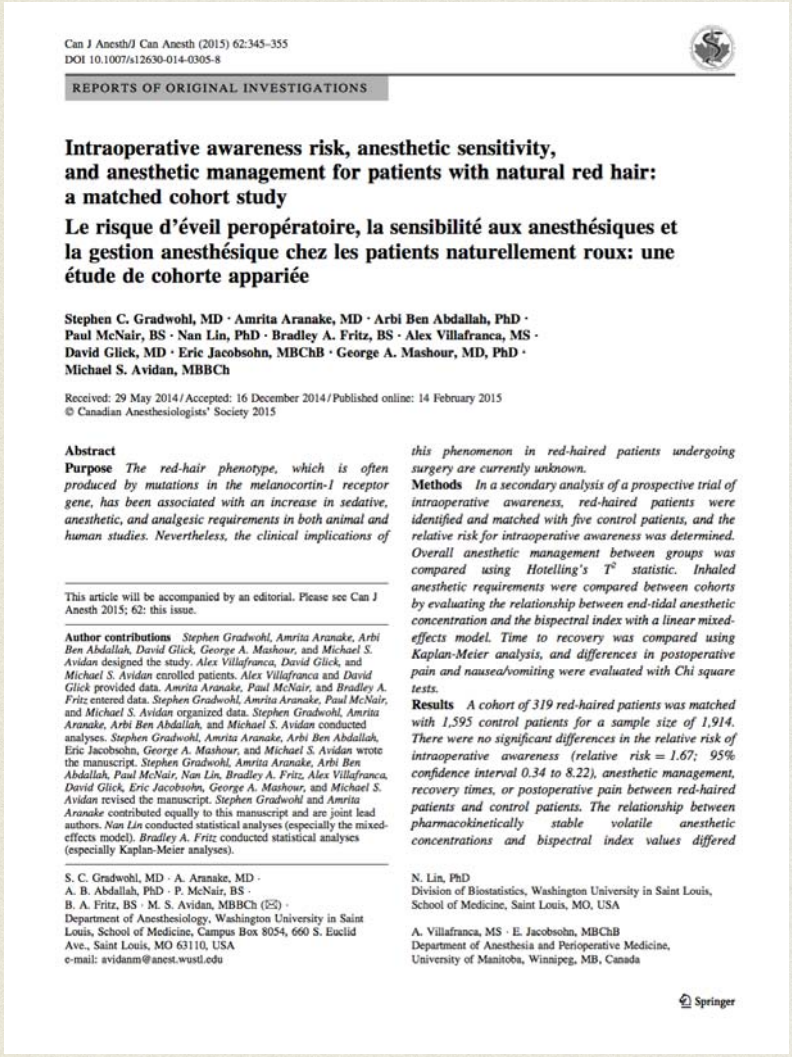
Findings

We found no evidence, that redheads had increased anesthetic requirement or faster speed of recovery after surgery. Nor was there any evidence of a difference in pain response (as measured by morphine requirement), pain intensity (as measured by a numerical rating scale) or other adverse effects after anaesthesia and surgery.

Key thoughts

Largely disputes claims made by Liem et al., as well as others. And basically everything I've said thus far…

REVIEW OF LITERATURE



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DOI 10.1007/s12630-014-0305-8

REPORTS OF ORIGINAL INVESTIGATIONS

Intraoperative awareness risk, anesthetic sensitivity, and anesthetic management for patients with natural red hair: a matched cohort study

Le risque d'éveil peropératoire, la sensibilité aux anesthésiques et la gestion anesthésique chez les patients naturellement roux: une étude de cohorte appariée

Stephen C. Gradwohl, MD · Amrita Aranake, MD · Arbi Ben Abdallah, PhD · Paul McNair, BS · Nan Lin, PhD · Bradley A. Fritz, BS · Alex Villafranca, MS · David Glick, MD · Eric Jacobsohn, MBChB · George A. Mashour, MD, PhD · Michael S. Avidan, MBBCh

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Abstract

Purpose *The red-hair phenotype, which is often produced by mutations in the melanocortin-1 receptor gene, has been associated with an increase in sedative, anesthetic, and analgesic requirements in both animal and human studies. Nevertheless, the clinical implications of this phenomenon in red-haired patients undergoing surgery are currently unknown.*

Methods *In a secondary analysis of a prospective trial of intraoperative awareness, red-haired patients were identified and matched with five control patients, and the relative risk for intraoperative awareness was determined. Overall anesthetic management between groups was compared using Hotelling's T^2 statistic. Inhaled anesthetic requirements were compared between cohorts by evaluating the relationship between end-tidal anesthetic concentration and the bispectral index with a linear mixed-effects model. Time to recovery was compared using Kaplan-Meier analysis, and differences in postoperative pain and nausea/vomiting were evaluated with Chi square tests.*

Results *A cohort of 319 red-haired patients was matched with 1,595 control patients for a sample size of 1,914. There were no significant differences in the relative risk of intraoperative awareness (relative risk = 1.67; 95% confidence interval 0.34 to 8.22), anesthetic management, recovery times, or postoperative pain between red-haired patients and control patients. The relationship between pharmacokinetically stable volatile anesthetic concentrations and bispectral index values differed*

This article will be accompanied by an editorial. Please see Can J Anesth 2015; 62: this issue.

Author contributions *Stephen Gradwohl, Amrita Aranake, Arbi Ben Abdallah, David Glick, George A. Mashour,* and *Michael S. Avidan* designed the study. *Alex Villafranca, David Glick,* and *Michael S. Avidan* enrolled patients. *Alex Villafranca* and *David Glick* provided data. *Amrita Aranake, Paul McNair,* and *Bradley A. Fritz* entered data. *Stephen Gradwohl, Amrita Aranake, Paul McNair,* and *Michael S. Avidan* organized data. *Stephen Gradwohl, Amrita Aranake, Arbi Ben Abdallah,* and *Michael S. Avidan* conducted analyses. *Stephen Gradwohl, Amrita Aranake, Arbi Ben Abdallah,* Eric Jacobsohn, *George A. Mashour,* and *Michael S. Avidan* wrote the manuscript. *Stephen Gradwohl, Amrita Aranake, Arbi Ben Abdallah, Paul McNair, Nan Lin, Bradley A. Fritz, Alex Villafranca, David Glick, Eric Jacobsohn, George A. Mashour,* and *Michael S. Avidan* revised the manuscript. *Stephen Gradwohl* and *Amrita Aranake* contributed equally to this manuscript and are joint lead authors. *Nan Lin* conducted statistical analyses (especially the mixed-effects model). *Bradley A. Fritz* conducted statistical analyses (especially Kaplan-Meier analyses).

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Springer

Purpose

The red-hair phenotype, which is often produced by mutations in the melanocortin-1 receptor gene, has been associated with an increase in sedative, anesthetic, and analgesic requirements in both animal and human studies. Nevertheless, the clinical implications of this phenomenon in red-haired patients undergoing surgery are currently unknown.

Sample Size

1914 (319 red-haired patients, 1,595 control patients), matched cohort study.

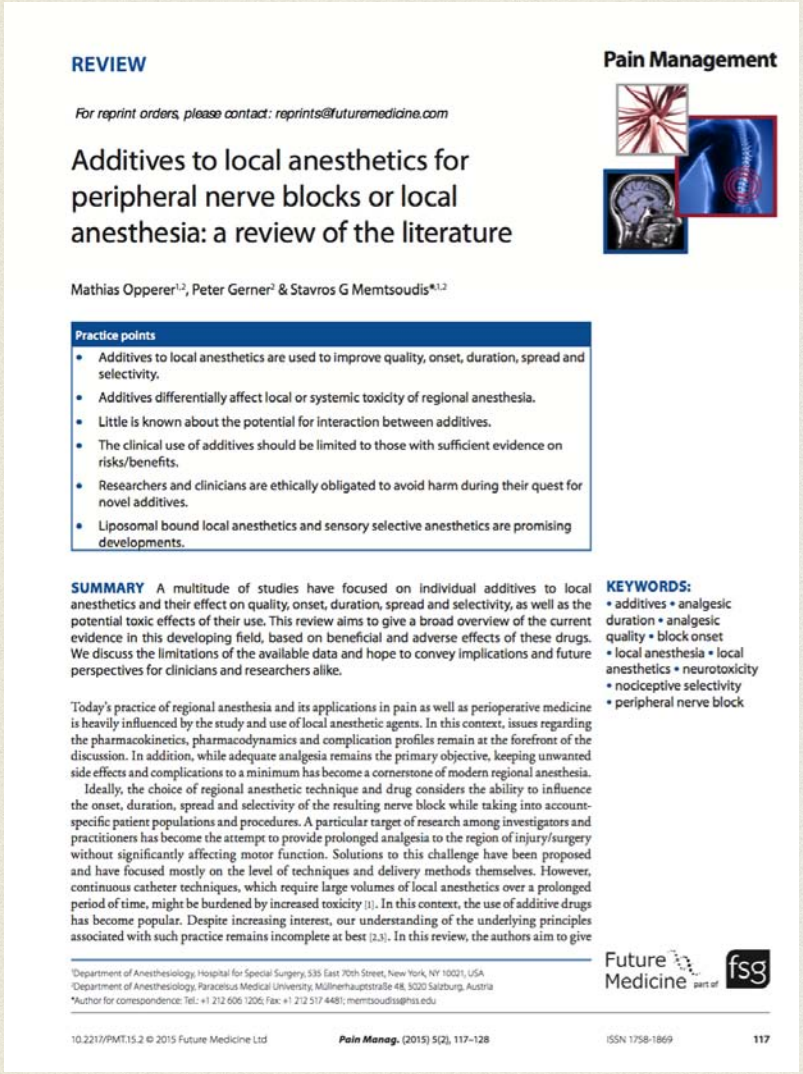
Findings

There were no demonstrable differences between red-haired patients and controls in response to anesthetic and analgesic agents or in recovery parameters. These findings suggest that perioperative anesthetic and analgesic management should not be altered based on self-reported red-hair phenotype.

Key thoughts

In this large matched historical cohort analysis, the red-hair phenotype was not associated with alterations in AWR, anesthetic management, anesthetic sensitivity, or recovery from general anesthesia. These findings are clinically important and contrast with published hypothesis-generating animal research and small proof-of-principle human studies.

REVIEW OF LITERATURE



REVIEW

Pain Management

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Additives to local anesthetics for peripheral nerve blocks or local anesthesia: a review of the literature

Mathias Opperer[1,2], Peter Gerner[2] & Stavros G Memtsoudis*[1,2]

Practice points

- Additives to local anesthetics are used to improve quality, onset, duration, spread and selectivity.
- Additives differentially affect local or systemic toxicity of regional anesthesia.
- Little is known about the potential for interaction between additives.
- The clinical use of additives should be limited to those with sufficient evidence on risks/benefits.
- Researchers and clinicians are ethically obligated to avoid harm during their quest for novel additives.
- Liposomal bound local anesthetics and sensory selective anesthetics are promising developments.

SUMMARY A multitude of studies have focused on individual additives to local anesthetics and their effect on quality, onset, duration, spread and selectivity, as well as the potential toxic effects of their use. This review aims to give a broad overview of the current evidence in this developing field, based on beneficial and adverse effects of these drugs. We discuss the limitations of the available data and hope to convey implications and future perspectives for clinicians and researchers alike.

KEYWORDS:
• additives • analgesic duration • analgesic quality • block onset • local anesthesia • local anesthetics • neurotoxicity • nociceptive selectivity • peripheral nerve block

Today's practice of regional anesthesia and its applications in pain as well as perioperative medicine is heavily influenced by the study and use of local anesthetic agents. In this context, issues regarding the pharmacokinetics, pharmacodynamics and complication profiles remain at the forefront of the discussion. In addition, while adequate analgesia remains the primary objective, keeping unwanted side effects and complications to a minimum has become a cornerstone of modern regional anesthesia.

Ideally, the choice of regional anesthetic technique and drug considers the ability to influence the onset, duration, spread and selectivity of the resulting nerve block while taking into account-specific patient populations and procedures. A particular target of research among investigators and practitioners has become the attempt to provide prolonged analgesia to the region of injury/surgery without significantly affecting motor function. Solutions to this challenge have been proposed and have focused mostly on the level of techniques and delivery methods themselves. However, continuous catheter techniques, which require large volumes of local anesthetics over a prolonged period of time, might be burdened by increased toxicity [1]. In this context, the use of additive drugs has become popular. Despite increasing interest, our understanding of the underlying principles associated with such practice remains incomplete at best [2,3]. In this review, the authors aim to give

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Clonidine

- One of the most commonly used additives to local anesthetics
- Dosages range from 50-250 mcg
- Mediates most of its effect locally, while most of the systemic analgesic effect of clonidine was linked to modulation of cytokines as evidenced by a reduction in postoperative levels of TNF-α in CSF or systemic interleukin-6 and CRP
- Addition of clonidine to ropivicaine for brachial plexus blocks prolonged the duration of the block by 2 hours

Dexmedetomidine

- The addition of dexmedetomidine marginally improved onset time of levobupivicaine in brachial plexus blocks, with a mean prolongation of sensory effects by 284 minutes

REVIEW OF LITERATURE

Strength	Level	Design	Randomization	Control
High	Level 1	Randomized control trial (RCT)	Yes	Yes
		Meta-analysis of RCT with homogeneous results	No	
	Level 2	Prospective comparative study (therapeutic)	No	Yes
		Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results	No	
	Level 3	Retrospective Cohort Study	No	Yes
		Case-control Study	No	Yes
		Meta-analysis of Level 3 studies	No	
	Level 4	Case Series	No	No
	Level 5	Case Report	No	No
		Expert Opinion	No	No
Low		Personal Observation	No	No

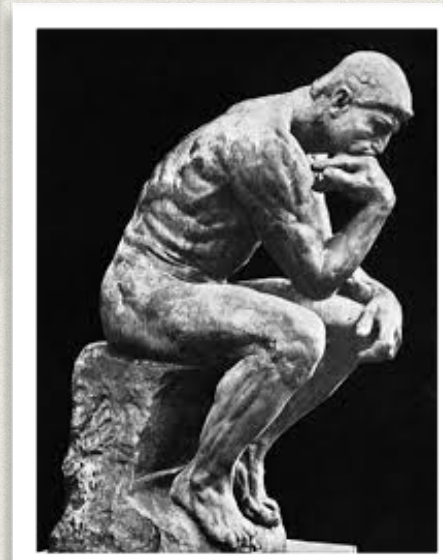
Image from: http://www.hydroassoc.org/research-101-levels-of-evidence-in-hydrocephalus-clinical-research-studies/

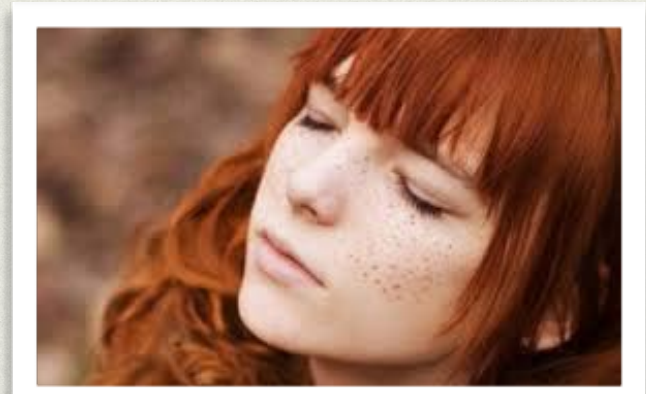
REVIEW OF LITERATURE

(LEVEL OF EVIDENCE)

	Author	Year	Sample Size	Subject	Design	P < 0.05	P < 0.001	Limitations (IMHO)
Level 1	**Chua et al.**	2004	39	Human	RCT	Red hair- Higher OAA/S, lower drowsiness VAS		Not blinded to hair color, pharmacokinetics of midazolam unmeasured
Level 2	**Myles et al.**	2012	468	Human	Prospective Matched Cohort		No significance found	Self-reported hair phenotype
Level 2	**Liem et al.**	2005	60	Human	Prospective	Red hair- more sensitive to cold pain perception and heat pain. Subcutaneous lidocaine less effective.	Red hair- more sensitive to cold pain tolerance	Women only, investigators and subjects not blinded to hair color
Level 2	**Liem et al.**	2004	20	Human	Prospective		Red hair required 19% higher desflurane MAC concentration	Small sample size
Level 2	**Xing et al.**	2004	40	Mice	Prospective	MC1R mutation required 5.5% increase in MAC (P =0.023)		Small sample size, mice
Level 3	**Gradwohl et al.**	2015	1914	Human	Retrospective Cohort		No significance found	Self-reported retrospective review for “red hair”. No MC1R testing, BIS as surrogate, multiple agents used, high-risk AWR patients were recruited originally; is this reproducible to the general population?
Level 5	**Galley et al.**	2005			Expert Opinion			

FUTURE ANESTHETIC IMPLICATIONS





FUTURE ANESTHETIC IMPLICATIONS

Genetic iStat???

- It is possible that in a short amount of time (years?) we would be able to more accurately tailor anesthetic (and a myriad of other pharmacological interventions) levels specific to a given genotype. This presentation and information has primarily focused on *one gene* nearly specific to *one phenotype,* who represent approximately 5% of the global population. What if we find more genetic variability that effects 20, 30, or even 90% of the population???

FUTURE ANESTHETIC IMPLICATIONS

MAC-Ginger…

If it is in fact true that redheads require more anesthetic, be it inhalational or local, or greater benzodiazepine requirement, the astute clinician could take a “mental MAC-Ginger” approach, such that:

MAC of Sevoflurane	MAC-Ginger of Sevoflurane	MAC-BAR of Sevoflurane
2.0%	2.38%	2.6%

(MAC-BAR-Ginger 3.094%!!)

MAC of Desflurane	MAC-Ginger of Desflurane	MAC-BAR of Desflurane
6.0%	7.14%	7.8%

QUESTIONS??

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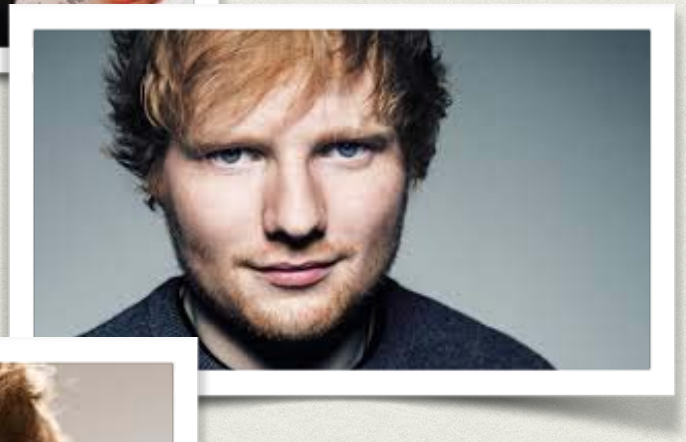
ED SAYS "THANKS FOR LISTENING"...



Sure Nathan... whatever...