ORIGINAL ARTICLE

Is pain tolerance in boxers altered by nucleotide polymorphism rs6746030 in the SCN9A gene?

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A Study Design
B Data Collection
C Statistical Analysis
D Manuscript Preparation
E Funds Collection

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Abstract

Background and Study Aim: In sport, pain plays a pivotal but dual role which is still not fully understood and requires closer cooperation between specialists in the fields of sports medicine, sports science and psychology. The aim of this study was the knowledge about the possible association between rs6746030 (G/A substitution) genotype variants and pain tolerance in boxers.

Material and Methods: Ninety-nine boxers completed the cold pressor test (CPT), a standard laboratory technique used to measure pain tolerance and the pain threshold. Heart rate and blood pressure were measured at three-time points during the CPT. Three hundred and thirty-two non-athletic subjects served as a control group.

Results: Chi-square test analysis showed no significant differences in genotype or allele frequencies between cases and control subjects (p = 0.963 for both genotypes and alleles). Contrary to the results of other studies, the *SCN9A* rs6746030 genotype did not affect phenotypic variables of pain.

Conclusions: Pain seems to be a complex trait. It is likely that several gene loci, each with a small but significant contribution, are responsible for this genetic component. Further large, well-designed studies are necessary to determine its genetic background.

Keywords: cold pressor test • genotype • pain threshold • pain tolerance

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INTRODUCTION

Pain is a necessary and informative sensory experience which encourages avoidance of danger and recuperative behaviour that promotes healing and protection of an injured or diseased area of the body [1]. However, in sport pain plays a pivotal but dual role which is still not fully understood and requires closer cooperation between specialists in the fields of sports medicine, sports science and psychology [2]. A lower threshold of pain is more effective as a preventive and precautionary factor [3]. On the other hand, a higher threshold of pain may allow sportspersons to continue competing in sports in situations where others cannot. In this context, a higher threshold of pain allows one to overcome the limits of pain and consequently to achieve success.

Long-term physical activity (in ballet dancers, similarly to sports professionals) may alter pain, due to which athletes may possess higher pain thresholds and higher tolerance than normally active persons [4]. Pain tests performed among competitive swimmers and non-competitive athletes showed that while pain thresholds differed little between the groups, pain tolerance levels were considerably different [5]. These observations were confirmed by Raudenbush et al. [6], who additionally found that physical contact of athletes is a factor that may desensitise them to pain.

Such data suggest that regular physical activity is associated with specific alterations in pain tolerance [2]. There are some factors other than physical activity [7] that can influence pain threshold values, including age [8], gender [9], stress [10] and supporting persons [11].

Coping with pain is not only an integral part of athletic training (in boxers, triathletes and marathon runners, among others) but is also one of the crucial skill in fighting sports. Because of the systematic exposure to brief periods of intense pain, athletes are forced to develop efficient pain-coping skills. Through physical experience, athletes learn not only how to minimise the impacts but, first of all, how to build the mental toughness which is necessary to push through simple pain and fatigue – to keep going as long as they can think and move [12].

Factors that may be responsible for the high inter-individual difference in pain responses and reporting of pain are still discussed [13]. While a variety of cultural, psychological and personal factors contribute to variability in pain tolerance [14], a crucial role may be played by genetic variability [15]. All nociceptive assays display moderate-to-high heritability (h^2 = 0.30-0.76) mediated by a limited number of apparent genetic loci [16, 17]. It is worth mentioning that pain genetics is complex. The heterogeneity of the investigated groups is difficult to deal with, as gender, age, temper and ethnicity have been shown to interact with a polymorphism in certain genes and may influence the experimental pain sensitivity.

The era of genetic analyses started in the early 2000s after the development of molecular biological methods, which have enabled researchers to apply genome-wide association studies (GWASs) to the field [18-20]. This has led to verification studies and analysis of possible associations of single-nucleotide polymorphisms (SNPs) with physiological traits [21-23].

The action and function of nociceptors may be modulated by the gene expression of ion channels or receptors in response to tissue damage and/or inflammatory processes [24-26]. Some of the investigations pointed to a crucial role of SCN9A gene mutations [27, 28], which can result in syndromes characterised by either excessive pain or insensitivity to pain. Apart from rare disease-associated mutations, there are multiple SNPs in the human SCN9A gene, raising the possibility that allelic differences in this gene might influence nociception in the general population [29].

SCN9A encodes the α-subunit of the voltage-gated sodium channel Nav1.7, which is expressed at high density in nociceptive neurons [30]. This protein plays a role in pain mechanisms, especially in the development of inflammatory pain. Of the nine voltage-gated sodium channel subtypes, Nav1.3, Nav1.7, Nav1.8 and Nav1.9 are expressed primarily in sensory nerves [31]. The Nav1.7 sodium channel encoded by the SCN9A gene is widely expressed in dorsal root ganglion neurons, and it has an essential role in nociceptive neurotransmission [32, 33]. A genetic association study revealed a significant association between the SCN9A SNP rs6746030 (G/A substitution) and pain [29]. On the other hand, an animal model did not confirm that finding, providing contradictory results [34].

Pain – *noun* the feeling of severe discomfort that a person has when hurt (NOTE: Pain can be used in the plural to show that it recurs: She has pains in her left leg.) [43].

Pain barrier – the point at which pain reaches its peak and begins to diminish, especially as experienced by an athlete [43].

Pain – is an emotion experienced in the brain, can be perceived as a warning of potential damage, but can also be present when no actual harm is being done to the body.

Pain tolerance – the maximum stimulus intensity, or the maximum time of continuous painful stimulation that a subject is willing to endure.

Pain threshold – an entirely subjective phenomenon. It is the point on a curve of increasing perception of a stimulus at which pain begins to be felt.

Genotype – a description of the genetic information carried by an organism. In the simplest case, the genotype may refer to the information carried at a single locus, as in A/A, A/a, or a/a.

Allele – either of a pair (or series) of alternative forms of a gene that can occupy the same locus on a particular chromosome and that control the same character.

Polymorphism – a piece of DNA that has more than one form (allele), each of which occurs with at least 1% frequency. Polymorphisms are a normal part of genetic variability.

Single nucleotide polymorphisms (SNP) – the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide.

Table 1. Demographic and phenotypic characteristics (mean values and standard deviations) of 99 boxers.

Variable	Mean, SD
Age (years)	22 ±4
BMI (kg/m^2)	23 ±3
Pain threshold (seconds)	37 ±22
Pain tolerance (seconds)	94 ±34
HR1 (beats/minute)	71 ±13
HR2 (beats/minute)	74 ±13
HR3 (beats/minute)	72 ±12
RRs1 (mmHg)	139 ±14
RRs2 (mmHg)	139 ±15
RRs3 (mmHg)	141 ±15
RRd1 (mmHg)	72 ±11
RRd2 (mmHg)	77 ±11
RRd3 (mmHg)	76 ±12

HR heart rate; **RRs** systolic blood pressure; **RRd** diastolic blood pressure; **HR1** resting heart rate; **HR2** pulse at pain threshold; **HR3** heart rate at pain tolerance; **RRs1** systolic blood pressure at rest; **RRs2** systolic blood pressure at pain threshold; **RRs3** systolic blood pressure at pain tolerance; **RRd1** diastolic blood pressure at rest; **RRd2** diastolic pressure at pain threshold; **RRd3** diastolic pressure at pain tolerance

The aim of this study was the knowledge about the possible association between rs6746030 (G/A substitution) genotype variants and pain tolerance in boxers. We hypothesised that the A allele of rs6746030 would be associated with an altered pain threshold.

MATERIAL AND METHODS

Participants

The experimental group consisted of 101 male boxers (aged 22 ± 4) with at least five years of experience, 99 of whom completed all measurements (two did not agree to participate in the full protocol of measurements of pain threshold and pain tolerance). Athletes who participated in the research were elite professional boxers and were selected from the leading representatives of Poland in that discipline. To establish the frequency of the SCN9A variant alleles in a Polish population, the rs6746030 genotype was additionally determined in a group of 332 consecutive newborns (180 females and 152 males) delivered in the County Hospital, Szczecin, Poland, which served as population control.

All measurements were performed by the same investigator in the morning, between 9 a.m. and 11 a.m., under the same conditions to avoid a circadian rhythm effect. The participants were informed about the nature of the experiment and had the possibility of withdrawal from the study for any reason. All participants gave written informed consent to participate in the research. The study was approved by the Bioethics Committee of the Regional Medical Chamber in Szczecin (No. 09 / KB / V / 2013).

Cold pressor test

The cold pressor test (CPT) is a standard method used in scientific research to measure pain and pain tolerance thresholds. In the test, participants immersed their right hand up to the wrist in a tank containing water circulated using a pump and maintained at 37°C for 2 min. The hand remained in the water in order to normalise skin temperature [35]. After that, participants relocated their hand to a glass container with a freezing-cold water mixture between 0 and 0.5°C, with an installed thermometer to observe the temperature. Their hand remained in the ice water until they were not able to withstand the pain any

Table 2. SCN9A genotype and allele frequencies in boxers and control groups.

Group	Number (%)			p (chi-square)	Number (%)		p (chi-square)
	GG	GA	AA		G	A	
Boxers (n = 101)	78 (77.2)	21 (20.8)	2 (2.0)	0.963	177 (87.6)	25 (12.4)	0.963
Controls (n = 332)	257 (77.4)	67 (20.2)	8 (2.4)		581 (87.5)	83 (12.5)	

GG homozygotes; **GA** heterozygotes; **AA** homozygotes; **G** allele; **A** allele.

longer. Participants were asked to state "Pain" when they experienced the first sensation of pain in hand. There were required to indicate the pain sensation when it began to hurt (pain threshold) and at the moment when the pain became unbearable (pain tolerance threshold). The upper limit of time during which the hand could be kept in a bucket was 120 s, but the participants were not informed about that cut-off point in advance. The pain tolerance/threshold was calculated in seconds. During testing the blood pressure and the pulse were measured at three different time points: 1) before putting the hand into the cold water, 2) at the moment when the participants reached the pain threshold, 3) at the time the test was over. All measurements were taken on the left hand.

All measurements were carried out in a sitting position. Blood pressure was recorded from a cuff on the left wrist (the right hand was submerged in water). Measurements were taken continuously every 30 seconds using an Omron Type 2 device (OMRON Corporation, Japan).

Genotyping

Genomic DNA was extracted from buccal swab samples, using Genomic Micro AX SWAB Gravity (A&A Biotechnology, Poland), and subsequently standardised to equal concentrations of 10 ng/µl, based on spectrophotometric absorbance measurement (260/280 nm). The SNP within the SCN9A gene was evaluated using a pre-validated allelic discrimination TaqMan real-time PCR assay (assay ID: C_29330435_10, 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 7500 FAST Real-Time PCR System (Applied Biosystems, USA) after 40 reaction cycles.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) for SCN9A was assessed separately in boxers and control subjects with a $\chi 2$ test using the "genetics" package for the programming language and environment R (http://www.r-project.org). Potential differences in genotype and allele frequency between boxers and control individuals were analysed using the c2 test. Checking the assumption of normality was carried out with the Shapiro-Wilk test. The independent samples t-test or non-parametric Mann-Whitney test was used to compare variables between genotype groups. Non-normally distributed data were presented as a median and interquartile range (IQR) and other data as a mean ± standard deviation. In the group of boxers, evaluation of the correlation between SCN9A rs6746030 gene polymorphism and selected phenotypic traits was performed. All calculations, except HWE, were performed with STATISTICA (StatSoft, version 10.0 www.statsoft.com). P values <0.05 were considered statistically significant.

RESULTS

Demographic and phenotypic characteristics of boxers are presented in Table 1. For both study groups, the observed SCN9A rs6746030 genotypes were distributed in Hardy-Weinberg equilibrium (in boxers p = 0.685 and control subjects p = 0.135). There were no significant differences between boxers and control subjects (p = 0.963 for both genotypes and alleles). Among the boxers, there were only 2 subjects with genotype AA for polymorphism rs6746030 of the SCN9A gene, and therefore AA homozygotes were pooled with GA heterozygotes. Owing to the low number of AA homozygotes (n = 2), the GA heterozygotes and AA homozygotes were pooled for further analyses (Table 2).

Table 3. Association of SCN9A rs6746030 polymorphism with measured traits in boxers (t-test unless stated otherwise).

Variable (phenotype indicator)	GG (n = 77)	GA+AA (n = 22)	p value*
HR1 (beats/minute)	71 ±14	69 ±11	0.482
HR2 (beats/minute)	74 ±13	74.7 ±13.4	0.730
HR3 (beats/minute)	73 ±12	70 ±11	0.289
RRs1 (mmHg)	139 ±14	137 ±13	0.584
RRs2 (mmHg)	140 ±15	137 ±13	0.400
RRs3 (mmHg)	141 ±15	138 ±17	0.317
RRd1 (mmHg)	73 ±12	70 ±10	0.262
RRd2 (mmHg)	78 ±11	74 ±11	0.202
RRd3 (mmHg)	77 ±11	73 ±14	0.148
Pain threshold (seconds)	37 (24÷46)	31 (24÷42)	**0.437‡**
Pain tolerance (seconds)	120 (67÷120)	106.5 (59÷120)	**0.439‡**

***p** value for correlation between SCN9A rs6746030 gene polymorphism and selected phenotypic traits; **HR** heart rate; **RRs** systolic blood pressure; **RRd** diastolic blood pressure **HR1** resting heart rate; **HR2** pulse at pain threshold; **HR3** heart rate at pain tolerance; **RRs1** systolic blood pressure at rest; **RRs2** systolic blood pressure at pain threshold; **RRs3** systolic blood pressure at pain tolerance; **RRd1** diastolic blood pressure at rest; **RRd2** diastolic pressure at pain threshold; **RRd3** diastolic pressure at pain tolerance; **GG** homozygotes; **GA** heterozygotes; **AA** homozygotes; **‡** Mann-Whitney test; **±** standard deviation.

There was no association between SCN9A genotype and any of the other phenotypic traits such as heart rate (HR1-HR3) and systolic (RRs1-RRs3) or diastolic (RRd1-RRd3) blood pressure. Also, there were no significant differences in CPT results (pain threshold and pain tolerance) between groups with different genotypes (GG vs GA+AA) (p = 0.437 and p = 0.439, respectively) (Table 3).

DISCUSSION

We investigated the potential association of a common SNP in the SCN9A gene (rs6746030: G>A) and pain tolerance in boxers. On the basis of the study group, it can be assumed that SCN9A rs6746030 is not a factor predisposing to professional boxing training and it does not influence the pain threshold or tolerance in the Polish population. We failed to confirm the initial hypothesis.

The pain was defined in 1979 in the scientific journal *Pain* – the official body of the International Association for the Study of Pain (IASP). This sensory phenomenon was characterised as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [36]. It means that pain must be considered in terms other than just pure sensation [2].

Pain is a highly subjective feeling, and there exists great inter-individual variability in sensitivity to pain. Environmental factors such as age, gender, physiological conditions, psychological, cultural and social influences may affect the subject's pain tolerance. There is a suggestion that about half of the variation in individual sensitivity to pain is related to the influence of genetic factors [37]. More than 350 candidate pain genes have been identified as potentially involved in hereditary differences in pain sensitivity. Although there have been many association studies to assess the impact of SNPs in different genes encoding receptors, enzymes and ion channels involved in pain modulation and analgesia, the findings have generally failed to be replicated or have been only partially replicated [38].

One of the pain candidate genes is SCN9A. The SCN9A gene encodes the alpha subunit of the sodium channel NaV1.7 located in nociceptors involved in transmitting pain signals. Rare lack-of-function mutations in the SCN9A gene cause

congenital insensitivity to pain. Conversely, gain-of-function mutations result in erythromelalgia, paroxysmal extreme pain disorder, some cases of small fibre neuropathy (a condition characterised by severe pain attacks and a reduced ability to differentiate between hot and cold), and many other disorders. The number of diseases caused by severe mutations in the SCN9A gene raises interest in whether any subtle and more common changes in this gene such as polymorphisms may be associated with differences in pain tolerance in the general population, or even among athletes of various disciplines.

A meta-analysis of 2 groups of British patients (one with knee osteoarthritis and one with multiple regional pain, in total 4295 samples) for polymorphism rs6746030 of the SCN9A gene showed a significant association of rs6746030 and multiple regional pain [OR of 1.40 (95% CI 1.08, 1.80; p = 0.0085)] [39]. The meta-analysis of symptomatic vs asymptomatic osteoarthritis did not detect an association with this polymorphism variant. That study revealed that the R1150W amino acid change in the NaV1.7 alpha-chain is associated with multiple regional pain. It was confirmed that rs6746030 is involved in genetic susceptibility to pain, but it does not appear to have a major role in osteoarthritis-specific pain [39].

In another study of 578 British subjects with a radiographic diagnosis of osteoarthritis and a pain score assessment, the rarer A allele was significantly associated with increased pain scores compared to the G allele (p = 0.016). In the same study, the A allele of rs6746030 was associated with an altered pain threshold, the effect being mediated through C-fibre activation, in a group of 186 healthy females characterised by their responses to a diverse set of noxious stimuli. The study found that individuals experience varying amounts of pain, per nociceptive stimulus, on the basis of their SCN9A rs6746030 genotype [29].

Another study conducted on a family with inherited erythromelalgia associated with Na(V)1.7 mutation A863P identified rs6746030 (the amino acid substitution R1150W) polymorphism in the SCN9A gene in the affected proband and several unaffected family members. This polymorphism depolarises activation (7.9-11 mV in different assays). The current-clamp analysis shows that the 1150W allele depolarises (6 mV) resting membrane potential and increases (approximately 2-fold) the firing frequency in response to depolarisation in dorsal root ganglion neurons in which it is present. These results suggest that polymorphisms in the Na(V)1.7 channel may influence susceptibility to pain [40]. The rs6746030 polymorphism of the SCN9A gene was also nominally associated with Parkinson disease-related pain susceptibility (p = 0.037), as well as with central and musculoskeletal pain subtypes independently [41]. In contrast to the previous studies, no association between polymorphism rs6746030 in SCN9A and the widespread chronic pain was observed in multiple independent population-based cohorts [34].

Inter-individual differences in pain sensitivity remain a major methodological challenge. There is experimental testing of pain, where the intensity and modality of evoked pain can be controlled, and some confounding factors can be eliminated. In this study, to assess *pain* and *pain tolerance thresholds* we used the cold pressor test (CPT), which is a simple but conventional laboratory procedure. This method allows the evaluation of differentiated subjective sensation of pain. CPT is a classic method which results in global sympathetic activation causing arteriolar vasoconstriction, leading to increased blood pressure without affecting the heart rate [42]. The cold pressor test involves immersion of the right hand in a bucket of crushed ice water after 2 minutes of normalising skin temperature in warm water (37°C) [35]. The test results are given as the time in seconds until the first sensation of pain, the point when the pain sensation begins to hurt *(pain threshold)* and the moment when the pain becomes intolerable *(pain tolerance threshold)*. Study participants underwent measurements of blood pressure and pulse at three-time points: before transferring the hand into cold water, at the moment when the subjects reached the pain threshold, and at the time the test was over. In this study, there were no significant associations of CPT test results (or other phenotypic traits) with various genotypes (GG vs GA+AA), so in this case, the genetic impact on sensitivity to experimentally induced pain in the group of boxers remains unclear. However, the observed lack of association of the SCN9A SNP and differences in pain sensitivity may be due to the small sample size, which is one of the limitations of the current study. Moreover, the differences between the studies may originate from ethnic differences, different cohorts (osteoarthritis and parkinsonian patients vs healthy athletes), and different methodology of pain evaluation and measurement. However, the results of the

current study suggest that the SCN9A rs6746030 SNP is not a factor predisposing to professional boxing training and it does not influence the pain threshold or tolerance in the Polish population.

CONCLUSIONS

Contrary to the results of other studies results, the SCN9A rs6746030 genotype did not affect phenotypic variables of pain. Pain seems to be a complex trait. It is likely that several gene loci, each with a small but significant contribution, are responsible for this genetic component. Further large, well-designed studies are necessary to determine its genetic background.

HIGHLIGHTS

The SCN9A genotype and allele distribution in Polish boxers and non-active subjects are similar.

In Polish boxers, there are no difference in pain threshold or pain tolerance between individuals of different SCN9A genotypes.

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