ORIGINAL RESEARCH

Opioid Receptor Mu 1 Gene (OPRM1) A118G Polymorphism and Emotional Modulation of Pain

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Purpose: The A118G polymorphism in the opioid receptor mu 1 gene (OPRM1) is associated with decreased opioid receptor availability, altered emotion, and increased pain. Given that emotions modulate pain (positive emotions inhibit pain, negative emotions enhance pain), we predicted that G allele carriers would experience impaired emotional modulation of pain compared to non-G allele carriers.

Patients and Methods: Emotional pictures (ie, erotica, neutral, attack) from the International Affective Picture System were used by permission from the authors to experimentally manipulate emotions in 64 adult participants while painful electrocutaneous stimulations were delivered in a cross-sectional study. Ratings of arousal and valence/pleasure were made in response to pictures, and pain ratings and a physiological measure of spinal nociception (ie, nociceptive flexion reflex, NFR) were collected in response to painful stimulations. Secondary analyses were conducted to examine the relationship between the A118G polymorphism and emotional modulation of pain/NFR.

Results: Exposure to emotional pictures elicited similar changes in valence, but G-carriers rated erotic pictures as more arousing. In non-carriers, pain was facilitated by attack pictures and pain and NFR were inhibited by erotic pictures relative to neutral pictures. Among G-carriers, pain was facilitated by negative emotional pictures but there was no pain or NFR inhibition by positive emotional pictures.

Conclusion: The altered response to pleasant stimuli further supports the role of opioids in appetitive behavior and describes how the A118G polymorphism may prevent carriers from inhibiting pain during pleasure.

Keywords: opioid receptor, genetics, emotion, pain, pain inhibition

Introduction

In healthy individuals, pain modulation allows organisms to respond adaptively to environmental demands. Disrupted pain modulation (eg, excessive facilitation, impaired inhibition) is associated with chronic pain disorders, like fibromyalgia and chronic tension-type headache.[1–3] Thus, understanding factors that impair pain modulation could provide insight into chronic pain risk mechanisms.

Emotions are one factor that modulates pain; positive emotions inhibit pain and negative emotions enhance pain (as long as emotional intensity/arousal is not too high).[4,5] Emotional modulation of pain can be investigated using the emotional controls of nociception (ECON) paradigm, in which emotionally laden pictures are shown to induce affective responses during which pain is evoked.[6–8] Previous research indicates that both pain and the nociceptive flexion reflex (NFR), a spinally mediated withdrawal reflex in the lower limb (assessed using EMG following painful sural nerve stimulations) that assesses spinal nociception, are typically modulated in parallel by ECON.[6–9] But they can also diverge from one another, suggesting separate circuits mediate their emotional modulation.[7,10]

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Endogenous opioids play a critical role in descending pain modulation[11] and emotional processing;[12] therefore, individual differences in opioidergic signaling may be related to altered emotional modulation of pain and NFR.[13] The OPRM1 gene (opioid receptor mu 1) codes for mu-opioid receptors[14] and affects emotion and pain processing.[15–18] Most individuals carry homozygous AA alleles (ie, AA-carriers), yet approximately 10–32% of humans carry a G allele of the OPRM1 exon 1 rs1799971 polymorphism, A118G (ie, G-carriers), in which guanine replaces adenine.[19] It has been hypothesized the A118G polymorphism causes a loss of function,[15] such that G-carriers have impaired functionality of mu-opioid receptors. Supporting this, G-carriers show altered emotional processing, including heightened sensitivity to social rejection and greater pleasure from social situations.[20,21] G-carriers also show impairments in descending pain modulation as evidenced by the need for higher doses of opioid analgesics following Cesarean section[22] and greater postoperative pain,[23,24] relative to AA-carriers.

To date, no study to our knowledge has investigated opioid receptor polymorphisms and their impact on affective modulation of pain and nociception. Thus, the present secondary analysis of data examines whether G-carriers display altered emotional modulation of pain and NFR relative to AA-carriers during ECON. AA-carriers are hypothesized to show typical emotional modulation of pain and NFR, with pain and NFR inhibition following pleasant pictures as well as pain and NFR facilitation following unpleasant pictures. Given evidence of dysregulated emotion and pain processing in G-carriers, it is hypothesized that G-carriers will show disrupted emotional modulation of pain and NFR, relative to AA-carriers.

Materials and Methods
Participants and Samples
Participants (N=144) were recruited at The University of Tulsa and Ohio University between 2006 and 2009.[25] Exclusion criteria were: <18 years, neurological, cardiovascular and/or circulatory problems, recent use of medications affecting pain (ie, analgesic, antidepressant, anxiolytic, and/or antihypertensive), phobia of snakes/spiders (included in imagery), chronic pain, or recent psychological trauma. Seventy-nine (55%) participants were female and 122 (85%) were White, non-Hispanic. Average age was 27.31 years (SD=13.86). Participants were compensated with $100 (Tulsa) or psychology research credit (Ohio). Due to high salt contamination from long-term storage, 64 participants produced usable DNA samples. Table 1 compares those with and without viable samples. Viable samples were from younger participants.

All participants provided verbal and written informed consent. This study complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013) and was approved by the Institutional Review Boards of The University of Tulsa (IRB#04-67) and Ohio University (IRB# 07F003).

Apparatus
During testing, participants sat in a comfortable chair in a room adjacent to the experimenter. A computer with two monitors controlled the experiment – one displayed emotional pictures and questionnaires to the participant and the other displayed physiological signals to experimenters.

A stimulating electrode (Nicolet, 019-401400, Madison, WI) was applied to the participant's left ankle over the retromalleolar pathway. Constant-current stimulators were used for painful stimulus delivery (Grass Model S88/S48, West Warwick, RI, at Tulsa; Digitimer DS7A, Hertfordshire, England, at Ohio). Max current=40 mA.

NFR was recorded by electromyogram (EMG) from two Ag-AgCl electrodes filled with conductive gel applied over the left biceps femoris, 10-cm superior to the popliteal fossa (reference electrode on femur lateral epicondyle). Sites were

Table 1 DNA Viability Group Age, Sex, and Race

OPRM1 Genotype	Age (Years)		Female		Non-Hispanic White	
	M	*SD*	N	%	N	%
Viable DNA	24.08*	10.60	38	59.4	56	87.5
Non-viable DNA	29.89	15.58	41	51.3	66	82.5

Notes: N = 64 for Viable DNA. N = 80 for Non-viable DNA. Viability groups were compared using t tests for age and chi-square tests for sex and race. *$p < 0.05$.

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cleaned with alcohol and exfoliated to minimize impedances to below 10 kΩ. Sample rate=1000 Hz. Recording amplifier was Grass Model 15LT at Tulsa and Delsys Bagnoli 2 at Ohio.

Stimulation Intensity Determination

Painful stimuli delivered during ECON were set to 120% of the NFR threshold to ensure that the nociceptive system was activated. Each stimulus was a train of five 1-ms pulses at 250-Hz. The validated and standardized procedure for assessing NFR threshold is described elsewhere.[26]

Electric Pain Threshold and Tolerance

Subjective thresholds were measured using a single, ascending staircase of electric stimulations. After each stimulation, participants rated their pain using a computerized scale ranging from 0 (no sensation) to 100 (maximum tolerable). Stimulation intensity was increased until participants reported a 100 on the subjective pain scale (or until 40-mA reached). Pain threshold=first stimulus as rated ≥50 on the pain scale. Pain tolerance=stimulus intensity rated 100 (or 40-mA if reached).

Emotional Controls of Nociception (ECON)

Attack (scenes of individuals in danger), neutral (eg, household objects), and erotica (humans in sexual acts) images from the International Affective Picture System were presented in pseudorandom order.[27] These contents were chosen because they reliably modulate pain and NFR.[7–9] Pictures were displayed for 6-s with 12 to 22-s inter-picture intervals. After each picture, participants rated how the picture made them feel on a valence/pleasure scale (1 to 9; higher scores=more pleasant, lower scores=more unpleasant) and an arousal scale (1 to 9; higher scores=greater arousal).[28]

Painful stimuli were delivered randomly throughout picture viewing (balanced across contents). Stimulations were delivered 3 to 5-s after picture onset or 11 to 21-s after inter-picture interval onset. Four painful stimuli were delivered during each picture content. Following each painful stimulus, the pain rating scale was presented. NFR magnitude=mean EMG of 90 to 150-ms post-electric stimulus interval minus mean EMG of 60 ms pre-electric stimulus baseline. Consistent with previous studies,[7,8,25] NFR magnitudes and pain ratings were converted to z scores to isolate the variance in pain/NFR due to emotional modulation:

$$z \text{ score} = \frac{\text{raw score} - \text{participant overall mean response}}{\text{participant overall SD}}$$

Genotyping

Saliva samples were collected from participants at the time of testing using a buccal swab. DNA samples were isolated from the saliva using the BuccalAmp DNA Extraction Kit (Epicentre Biotechnologies, Madison, WI, USA) and stored at −80°C. A nanodrop spectrometer indicated high levels of salt (ie, peaks at 230 nm) within the saliva samples. Thus, a protocol for ethanol precipitation of DNA was followed to remove contaminants from the DNA samples.[29] Next, samples were amplified using OPRM1 exon 1 primers (forward primer = AAGGTGGGAGGGGGCTATAC; reverse primer = CCTTAAGCCGCTGAACCCT) and polymerase-chain reaction (PCR). Gel electrophoresis was then conducted on the PCR products to determine their viability and to determine if additional purification was necessary. Viable samples were indicated by band visualization on the gels. Prior to purification of the PCR product, 13% of samples within the entire dataset were accompanied by band visualization, whereas 40% of samples were accompanied by band visualization after PCR purification. Thus, ethanol precipitation, PCR, and gel electrophoresis were conducted on all 144 samples to select usable samples. Of the 144 samples, 68 did not produce a band and were removed from subsequent analyses, leaving 76 included samples. Included samples were then sequenced using Sanger Sequencing services provided by Eurofins Genomics.

Chromatogram files produced from Sanger Sequencing showed all bases in the PCR product, including the locus of interest for this study (rs1799971). Chromatograms (n = 12) that were unreadable at rs1799971 due to interference from other peaks were removed. The remaining chromatograms were then assessed at rs1799971 for A118G polymorphisms to

code participants as G-carriers (n = 11) or non-carriers (n = 53). Since the entirety of exon 1 on the OPRM1 gene was amplified with PCR, heterozygotes for other base pairs throughout exon 1 could be identified. Two heterozygotes, both from the non-carrier group, had the same polymorphism. This second variant resulted in an adenine substitution with thymine at the 17th base position of exon 1 of the OPRM1 gene (A17T). This variant also resulted in substitution of a nonpolar amino acid (alanine) with another nonpolar amino acid (valine) on the sixth amino acid residue (A6V) of the OPRM1 receptor gene (UCSC genome browser, chr6:154,360,695–154,360,697). Effects on the OPRM1 receptor's structure as a result of the missense variant were predicted using a protein modeling program from Imperial College of London.[30] Results were verified using the missense variant analyzer PolyPhen-2.[31] The polymorphism was not deleterious in both cases, so data provided for these participants were included.

Statistical Approach

Consistent with past research, two groups were formed based on the presence or absence of the G allele.[15,23] G carrier and non-carrier groups were not further split by sex due to the small sample size available t-tests or chi-square tests were used to analyze group differences in age, sex, and race/ethnicity.

To analyze valence, arousal, pain, and NFR, 3 (picture content) x 2 (genotype) mixed repeated measures ANOVAs were conducted, with the Picture Content x Genotype interaction being the effect of interest. In the event of a significant interaction, the simple effect of picture content was examined for each group as is typically done in studies of emotional modulation of pain/NFR,[32–35] given that this effect best characterizes group differences in emotional modulation. However, a priori planned comparisons of picture content were also conducted even in the absence of a significant interaction to avoid a type II error due to small sample size. One-tailed tests were used given the large body of evidence demonstrating emotional modulation of pain/NFR.[6,25]

Results
Comparing Participants with and without Viable DNA

Table 2 shows mean (SE) differences between DNA viability groups for valence, arousal, pain, and NFR. Table 3 shows the results of a 2 (viable vs non-viable) x 3 (picture content) mixed repeated measures ANOVAs that found that DNA

Table 2 DNA Viability Group Means and SEs for Valence, Arousal, Pain, and NFR

Variable	Viable DNA		Non-Viable DNA	
	M	**SE**	**M**	**SE**
Valence[a]				
Attack	2.64	0.15	3.14	0.13
Neutral	4.87	0.09	5.15	0.08
Erotica	6.00	0.19	6.16	0.17
Arousal[a]				
Attack	5.97	0.24	5.55	0.21
Neutral	2.86	0.17	2.46	0.15
Erotica	5.42	0.24	5.42	0.21
Pain[b]				
Attack	0.33	0.06	0.23	0.05
Neutral	−0.06	0.04	−0.04	0.04
Erotica	−0.27	0.05	−0.31	0.05
NFR[b]				
Attack	0.01	0.06	0.14	0.05
Neutral	0.05	0.04	0.02	0.04
Erotica	−0.12	0.06	−0.2	0.05

Notes: [a]N = 144. [b]N = 143.

Table 3 DNA Viability Group Differences ANOVAs

Variable	ANOVA				
	Effect	**F**	**df**	**p-values**	**η^2**
Valence[a]					
	G	6.76	1, 142	0.010	0.05
	PC	224.82	2, 141	<0.001	0.76
	G × PC	0.63	2, 141	0.534	<0.01
Arousal[a]					
	G	1.32	1, 142	0.252	<0.01
	PC	207.51	2, 141	<0.001	0.75
	G × PC	1.70	2, 141	0.187	0.02
Pain[b]					
	G	3.55	1, 141	0.062	0.03
	PC	42.33	2, 140	<0.001	0.38
	G × PC	0.47	2, 140	0.628	<0.01
NFR[b]					
	G	0.09	1, 141	0.768	<0.01
	PC	9.36	2, 140	<0.001	0.12
	G × PC	1.49	2, 140	0.229	0.02

Notes: [a]N = 144. [b]N = 143. G = DNA viability group; Standardized versions for pain and NFR (nociceptive flexion reflex) measures were used in ANOVA testing.
Abbreviation: PC, Picture Content.

viability groups did not differ on valence, arousal, pain, and NFR during picture viewing, except that the viable group had generally lower valence/pleasure ratings, $p = 0.010$.

Viable Participant Characteristics by OPRM1 Genotype

For the samples that were viable, characteristics were evaluated by OPRM1 genotype (Table 4). An independent samples *t*-test showed that G-carriers and non-carriers did not differ by age under conditions of unequal variance, t(11.24) = −1.61, $p = 0.135$. Furthermore, results of chi-square tests showed proportion of females [X^2(1, N = 64) = 2.92, $p = 0.088$] and proportion of White, non-Hispanics [X^2(1, N = 64) = 1.90, $p = 0.168$] did not differ by genotype. Moreover, genotype quality and frequencies did not significantly deviate from Hardy-Weinberg Equilibrium expected values ($X^2 = 0.554$, df = 1, $p > 0.05$).
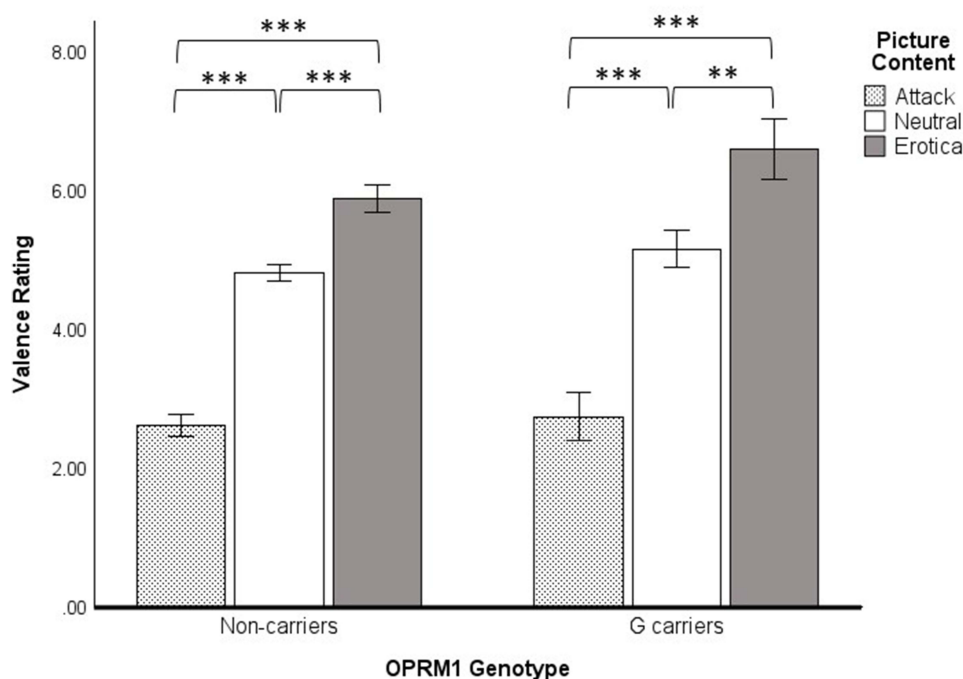
Valence Ratings

For valence ratings (Figure 1), there was a significant main effect of picture content, $F(2, 61) = 73.60$, $p < 0.001$, $\eta^2 = 0.71$, but no main effect of genotype, $F(1, 62) = 2.55$, $p = 0.116$, $\eta^2 = 0.04$. Participants reported greater pleasure (higher valence ratings) during erotica than during neutral or attack contents, ps < 0.001. Furthermore, they reported more displeasure (lower valence ratings) during attack content compared to erotica and neutral contents, ps < 0.001. The picture content by genotype interaction was non-significant, $F(2, 61) = 0.45$, $p = 0.643$, $\eta^2 = 0.01$. Nonetheless, a priori simple effects of picture content were probed for each genotype group. As shown in Figure 1, the simple effect was significant in the non-carrier group, $F(2, 61) = 92.65$, $p < 0.001$, $\eta^2 = 0.752$, as well as the G-carrier group, $F(2, 61) =$

Table 4 OPRM1 Genotype Group Age, Sex, and Race

RM1 Genotype	Age (Years)		Female		Non-Hispanic White	
	M	**SD**	**N**	**%**	**N**	**%**
Non-carriers	22.70	8.67	34	64.2	45	84.9
G-carriers	30.73	16.06	4	36.4	11	100.0

Notes: N = 53 for non-carriers. N = 11 for G-carriers. Genotype groups were compared using t tests for age and chi-square tests for sex and race.

Figure 1 Valence ratings for OPRM1 A118G carriers and non-carriers for attack, neutral, and erotica picture contents. Results depict a priori planned comparisons of the simple effect of Picture Content using Fisher's LSD tests. **p < 0.01. ***p < 0.001.

25.48, $p < 0.001$, $\eta^2 = 0.455$. Valence ratings for the three picture contents in each group were significantly different from each other, $ps < 0.001$. Thus, there were no significant group differences in valence appraisals of the picture stimuli.

Arousal Ratings

For arousal ratings (Figure 2), there was a significant main effect of picture content, $F(2, 61) = 66.55$, $p < 0.001$, $\eta^2 = 0.69$, that was qualified by a significant Picture Content x Genotype interaction, $F(2, 61) = 3.51$, $p = 0.036$, $\eta^2 = 0.10$. The simple effect of picture content was significant for non-carriers, $F(2, 61) = 69.94$, $p < 0.001$, $\eta^2 = 0.70$, and for G-carriers, $F(2, 61) = 27.78$, $p < 0.001$, $\eta^2 = 0.48$. As shown in Figure 2, in the non-carrier group, attack content elicited higher arousal than either neutral or erotica and erotica content elicited higher ratings than neutral content ($ps < 0.001$). In the G-carrier group, while arousal ratings were significantly higher in response to attack and erotica content than in neutral content ($p < 0.001$), arousal ratings for attack were not significantly higher than in erotica content ($p = 0.390$). Thus, erotica elicited relatively greater arousal in the G-carrier group than the non-carrier group. The main effect of genotype was non-significant for arousal ratings, $F(1, 62) = 0.057$, $p = 0.812$, $\eta^2 = 0.001$.

NFR Threshold and Pain Threshold

NFR thresholds for non-carriers ($M = 11.52$, $SD = 7.84$) and G-carriers ($M = 7.38$, $SD = 4.34$) were not significantly different, $t(62) = 1.69$, $p = 0.096$. Similarly, pain threshold did not differ, $t(62) = 1.22$, $p = 0.227$, between non-carriers ($M = 13.66$, $SD = 8.61$) and G-carriers ($M = 10.36$, $SD = 5.06$).

Emotional Modulation of Pain Ratings

Analysis of pain ratings showed a significant main effect of picture content, $F(2, 61) = 9.13$, $p < 0.001$, $\eta^2 = 0.23$, but no significant main effect of genotype, $F(1, 62) = 1.67$, $p = 0.201$, $\eta^2 = 0.03$ or Picture Content x Genotype interaction, $F(2, 61) = 1.20$, $p = 0.308$, $\eta^2 = 0.04$. Nonetheless, a priori simple effects of picture content were probed for each genotype group (Figure 3). The simple effect of picture content was significant in the non-carrier group, $F(2, 61) = 20.73$, $p < 0.001$, $\eta^2 = 0.41$, but not in the G-carrier group, $F(2, 61) = 1.94$, $p = 0.153$, $\eta^2 = 0.06$. For the non-carrier group, pain ratings were greater in the attack content than in the other contents, $ps < 0.001$, and pain ratings were lower in the erotica
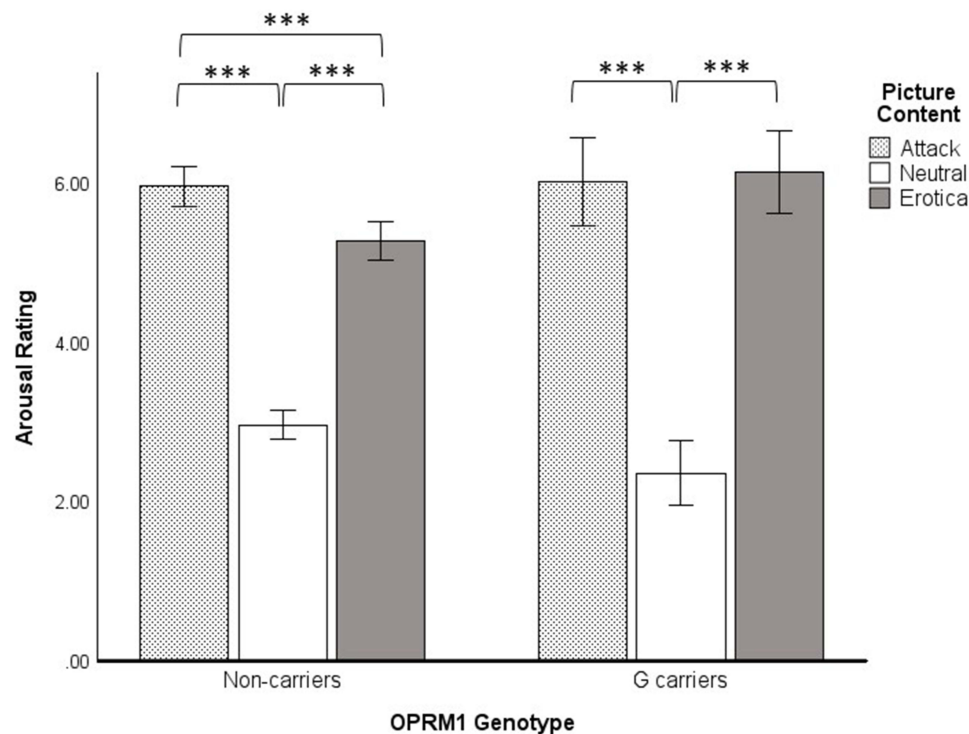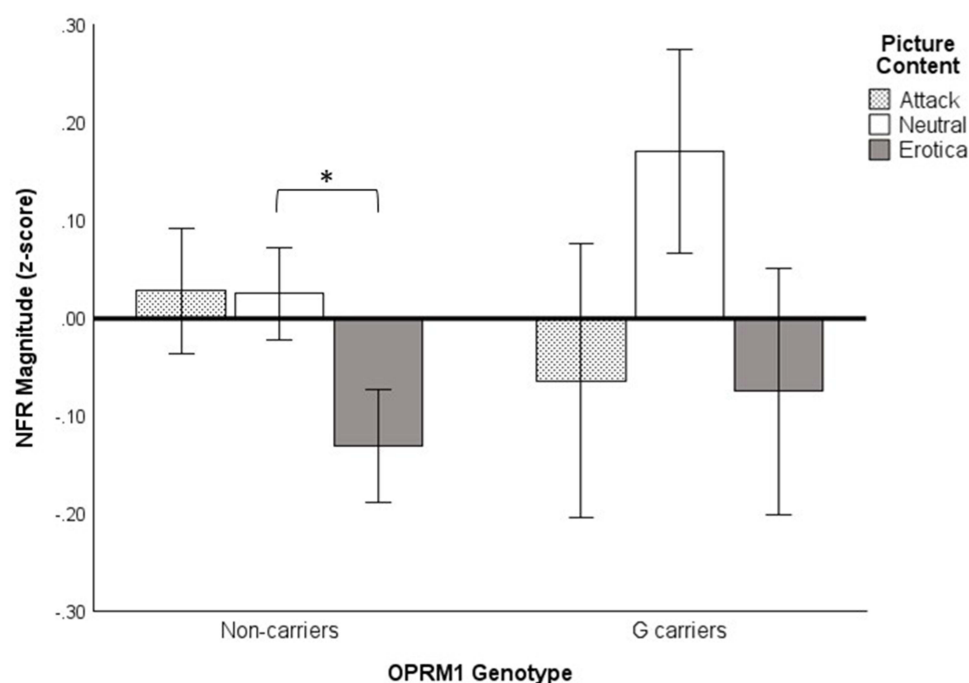
Figure 2 Arousal ratings for OPRM1 A118G carriers and non-carriers for attack, neutral, and erotica picture contents. Results depict a priori planned comparisons of the simple effect of Picture Content using Fisher's LSD tests. ***p < 0.001.
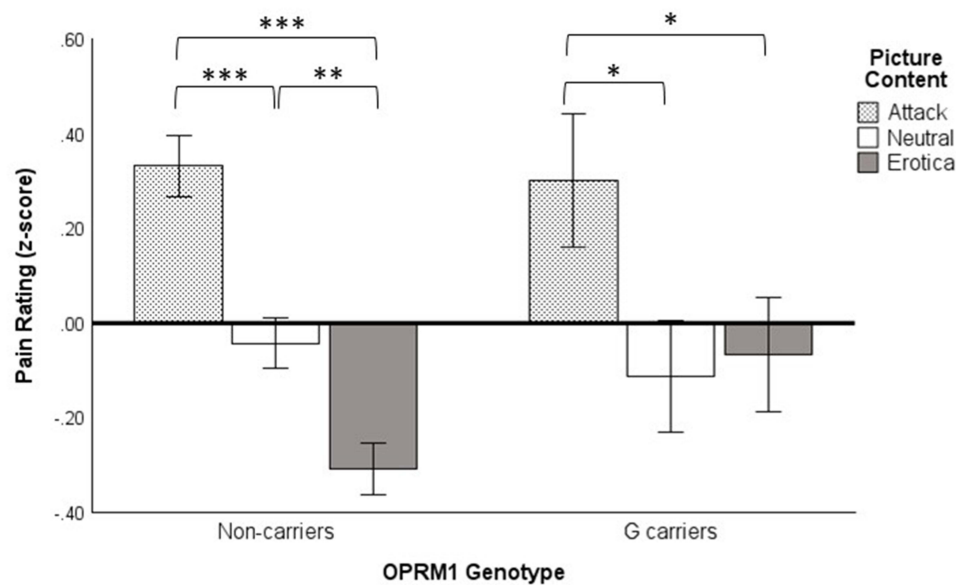
Figure 3 Pain ratings for OPRM1 A118G carriers and non-carriers for attack, neutral, and erotica picture contents. Results depict 1-tailed a priori planned comparisons of the simple effect of Picture Content using Fisher's LSD tests. *p < 0.05. **p < 0.01. ***p < 0.001.

content than in the other contents, ps < 0.01. The G-carrier group showed significantly greater pain ratings in attack content than in neutral or erotica content (ps < 0.05), but pain ratings for erotica and neutral content were not significantly differently ($p = 0.409$). Thus, G-carriers did not demonstrate pain inhibition while viewing erotica.

Figure 4 NFR scores for OPRM1 A118G carriers and non-carriers for attack, neutral, and erotica picture contents. Results depict 1-tailed a priori planned comparisons of the simple effect of Picture Content using Fisher's LSD tests. *p < 0.05.

Emotional Modulation of NFR Magnitudes

For NFR magnitudes, there were no significant effects of picture content, $F(2, 61) = 2.15, p = 0.125, \eta^2 = 0.07$, genotype, $F(1, 62) = 1.11, p = 0.295, \eta^2 = 0.02$, or Picture Content x Genotype interaction, $F(2, 61) = 0.52, p = 0.598, \eta^2 = 0.02$. Even so, a priori simple effects of picture content were explored by genotype group (Figure 4). Analyses of the simple effects of picture content were non-significant for both non-carriers, $F(2, 61) = 2.03, p = 0.140, \eta^2 = 0.06$, and G-carriers, $F(2, 61) = 1.19, p = 0.310, \eta^2 = 0.04$. In pairwise comparisons, NFR magnitudes were only significantly different between neutral content and erotica content among non-carriers, $p = 0.030$. Thus, inhibition of NFR by erotica was not observed in the G-carriers.

Discussion

The present study investigated how emotional modulation of pain (pain inhibition during pleasant stimuli and pain facilitation during unpleasant stimuli) is affected by the A118G polymorphism in the OPRM1 gene. Participants who did not carry the A118G polymorphism displayed pain, arousal, and valence ratings that were in line with previous research in emotional modulation.[6,25,36] They reported positive stimuli as being more pleasant (higher valence) and more arousing than neutral stimuli and reported negative stimuli as being more unpleasant and more arousing than neutral. They also reported that negative stimuli were more arousing than positive stimuli. Further, participants reported greater subjective pain during images of attack and less subjective pain during images of erotica, and NFR was inhibited by erotica. Carriers of the A118G polymorphism, while having similar modulation of valence/pleasure ratings as the non-carriers, showed altered responses to pleasant (erotica) stimuli. Specifically, G-carriers reported enhanced arousal to erotica, yet despite this, they showed impaired pain and NFR inhibition in response to erotica.

Appetitive Behavior and Pain Inhibition

In human participants, the A118G polymorphism has been shown to decrease opioid receptor availability in the anterior insula, amygdala, and thalamus.[15] These areas of the brain, all of which are associated with affective processing,[37,38] are suppressed in those with the A118G polymorphism. With regards to affect and the insular cortex, stimulation to the anterior insula in both non-human primates and rats suppresses appetitive behavior.[39,40] It can then be inferred that suppression of the anterior insula, which is seen with A118G carriers, may lead to the opposite effect, ie, enhanced appetitive behavior.
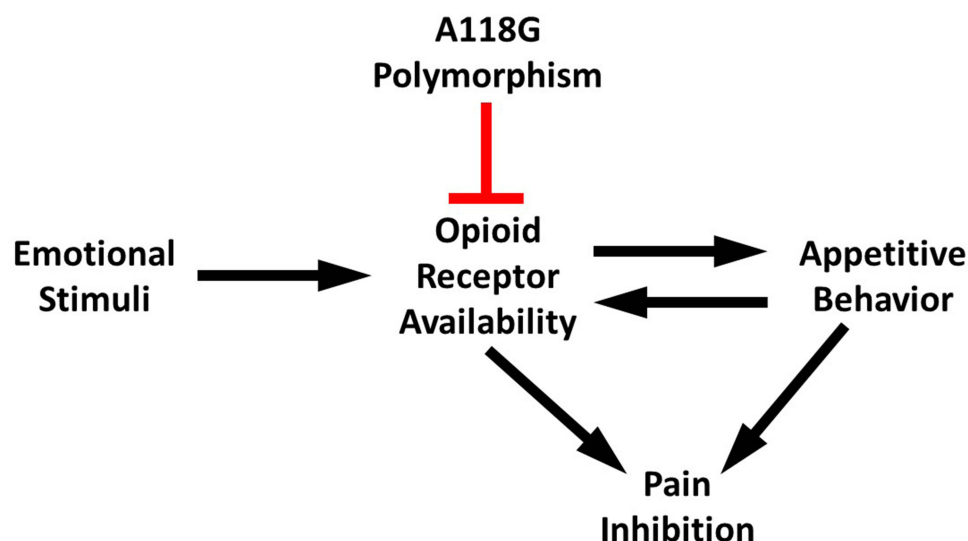
Figure 5 Possible pathway in which the A118G polymorphism impairs pleasure-induced pain inhibition.

Mu opioid receptor utilization in the amygdala is implicated in analgesic response and suppression of norepinephrine,[41,42] and opioid antagonists are associated with increases in norepinephrine.[42] With carriers of the A118G polymorphism showing higher sensitivity to social rejection, more affectionate relationships, and more social pleasure,[20,21] an increase in norepinephrine could explain the observed characteristics, as well as the higher arousal ratings for pleasurable stimuli noted in this study.

Appetitive motivation is normally associated with a surge of opioids, which stimulates opioid-mediated inhibition of pain.[43] This was not seen in G-carriers, suggesting that the typical inhibiting pathway may be disrupted. Given the role of opioids in pleasure and reward,[44] changes in participant reactions to pleasant stimuli as a result of reduced opioid receptor functionality are in line with expectations. This disruption of emotional modulation would impact how pain is reported in response to emotional stimuli. Opioid inhibiting pathways, either through opioid antagonists or deleterious polymorphisms of opioid receptors, would effectively make the pleasure-induced inhibition of pain impaired in G-carriers. Having established the role of opioids in pleasure and pain, carriers of the A118G polymorphism may be at risk for blunted inhibition of pain during pleasurable events. Figure 5 illustrates how the A118G polymorphism inhibits opioid receptor availability, thereby altering appetitive behavior and pain inhibition in response to emotional stimuli.

Implications

The novelty of the present study stems from the integration of opioid receptor polymorphisms with measures of affect and subjective pain. While previous studies have included a combination of the measures, no study to our knowledge has investigated them together. The present study provides preliminary evidence that pleasure-induced pain inhibition is attenuated in G-carriers. This vital pain regulating mechanism may be impaired in these individuals, potentially resulting in a vulnerability for a chronic pain disorder. It was already suggested that the A118G polymorphism could lead to individuals requiring a higher opioid dosage in order to experience normal analgesic effects.[22] With the additional finding that G-carriers exhibit a reduction in the pleasure-induced inhibition of pain, treatments that utilize cognitive-emotional procedures to suppress pain may not be as effective (eg, pleasant imagery). Treatment for individuals with the polymorphism should keep in mind the potentially impaired response to medications and emotion regulation therapies.

However, it is worth noting that the G-carrier group was older and had a higher proportion of men than the non-carrier group (albeit non-significant in both cases). Thus, results should be interpreted with caution. Indeed, given that chronic pain risk is higher in women,[45] our findings might underestimate the risk of being a G-carrier on impaired pleasure-induced pain inhibition and chronic pain.

Limitations

There were limitations in this study, one being low sample size. As a result of the low frequency of the A118G polymorphism in the population, there was a small sample of G-carriers in our study. Contamination present in the DNA samples also reduced the number of available samples to be analyzed. This reduced the power of the statistical tests performed and likely contributed to the lack of significant Picture Content x Genotype interactions for pain and NFR. As a result, the carrier group was unable to be split by sex to investigate potential interactions with the A118G polymorphism and pain. For example, female patients with lumbar pain who were carriers for the G allele, compared to male patient G-carriers, reported higher pain over a year.[46] Additionally, pain ratings in G-carriers were higher in women than men.[47] Thus, confounding effects of sex could be possible. Further, there are limitations in the scale of the genomic analysis performed in the current study, as only exon 1 of the OPRM1 gene was examined. There are other mutations that could result in reduced opioid receptor functionality, above and beyond the reduced functionality of the A118G polymorphism. Variations on other genes could also have an impact on the observed results, as seen with the relationship of serotonin transporter polymorphisms with the emotional modulation of pain.[25] Future studies should look to genome-wide analysis to limit the genetic uncertainty that is the nature of single-gene studies.

Summary

The present study found that the OPRM1 A118G polymorphism disrupts typical emotional modulation of pain. Although increased appetitive behavior is followed by pain inhibition in normal genotypes, this was not seen in carriers, despite greater arousal in response to appetitive stimuli. Instead, pain inhibition (and to some degree NFR inhibition) in response to appetitive stimuli was impaired leaving only pain facilitation in response to unpleasant stimuli. This imbalance in pain modulation could place G-carriers at risk for chronic pain.

Acknowledgments

Disclosure

The authors have no conflicts of interest to report for this work.

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