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Polymorphisms of catechol-O-methyltransferase (*COMT* rs4680:G>A) and μ-opioid receptor (*OPRM1* rs1799971:A >G) in relation to pain perception in combat athletes

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ABSTRACT: In athletes, pain has diverse functions and a complex etiology. Its role is not limited to indicating the limits of the body, especially in areas that are exposed to maximal forces and stresses and consequently vulnerable to damage or injury. Several common single nucleotide polymorphisms (SNPs) have been recently associated with inter-individual differences in pain perception. Among several other markers, catechol-O-methyltransferase (*COMT* rs4680:G>A) and the μ-opioid receptor (*OPRM1* rs1799971:A >G) were proposed as key factors for pain perception. The aim of the current study was to investigate the potential association between *COMT* and *OPRM1* genotypes and pain perception as well as the relation with elite athlete status. The study involved 395 healthy men, aged 18 to 28 years; 214 combat sports athletes comprised the experimental group and 181 non-athletes comprised the control group. DNA was extracted from buccal cells donated by the subjects, and genotyping for *COMT* rs4680 and *OPRM1* rs1799971 was carried out using real-time PCR. Measurement of the pain threshold and pain tolerance was performed using an algometer and the cold pressor test. The genotype distribution of *COMT* and *OPRM1* polymorphisms did not differ between combat athletes and the control group (p=0.500 and p=0.390). Pain threshold and pain tolerance as both quantitative and qualitative measures did not differ with respect to *OPRM1* and *COMT* polymorphism in either the combat or the control group for any of the analysed genetic models.

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INTRODUCTION

Pain perception (meaning not just physiological processing of nociceptive signals but rather conscious recognition and awareness of painful stimuli) can be modulated and modified (enhanced or abolished) by many environmental factors, including psychological and personality-related factors, somatization and catastrophizing, as well as physical activity.

Pain is an unavoidable part of the athletes' sport experience, regardless of whether the discipline involves contact with other athletes or not. In theory and clinical practice, physical activity is considered as one of the significant elements of prevention and treatment of pain. Numerous studies indicate that regular exercise reduces intensity of pain [1,2]. Furthermore, research on athletes shows an increase in the pain threshold and a higher tolerance to pain compared to physically inactive people [3,4]. These observations were confirmed by Raudenbush et al. [5], who additionally found that physical contact of athletes is a factor that may desensitize them to pain. Such data suggest that regular physical activity correlates with specific alterations in pain perception [6]. Reduced sensitivity to pain among athletes can be considered as a factor that increases the chance of achieving success in sport, but at the same time it can pose a potential threat to health, and in extreme cases, even to an athlete's life [7].

Although the relative impact of genetic versus environmental factors in human pain perception remains unclear, some explanation in this field is provided by animals models, in which heritability for nociceptive and analgesic sensitivities in mice is estimated to range from 28 to 76% [8]. Even though animal studies have provided a list of candidate 'pain genes', only a few of them have been identified as genes which are associated with the perception of pain in humans. These differences in pain sensitivity among humans and a growing amount of scientific research suggest that genetic factors might explain part of the observed variability [9].

Beside rare mutations, causing hereditary pain disorders, there are several common single nucleotide polymorphisms (SNPs) that have been recently associated with inter-individual differences in pain perception. Among the best characterized pain-related polymorphisms, there are variants of catechol-O-methyltransferase (*COMT*) and μ-opioid receptor (*OPRM1*) genes.

COMT is an enzyme that is involved in a number of physiological functions, including degradation of catecholamine neurotransmitters after their release in the synaptic cleft. A single *COMT* gene, located on chromosome 22q11, encodes both the acid-soluble (S-COMT) and membrane-bound (MB-COMT) forms of this enzyme. Compared to other tissues, the enzyme displays higher expression in the central nervous system (CNS) and the liver and degrades catecholamines such as dopamine, adrenaline, and noradrenaline. In general, low individual COMT activity has been related to increased pain sensitivity. The best-documented functional variation in the *COMT* gene is a G>A transition (rs4680), resulting in Val158Met amino acid substitution. This polymorphism is the only common non-synonymous SNP in the *COMT* gene and it is believed to decrease the enzyme stability and activity in Met-homozygous individuals to approximately 20–40% of that described in homozygotes for the Val variant. In an *in vitro* study, Diatchenko and colleagues observed that reduced COMT enzymatic activity enhanced pain sensitivity and that inhibition of COMT in rats resulted in a profound increase in pain sensitivity [10]. Hence, the *COMT* rs4680 SNP may potentially influence individual pain sensitivity and be one of the factors underlying the observed variability in pain perception.

The human OPRM1 gene is located on chromosome 6q24-q25 and spans over 200 Kb, with at least 9 exons and 19 different splice variants. The gene expression is under the control of multiple promoters, and its sequence comprises more than a hundred SNPs. Among these, 118A>G SNP (rs1799971) has been most extensively studied, primarily in pharmacogenetic research on opioid drugs. The variant allele (118G) has a frequency of 27%–48% in Asians, 11%–17% among Caucasians, 2.2% in African Americans, and 0.8% in sub-Saharan Africans. [11]. This SNP is located in exon 1 of the gene (substitution of an adenine with a guanine) and results in the change of a single amino acid at position 40 of the μ-opioid receptor protein (asparagine to aspartic acid, N40D), leading to the loss of a N-glycosylation site in the extracellular region of the receptor. The μ opioid receptor binds both exogenous and endogenous opiates, and it was observed that the 118G allele increased the ability of the receptor to bind β-endorphin. Hence, it can potentially modulate both the response to opioid therapy and the individual pain threshold [12]. What is more, the high central concentration of endorphins may decrease the density of opioid receptors and consequently it may influence pain perception.

Exploring the genetic basis of human variation in pain is vital to understanding the molecular basis of pain sensitivity, variable responses to analgesic drugs, and treatment individualization. Recent studies demonstrated that specific gene variants may influence pain sensitivity and analgesic drug responses [13,14]. *COMT* and *OPRM1* genes seem to be candidates for genetic markers of performance in selected sports among other previously investigated markers [15]. Since pain is an unavoidable part of the athletes' sport experience (especially in the case of combat sports), genetic variants with an impact on pain perception may be among factors related to individual predisposition to professional combat competition.

The aim of the current study was to investigate the potential association of *COMT* and *OPRM1* genotypes with experienced elite combat athlete status. Furthermore, the association between *COMT* and *OPRM1* genotypes and pain perception (pain threshold and pain tolerance), both in combat athletes and the control group, was evaluated.

MATERIALS AND METHODS

Participants

The study involved 395 healthy men, aged 18 to 28 years. The experimental group consisted of 214 combat athletes aged 18 to 28 (24.7 ± 6.6) years, with at least five-year long experience, including: boxing (n = 101), karate (n = 85) to a minimum level of 1 KYU and different martial arts (n = 28). The control group consisted of 181 students of the Faculty of Physical Culture, University of Szczecin, Poland, not involved in any sport at a professional level, aged between 18 and 26 (21.1 ± 1.8) years. All subjects were genotyped for common variants of *COMT* and *OPRM1* genes, and were included in a case-control study. Pain sensitivity was evaluated by means of the cold pressor test (CPT) (a subgroup of 211 cases and all 181 controls) and the pressure pain test (PPT) (all 214 cases and a subgroup of 92 controls) in subsets of individuals who agreed to participate in these parts of the study.

The Pomeranian Medical University Ethics Committee (Szczecin, Poland) approved the study and written informed consent was obtained from each participant. The study complied with the guidelines set out in the Declaration of Helsinki.

Genotyping

Genomic DNA was extracted from buccal swab samples, using Genomic Micro AX SWAB Gravity (A&A Biotechnology, Poland), and subsequently standardized to equal concentrations of 10 ng/μl, based on spectrophotometric absorbance measurement (260/280 nm).

Genotyping for *COMT* rs4680 and *OPRM1* rs1799971 SNPs was performed using a pre-validated allelic discrimination TaqMan real-time PCR assay (assay IDs: C__25746809_50 and C___8950074_1_, Life Technologies, USA), and TaqMan GTXpress Master Mix (Life Technologies, USA). All reactions were run in a final volume of 12 μl. Fluorescence data were captured using the ViiA7 Real-Time PCR System (Applied Biosystems, USA) after 40 reaction cycles. Specific genotypes were assigned to individual samples after analysis with TaqMan Genotyper software (Thermo Fisher Scientific, USA).

Cold pressor test (CPT)

While testing, the participants submerged their right hand below the wrist into a container with water at 37°C agitated by a pump for 2 min to acclimatize the skin [16]. Subsequently, the participants relocated their hand into a glass container with a freezing-cold water mixture between 0°C and 0.5°C, with an installed thermometer to observe the temperature. The hand was kept in the ice water until the participants were not able to withstand the pain any longer. The participants were asked to say "pain" when they experienced the first physical sensation of pain in the hand. There were required to specify the sensation of pain as it began (pain threshold) and again when the pain began to be unbearable (pain tolerance threshold). The upper limit of time during which the hand could be left in the container was 120 seconds, but the participants were not informed about the cut-off moment. The tolerance of pain was calculated in seconds.

Pressure pain test (PPT)

Measurement of the sensitivity of tissues to compression was performed using an algometer manufactured by Quirumed (Spain). The device is a force gauge, ranging from 0 to 10 kg, fitted with a disc-shape rubber tip bearing a surface of exactly 1 cm^2. The results obtained by the individuals were classified in one of the two measurement intervals, i.e. below or above 10 kg. Before the measurement of sensitivity to compression was taken, each participant was in the same manner informed about the purpose and course of the study and received guidance on behaviour. Three test measurements were also carried out so that the participant could prove the compression arousing pain. He was also able to react in a timely manner and complete the measurement of pressure.

The test was conducted in a sitting position, with the right upper limb, bent at the elbow, being placed on the table. The participants were asked to put the hand on the table. First, the researcher evaluated the point of contact by palpation, then applied the pressure head between the thumb and forefinger at an angle of 90° and compressed it against the body with an increasing force, at the rate of 100 g/s. The measurement results were visible only to the person conducting the test.

All measurements were performed by the same investigator, in the morning hours and under the same conditions.

Statistical analyses

Since distributions of most of the analysed quantitative parameters were significantly different from a normal distribution (Shapiro-Wilk test), we used the non-parametric Mann-Whitney U-test to compare them between groups. The chi^2 test was used to compare qualitative variables between genotype groups. $P<0.05$ was considered statistically significant.

RESULTS

The observed distribution of *COMT* rs4680 and *OPRM1* rs1799971 genotypes was in concordance with the Hardy-Weinberg equilibrium, both in athletes and the control group ($p>0.1$).

The athletes were significantly older, shorter and had a higher mean BMI value compared with the control group (Table 1). The genotype distribution of *COMT* and *OPRM1* polymorphisms did not differ between combat athletes and the control group ($p=0.500$ and $p=0.390$, respectively, Table 2). Since *OPRM1* GG homozygotes were observed only in single individuals, AG and GG genotypes were pooled together for further analyses. Pain threshold and pain tolerance as both quantitative and qualitative($\leq$10.0 kg/cm^2 vs >10.0 kg/cm^2) measures did not differ with respect to *OPRM1* and *COMT* polymorphisms in either the combat or control group for any of the analysed genetic models (Tables 3-4).

TABLE 1. Demographic and anthropometric data of the combat athletes and control group.

Variables	Combat athletes (n = 214) Mean ± SD	Control group (n = 181) Mean ± SD	*p*-value
Age (years)	24.67 ± 6.57	21.1 ± 1.8	**0.0002**
Height (cm)	178.6 ± 7.04	181.6 ± 7.4	**0.0002**
Body mass (kg)	78.21 ± 13.15	77.7 ± 9.6	0.75
BMI (kg/m^2)	24.46 ± 3.33	23.5 ± 2.1	**0.006**

P-values evaluated by means of Mann-Whitney U-test. Mean and standard deviations are given.

TABLE 2. Observed *COMT* rs4680 and *OPRM1* rs1799971 genotype and allele frequencies in cases and control subjects.

Group	**COMT rs4680:G>A**						
	GG	**GA**	**AA**	**p**	**G**	**A**	**p**
Athletes (n=214)	58 (27.1)	106 (49.5)	50 (27.1)	0.500	222 (51.9)	206 (48.1)	0.286
Controls (n=181)	40 (22.1)	94 (51.9)	47 (26.0)		174 (48.1)	188 (51.9)	
Group	**OPRM1 rs1799971 G>A**						
	AA	**AG**	**GG**	**p**	**A**	**G**	**p**
Athletes (n=214)	178 (83.2)	34 (15.9)	2 (0.9)	0.390	390 (91.1)	38 (8.9)	0.984
Controls (n=181)	149 (82.3)	32 (17.7)	0 (0)		330 (91.2)	32 (8.8)	

P-values evaluated by means of chi^2 test. Numbers and percentages (in parentheses) are given.

TABLE 3. *COMT* rs4680:A>G genotype in relation to cold pressor test (CPT) and pressure pain test (PPT) measurements in combat athletes and control subjects.

Combat athletes' genotypes (n=211)					**p** [a]	
Phenotype	AA (n=48)	AG (n=105)	GG (n=58)	GGvs.AG	GGvs.AA	AGvs.AA
CPT1 (s)	20.8 ±25.2	25.1 ± 27.2	28.90 ± 29.42	0.41	0.16	0.4
CPT2 (s)	92.5 ± 33.0	100.1 ± 31.4	100.07 ± 32.48	0.94	0.18	0.075
Combat athletes' genotypes (n=214)						
	AA (n=50)	AG (n=106)	GG (n=58)		p [b]	
PPT1 ≤10 kg/cm^2	39 (78.0%)	74 (69.8%)	45 (77.5%)		0.41	
PPT1 >10 kg/cm^2	11 (22.0%)	32 (30.2%)	13 (22.4%)			
PPT2 ≤10 kg/cm^2	6 (12.0%)	10 (9.4%)	2 (3.5%)		0.24	
PPT2 >10 kg/cm^2	44 (88.0%)	96 (90.6%)	56 (96.6%)			
Control group genotypes (n=181)					**p** [a]	
Phenotype	AA (n=47)	AG (n=94)	GG (n= 40)	GGvs.AG	GGvs.AA	AGvs.AA
CPT1 (s)	26.5 ±22.9	25.5 ± 23.9	28.38 ± 25.16	0.47	0.76	0.62
CPT2 (s)	86.9 ± 35.4	90 ± 34.4	88.73 ± 36.02	0.40	0.84	0.60
Control group genotypes (n=92)						
	AA (n=24)	AG (n=50)	GG (n= 18)		p [b]	
PPT1 ≤10 kg/cm^2	24 (100%)	50 (100%)	17 (94.44 %)		0.13	
PPT1 >10 kg/cm^2	0 (0%)	0 (0%)	1 (5.56%)			
PPT2 ≤10 kg/cm^2	9 (37.5 %)	23 (46.0%)	5 (27.78%)		0.38	
PPT2 >10 kg/cm^2	15 (62.5%)	27 (54.0%)	13 (72.22%)			

CPT1 – pain threshold; CPT2 – pain tolerance; PPT1 – pain threshold; PPT2 – pain tolerance. [a] Mann-Whitney U-test. [b] chi^2 test.

DISCUSSION

Sensitivity to pain is a subjective feeling and varies widely between individuals. There is a suggestion that about half of the variation in individual sensitivity to pain is associated with the influence of genetic factors [17]. More than 350 candidate pain genes have been identified as potentially involved in hereditary differences in pain sensitivity [18]. The contribution of each gene is likely to have only a subtle effect on this multiplicity of mechanisms, making its signal difficult to detect. Even though the individual gene effects may be small, interactions between the genes and the environment may make a substantial contribution to the final manifestation of pain sensitivity. In spite of recent technological progress, it is still necessary to choose candidate genes within the identified regions based on their biological role and examine them for informative polymorphisms [19].

Low COMT activity has been associated with increased pain sensitivity in human pain studies, and COMT inhibitors sensitize to thermal and mechanical pain in animal studies [20]. Since the *COMT* gene is highly polymorphic and some of the common COMT variants may influence enzyme activity, many authors have pointed to *COMT*

TABLE 4. *OPRM1* rs1799971 A>G genotype in relation to cold pressor test (CPT) and pressure pain test (PPT) measurements in combat athletes and control subjects.

Combat athletes' genotypes (n=211)			
Phenotype	AA (n=175)	AG+GG (n=36)	p [a]
CPT1 (s)	25.2 ± 27.3	24.7 ± 28.5	0.92
CPT2 (s)	98.5 ± 32.0	98.0 ± 32.6	0.95
Combat athletes' genotypes (n=214)			
	AA (n=178)	AG+GG (n=36)	p [b]
PPT1 ≤10 kg/cm^2	130 (73.0%)	28 (77.8%)	0.68
PPT1 >10 kg/cm^2	48 (27.0%)	8 (22.2%)	
PPT2 ≤10 kg/cm^2	13 (7.3%)	5 (13.9%)	0.20
PPT2 >10 kg/cm^2	165 (92.7%)	31 (86.1%)	
Control group genotypes (n=181)			
Phenotype	AA (n=149)	AG+GG (n=32)	p [a]
CPT1 (s)	25.5 ± 24.4	29.3 ± 20.8	0.27
CPT2 (s)	85.1 ±35.1	90.4 ± 33.8	0.43
Control group genotypes (n=92)			
	AA (n=76)	AG+GG (n=16)	p [b]
PPT1 ≤10 kg/cm^2	75 (98.7%)	16 (100%)	1.00
PPT1 >10 kg/cm^2	1 (1.3%)	0	
PPT2 ≤10 kg/cm^2	31 (40.8%)	6 (37.50%)	1.00
PPT2 >10 kg/cm^2	45 (59.2%)	10 (62.30%)	

CPT1 – pain threshold; CPT2 – pain tolerance; PPT1 – pain threshold; PPT2 – pain tolerance. [a] Mann-Whitney U-test. [b] chi^2 test.

genetic diversity as one of the factors associated with individual differences in pain sensitivity [14]. In the *COMT* gene the only commonly occurring SNP changes the sequence of the encoded protein rs4680G>A, leading to the transition of valine 158 (stable variant COMT H (GG)) into methionine (unstable variant COMT L (AA)). There are many reports on the effect of the *COMT* gene polymorphism on life processes, and the *COMT* polymorphic variants are associated with various disorders. An association between the rs4680 *COMT* variant and chronic pain syndromes, such as migraine, back pain, headaches or mandibular joint pain, has been observed in many independent populations [21,22]. It was observed that AA individuals have a tendency to greater sensitivity to pain than GG homozygotes [21]. Nonetheless, differences between individuals in pain sensitivity are the main methodological challenge in this field of research.

In this study we examined the association of a common SNP in the *COMT* gene (rs4680:G>A) and pain perception in athletes and a control group using two different diagnostic methods involving thermal and mechanical stimuli. Combat athletes did not differ in the frequency of the *COMT* genotype compared to the control group (Table 2). In both examined groups we observed no significant differences in CPT and PPT (current perception threshold and pressure pain tolerance) between groups with various genotypes (GG vs GA vs AA). Similar research was carried out by Kambur et al. [23] among breast cancer patients who reported an association of high tolerance and low sensitivity to cold and heat pain with the rs4680 variant.

However, a distinct majority of scientific reports do confirm a connection between sensitivity to pain and the activity of the *COMT* gene. According to their results, GG homozygotes are decidedly more resistant to pain stimuli than AA [24,25].

The study by Nackley et al. [26] demonstrated that not only rs4680:A>G but also other, silent SNPs (not associated with amino acid sequence alterations) may influence COMT activity, by affecting RNA stability, which finally results in reduced protein function. Hence, the effect of the *COMT* haplotype on enzyme activity, together with ethnic differences in allele frequencies and linkage of single loci, may be among the reasons for the observed discrepancies between the results of different studies.

The athletes in our study whose genotype contained one or two copies of the G allele were not more resistant to pain when compared to healthy non-athletes. Therefore, our results indicate a lack of association between the specific *COMT* gene allele with cold and pressure pain in both studied groups. This also indicated that the individual variability in pain sensitivity may be associated with other gene variants or non-hereditary factors such as the activity of the

sympathetic system (significant in the cold pressor test), the endogenous system of pain inhibition, psychological characteristics or environmental factors.

Another SNP analyzed in both groups was located in the gene encoding the μ-opioid receptor (μ-opioid *OPRM1*). Previous studies have shown that carriers of the AA *OPRM1* genotype require significantly lower daily doses of morphine than patients with other genotypes [27]. This was confirmed by a study on patients following abdominal hysterectomy and Caesarean section. This suggests that the minor G allele of rs1799971 may contribute to a decrease in sedation score in carriers, and thus merits further investigation in additional, larger postoperative patient populations [28].

In the group of combat athletes and in the control group we assessed the relationship between the rs1799971 *OPRM1* gene variant and selected phenotypic features. In the control group, none of the participants had the GG genotype, and among athletes there were only 2 people with the GG genotype of the rs1799971 *OPRM1* gene variant, and therefore we combined GG homozygotes with GA heterozygotes. We found no significant differences in CPT and PPT between groups with different genotypes (GA+ AA vs GG).

Our findings indicate no association between the *OPRM1* rs1799971A>G variant and pain sensitivity in both groups. The assessment of an association between the pain threshold and tolerance to pain caused by various physical stimuli (cold, pressure) and *OPRM1* gene polymorphism showed no relationship with the genotype. Hence the influence of genetic factors on the experimentally induced pain sensation in the group of combat athletes remains unclear. Most studies confirm that the presence of the G allele is associated with a higher tolerance to pain. It is worth noting that the low prevalence or lack of the G allele in the studied population strongly limits the interpretation of the results.

The examined individuals belong to the elite of Polish combat athletes. They perceive pain as an immanent part of their long daily training sessions. In the light of the studies we observed no association of low sensitivity to pain in athletes with the selected *COMT* and *OPRM1* gene variants. Possibly, as suggested by other researchers, perception of pain may be more influenced by psychological factors, gender, and ethnic origin than the genetic component [29]. On the other hand, many reports confirm that the perception of pain is a polygenic trait; hence further studies should be extended with more genes and intergenic interactions [30].

Most studies of genetic determinants of pain refer to people reporting pain in various diseases or acute inflammatory pain resulting from controlled tissue damage (surgery). Few focus on experimentally induced pain in healthy individuals. It is very important to accurately define the phenotype of pain because even subtle differences may activate completely different paths of pain physiology [31]. Experimental pain is a substitute for clinical pain, as the precise relationship between experimental-pain and clinical-pain experiences is not clearly established [32].

Thus, the identification of factors that determine a higher tolerance to pain in athletes would significantly contribute to the understanding, prediction and modulation of behaviours in the case of injuries and in adopting appropriate interventions. It would also help in designing appropriate training or educational programmes not only for athletes but also for people affected by pain. Additional research to further characterize the role of *COMT* and *OPRM1* in pain and analgesia could provide important information for therapeutic interventions.

As for professional athletic performance, numerous genetic variants have been recently investigated and associated with predisposition and performance in multiple sports: endurance- [33,34,35] and power-related ones [36,37]. However, some genotypes were not confirmed as genetic markers of exercise performance in the Polish population [38], and further studies are needed.

This study can be considered fully innovative, although limited by the inability to compare the results with literature data (due to the lack of studies on athletes). Additional limitations of this study are the small sizes of study groups and the small number of examined SNPs.

CONCLUSIONS

COMT rs4680 and *OPRM1* rs1799971 polymorphisms are not related to the perception of pain (pain threshold and pain tolerance) measured by CPT and PPT in Polish athletes and non-athletes. The individual variability in pain sensitivity may be associated with other gene variants or non-hereditary factors.

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