Scandinavian Journal of Pain 2 (2011) 1–2

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment and review

Redheads, pain mechanisms and genetics: Lessons learned from inconclusive studies

Audun Stubhaug*

Department for Pain Management and Research, Oslo University Hospital, Oslo, Norway

Why do some people experience no pain after stimuli/injuries that lead to severe pain in others? Moreover, why are some people developing chronic disabling pain after minor injuries while others are pain free after major multi-trauma? These questions are of major interest to patients, clinicians, and to health providers. Experienced clinicians have long acknowledged the huge inter-individual variation in pain sensitivity. However, it is poorly known how differences in pain sensitivity may influence diagnosis, as well as the course of illness, and the effect of treatment.

What has this to do with hair-color? Nothing, except for the genuine red/copper tone color combined with pale skin seen in a few of us. Most people with this phenotype are homozygote for a mutant melanocortin receptor gene leading to dysfunctional melanocortin receptors (MC1R). Dysfunctional MC1Rs result in high eumelanin (yellow-red) to pheomelanin (dark brown) ratio. Except for the visible effects (red hair and pale skin), there is now evidence that this mutation also affects pain sensitivity and opioid analgesic effectiveness [1]. However, as with several findings of associations between phenotypes and polymorphisms, there are conflicting results. While Liem and colleagues found that red hair was associated with increased pain sensitivity and reduced effect of analgesics [2], Mogil et al. found reduced sensitivity to pain and increased effect of kappa-opioid analgesics [1].

In this issue of the Scandinavian Journal of Pain, Andresen et al. present a new study comparing pain sensitivity and pain mechanisms in redheads with controls [3]. In this study outcomes recorded were pressure pain tolerance measured in forearm muscle, cutaneous heat pain tolerance in lower arm, and area of pinprick hyperalgesia and brush allodynia after heat injury and subsequent topical capsaicin. Redheads were less sensitive to pinprick hyperalgesia, but did not differ from controls for other outcomes. Before we are drawing the conclusion about redheads, let us look into pain genetics more generally.

How much of the large inter-individual difference in pain sensitivity is explained by genes? Two recent twin studies found that 30–60% of the variability can be explained by genetic factors [4,5], results similar to findings by Mogil et al. in rodents [6]. These studies indicate that genes may be identified that increase risks for acute pain and for chronification of acute pain.

The importance of pain sensitivity for pain as a symptom of serious illness.

This was recently shown by Granot et al. in a study of painful versus painless cardiac ischemia [7]. In persons hospitalized with cardiac ischemia, pain sensitivity differed between those presenting with pain as a main symptom and those presenting with other symptoms. Those who were sensitive to pain were more likely to present with painful ischemia, and thus they were most likely to receive an early correct diagnosis and treatment [7]. For specific diagnosis associated with pain, e.g., rheumatoid arthritis, the underlying pain sensitivity may explain the discrepancy between laboratory signs of illness severity and pain. Most importantly, underlying differences in pain sensitivity may explain why only a small number of patients with nerve injuries go on to develop chronic pain.

One special finding in both animal and human genetics is the lack of correlation between candidate genes and different pain models. Since genes may regulate peripheral pain transducers, neuronal conduction, general regulatory mechanisms of neuronal activity, as well as the immune system's involvement in plasticity of the pain regulatory systems, it is no surprise that both genes that regulate pain sensitivity in general as well as genes that regulate sensitivity to specific stimuli have been identified.

As shown most elegantly by Waxman and colleagues, single polymorphisms in one gene coding for a sodium channel (Na_v 1.7) can give diverse phenotypes, ranging from *insensitivity to pain* to *extremely severe pain* syndromes [8]. These findings give hope that specific sodium-channels blockers may be developed for human use, for specific treatment of pathologic pain without interfering with other functions.

Analgesic efficacy has been linked with the human catechol-O-methyltransferase (*COMT*) gene [9,10], the *OPRM1* gene [11], the *CYP2D6* gene [12], the *MC1R* gene [1] and the gene encoding cyclooxygenase-2 (*COX-2*) gene [13]. Again, except for CYP2D6, contradictory findings are frequent. The lack of clean phenotypes and lack of adequately sized studies have been limiting factors for progress.

Genes associated with the chronification of pain have recently been identified [14]. CACNG2 encodes for a protein involved in

DOI of refers to article:10.1016/j.sjpain.2010.08.005.
* Tel.: +47 23073696; fax: +47 20373690.
E-mail address: audun.stubhaug@medisin.uio.no

1877-8860/$ – see front matter
doi:10.1016/j.sjpain.2010.12.003

the transport of glutamatergic receptors as well as possibly being a Ca channel subunit [14]. Human CACNG2 polymorphisms were associated with chronic pain in a cohort of breast cancer patients [14].

Most interestingly, Costigan et al. found that a common polymorphism coding for a potassium channel subunit involved in neuronal excitability was associated with higher pain scores in five of six independent patient cohorts [15]. This channel is constitutively expressed in sensory neurons and markedly downregulated following nerve injury, indicating a specific role in chronification after injuries.

Now, as technology makes genome-wide association studies (GWAS) possible, mapping more than one million single-nucleotide polymorphisms (SNPs) from each subject can be done, and new candidate genes and new mechanisms may be found. However, the crucial need for adequately sized studies becomes even more important [16]. For GWAS studies, 1000–3000 carefully phenotyped subjects are needed to gain adequate power [17]. This means that large multicenter trials may be the only way forward.

Before we start doing this, one lesson from the studies in redheads should be brought forward. As pointed out by Andresen et al. [3], slightly different test protocols may explain the divergent findings between Liam et al. [2] and the current study by Andresen et al. [3]. Low rates of skin heating (<0.5 °C/s) activate mainly C-fibers whereas high rates (>0.9 °C/s) predominantly activates Aδ-fibers. This underscores the fact that both for experimental and clinical outcomes, lack of reproducible and well-characterized phenotypes limits progress in this field of research. The finding of reduced sensitivity in redheads for pinprick hyperalgesia reported in this issue of the Scandinavian Journal of Pain by Lars Arendt-Nielsen's group is interesting [3]. If replicated, this may indicate a contribution of the melanocortin receptor gene to pain plasticity.

References

[1] Mogil JS, Wilson SG, Chesler EJ, Rankin AL, Nemmani KV, Lariviere WR, Groce MK, Wallace MR, Kaplan L, Staud R, Ness TJ, Glover TL, Stankova M, Mayorov A, Hruby VJ, Grisel JE, Fillingim RB. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci USA 2003;15(100):4867–72.

[2] Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. Anesthesiology 2005;102:509–14.

[3] Andresen T, Lunden D, Drewes AM, Arendt-Nielsen L. Pain sensitivity and experimentally induced sensitisation in red haired females. Scand J Pain 2011;2:3–6.

[4] Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. Brain 2007;130:3041–9.

[5] Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain 2008;136:21–9.

[6] Mogil JS, Wilson SG, Bon K, Lee SE, Chung K, et al. Heritability of nociception I. Responses of eleven inbred mouse strains on twelve measures of nociception. Pain 1999;80:67–82.

[7] Granot M, Khoury R, Berger G, Krivoy N, Braun E, Aronson D, Azzam ZS. Clinical and experimental pain perception is attenuated in patients with painless myocardial infarction. Pain 2007;133:120–7.

[8] Waxman S. Nav1.7, its mutations, and the syndromes that they cause. Neurology 2007;69:505–7.

[9] Rakvag TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan HE, Skorpen F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005;116:73–8.

[10] Rakvag TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain 2008;4:64.

[11] Reyes-Gibby CC, Shete S, Rakvag T, Bhat SV, Skorpen F, Bruera E, Kaasa S, Klepstad P. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. Pain 2007;130:25–30.

[12] Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351:2827–31.

[13] Lee YS, Kim H, Wu TX, Wang XM, Dionne RA. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 2006;79:407–18.

[14] Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, Dorfman R, Abitbul-Yarkoni M, Lu Y, Elahipanah T, delCanho S, Minert A, Fried K, Persson AK, Shpigler H, Shabo E, Yakir B, Pisanté A, Darvasi A. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res 2010;20:1180–90.

[15] Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, Wu T, Kiselycznyk C, Poddar M, Lu Y, Diatchenko L, Smith S, Cobos EJ, Zaykin D, Allchorne A, Shen PH, Nikolajsen L, Karppinen J, Männikkö M, Kelempisioti A, Goldman D, Maixner W, Geschwind DH, Max MB, Seltzer Z, Woolf CJ. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain 2010;133:2519–27.

[16] Mogil JS. Are we getting anywhere in human pain genetics? Pain 2009;146:231–2.

[17] Max MB, Stewart WF. The molecular epidemiology of pain: a new discipline for drug discovery. Nat Rev Drug Discov 2008;7:647–58.