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μ-Opioid Receptor Gene A118 G Variants and Persistent Pain Symptoms Among Men and Women Experiencing Motor Vehicle Collision

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Abstract: **The μ-opioid receptor 1 (OPRM1) binds endogenous opioids. Increasing evidence suggests that endogenous OPRM1 agonists released at the time of trauma may contribute to the development of posttraumatic musculoskeletal pain (MSP). In this prospective observational study, we evaluated the hypothesis that individuals with an AG or GG genotype at the *OPRM1* A118 G allele, which results in a reduced response to opioids, would have less severe MSP 6 weeks after motor vehicle collision (MVC). Based on previous evidence, we hypothesized that this effect would be sex-dependent and most pronounced among women with substantial peritraumatic distress. European American men and women ≥18 years of age presenting to the emergency department after MVC and discharged to home after evaluation (N = 948) were enrolled. Assessments included genotyping and 6-week evaluation of overall MSP severity (0–10 numeric rating scale). In linear regression modeling, a significant A118 G Allele × Sex interaction was observed: an AG/GG genotype predicted reduced MSP severity among women with substantial peritraumatic distress (β = –.925, *P* = .014) but not among all women. In contrast, men with an AG/GG genotype experienced increased MSP severity at 6 weeks (β = .827, *P* = .019). Further studies are needed to understand the biologic mechanisms mediating observed sex differences in A118 G effects.**

Perspective: ***These results suggest a sex-dependent mechanism by which an emotional response to trauma (distress) contributes to a biologic mechanism (endogenous opioid release) that increases MSP in the weeks after stress exposure. These results also support the hypothesis that endogenous opioids influence pain outcomes differently in men and women.***

Key words: *Opioid-induced hyperalgesia, A118 G, μ-opioid receptor 1, motor vehicle collision, pain.*

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More than 11 million Americans experience motor vehicle collision (MVC) each year; 4 million of these individuals present to U.S. emergency departments after the MVC for evaluation.[11] More than 90% of these individuals are discharged to home without fracture or other identifiable injury,[39] yet persistent musculoskeletal pain (MSP) in this population is a common and costly public health problem.[13] Mechanisms of chronic MSP development remain poorly understood.

One mechanism that may contribute to the development of chronic MSP after MVC is neuronal sensitization by endogenous opioids. Stressful events such as MVC have been shown to trigger the release of endogenous opioids.[26,49] The binding of endogenous opioids to μ-opioid receptors such as the μ-opioid receptor 1 (OPRM1) has been shown to produce a bimodal response: initial analgesia followed by more persistent opioid-induced hyperalgesia (OIH).[3,14,25,26] The most common genetic variant in the OPRM1 receptor is A118 G[33]; the presence of a G nucleotide at A118 G has been shown to result in reduced OPRM1 receptor-binding affinity[6,42] and less OPRM1 receptor expression.[24] This results in less messenger RNA in response to OPRM1 binding in those with a G allele and a relative decrease in opioid effect.[22,29] Thus, those with one or more copies of the G allele at A118 G would be expected to be protected from the downstream cellular effects of endogenous opioids that result in persistent hyperalgesia after stress exposure. Consistent with this hypothesis, a recent study found that women sexual assault survivors with one or more copies of the G allele at A118 G were found to have a reduced MSP burden 6 weeks after sexual assault compared to those with an AA genotype.[4]

Currently, human data supporting the contribution of endogenous OIH to persistent pain after stress exposure is limited to the single study of sexual assault survivors referenced above. The findings have not been replicated, and in addition, no studies have assessed for evidence that the contribution of OIH to persistent pain outcomes is a more general phenomenon that may apply to other stress exposures aside from rape. In the present analysis, we used the A118 G genetic variant to evaluate our primary hypothesis that OIH contributes to persistent MSP after MVC. Because of substantial evidence that the effect of OIH is sex-dependent (including those of A118 G[17,36]), and because the G allele was found to be protective against persistent MSP among women sexual assault survivors, we hypothesized that the protective effect of one or more copies of the G allele would be greater in women. In addition, because stress severity has been found to influence the magnitude of endogenous opioid release,[26,37,41,46] we hypothesized that OIH (and therefore the protective effect of a G allele at A118 G) would be greater among women with substantial peritraumatic distress in the early aftermath of MVC. (All women sexual assault survivors in the previous study experienced substantial distress.[4]) Finally, because of evidence that clinical pain states may result in OIH,[2,15,43] in secondary analyses we evaluated for evidence of a greater protective effect of A118 G among individuals who reported high levels of pain prior to the MVC.

Methods

Study Design and Population

The details of the MVC study have been reported.[38] In brief, individuals ≥18 and ≤65 years of age presenting to 1 of 8 emergency departments in 4 no-fault insurance states within 24 hours of MVC who did not have fracture or other injury requiring hospital admission were enrolled. Patients who were not alert and oriented were excluded, as were pregnant patients, prisoners, patients unable to read and understand English, patients taking a β-adrenoreceptor antagonist, or patients taking opioids above a total daily dose of 30 mg of oral morphine or equivalent. In addition, because genetic analyses are potentially biased by population stratification,[12] enrollment was also limited to non-Hispanic whites (the most common ethnicity at study sites). Informed consent was obtained from all participants, and institutional review board approval was obtained at all study sites.

DNA Collection and Genotyping

Study personnel collected blood samples at the time of enrollment using PAXgene DNA tubes (PAXgene blood DNA kit; Qiagen, Valencia, CA). Following DNA purification, genotyping using the Sequenom platform (Sequenom, San Diego, CA) was performed at rs1799971 (A118 G). Two HapMap samples and 2 repeat samples were included in each genotyping batch (of 96 samples). Repeated genotyping demonstrated >98% call agreement.

Assessments

Overall pain intensity in the emergency department and during the month prior to MVC were assessed using verbal 0 to 10 numeric rating scales. Verbal scores have advantages in acute care settings, and verbally administered numeric rating scales have been validated as a substitute for visual analog scales in the emergency department.[7] Past pain scores were calculated by summing the 0 to 10 pain severity scores from each of 20 body regions (scale of 0–200). Individuals reporting a score of 10 or more were defined as having high levels of past pain. This cutoff of 10 was used because 1) this represents the top quartile of pre-MVC pain in this relatively young, healthy study cohort, and 2) although the scale has a high upper range, a score of 10 represents several regions of moderate or severe pain or a large number of body regions with some pain. Average overall pain intensity in the past week [0–10 numeric rating scale] was evaluated 6 weeks after the MVC via web-based questionnaire or telephone interview. Stress severity in the emergency department was measured using the Peritraumatic Distress Inventory.[9] The Peritraumatic Distress Inventory is a 13-item questionnaire assessing life threat, loss of control, helplessness/anger, and guilt/