The BDNF-increasing allele is associated with increased proportion of fast-twitch muscle fibers, handgrip strength and power athlete status

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ABSTRACT

The brain-derived neurotrophic factor (BDNF) is involved in neurogenesis and formation of regenerated myofibers following injury or damage. Recent study suggests that the *BDNF* overexpression increases the proportion of fast-twitch muscle fibers, while the *BDNF* deletion promotes a fast-to-slow transition. The purpose of this study was to evaluate the association between the *BDNF* gene rs10501089 polymorphism (associated with blood BDNF levels), muscle fiber composition and power athlete status. Muscle fiber composition was determined in 164 physically active individuals (113 males, 51 females). *BDNF* genotype and allele frequencies were compared between 508 Russian power athletes, 178 endurance athletes and 190 controls. We found that carriers of the minor A-allele (the BDNF-increasing allele) had significantly higher percentage of fast-twitch muscle fibers than individuals homozygous for the G-allele (males: 64.3 (7.8) *vs*. 50.3 (15.8)%, $P = 0.0015$; all participants: 64.1±7.9 *vs*. 49.6±14.7%, $P = 0.0002$). Furthermore, the A-allele was associated ($P = 0.036$) with greater handgrip strength in a sub-group of physically active subjects ($n = 83$) and over-represented in power athletes compared to controls (7.7 *vs*. 2.4%, $P = 0.0001$). The presence of the A-allele (i.e., AA+AG genotypes) rather than GG genotype increased the odds ratio of being a power athlete compared to controls (OR: 3.43, $P = 0.00071$) or endurance athletes (OR: 2.36, $P = 0.0081$). In conclusion, the rs10501089 A-allele is associated with increased proportion of fast-twitch muscle fibers and greater handgrip strength, and these may explain, in part, the association between the AA/AG genotypes and power athlete status.

Key words: athletic status, genetics, polymorphisms, skeletal muscle

INTRODUCTION

Skeletal muscles are composed of a variety of muscle fibers with specialized functional properties. The recognition that muscle fibers differ in molecular composition and functional properties has contributed to our understanding of muscle physiology. Based on their myosin ATPase activity and metabolic profile, slow-twitch fibers have high oxidative metabolism and are more suited for long-lasting, low-intensity contractile activity, while several subtypes of fast-twitch fibers are more suited for high speed and anaerobic power (1). It has been widely reported that there are large interindividual differences in the fiber composition of human skeletal muscle (18). Genetic variations (i.e., the cumulative contribution of gene polymorphisms) are suspected of being responsible for 40–50% of the inheritance in the muscle fiber composition (37). Polymorphisms may be associated with differences in gene expression or protein structures and can partly explain interindividual differences in the muscle fiber composition and therefore in the potential for developing aerobic or anaerobic capacities (1,35).

There is compelling evidence based on animal studies suggesting that the brain-derived neurotrophic factor (BDNF) may be one of some key proteins to skeletal muscle fiber-type specification. An earlier study showed that muscle-derived BDNF is important for the survival and maturation of motor neurons and fast-twitch muscle fibers during neonatal development of the neuromuscular system (27). During postnatal development, muscles that contain more fast-twitch fibers in their composition (e.g., gastrocnemius or extensor digitorum longus) express higher levels of BDNF compared with muscles lacking fast-twitch fibers (e.g., soleus) (27,29). In turn, muscle-specific *BDNF* deletion reduces motor end plate size in the extensor digitorum longus muscle and promotes a fast-to-slow transition in fast IIb muscle fibers (10). However, *BDNF* overexpression in the adult muscle increases fast-type

gene expression and the proportion of fast IIb muscle fibers (10). Although it is not clear how BDNF controls the fast-type muscle fiber program, three models have been proposed: i) BDNF might affect myofiber identity and motor end plate structure indirectly; ii) BDNF could act as an autocrine factor to influence the expression of transcriptional regulators involved in the specific gene expression of fast-twitch fibers; or iii) BDNF could act as a paracrine factor to regulate the differentiation of satellite cells (10).

Based on the aforementioned background, it is plausible to assume that DNA sequence variants associated with altered BDNF levels can contribute to muscle fiber-type specification. Interestingly, two co-inherited single nucleotide polymorphisms (rs728635 and rs75601975) were strongly associated with human blood BDNF levels (15). The most associated and therefore the main contributor to blood BDNF levels was rs728635 with a *P*-value of 3.4×10^{-16}, for which the T-allele was associated with elevated protein levels. By assuming that BDNF is a key component of the fast-twitch phenotype in skeletal muscle, one might hypothesize that the BDNF-increasing allele should be associated with an increased proportion of fast-twitch fibers in human muscles, which might be interesting for strength and power athletes. To the best of our knowledge, this has not yet been evaluated. Athletes from sports requiring greater anaerobic demand, strength and power have higher prevalence of fast-twitch fibers, such as sprinters and weightlifters (36,42).

Therefore, the purpose of this study was to evaluate the association between the BDNF-increasing allele and the proportion of fast-twitch muscle fibres in physically active individuals. We tested the hypothesis that the BDNF-increasing allele is associated with a higher prevalence of fast-twitch fibres. In addition, the relationship between the *BDNF* polymorphism and handgrip strength was investigated in physically active individuals, and

the frequency of the BDNF-increasing allele was compared between elite athletes and non-athletes using a case-control approach. If the BDNF-increasing allele is associated with the proportion of fast-twitch fibers, it is expected to be associated with greater strength and to be more frequent among strength and power athletes.

METHODS

Experimental Approach to the Problem

In the present study, we used the genotypes of the rs10501089 polymorphism (found in our database) as representative of the rs728635 genotypes, given that they are in 100% linkage disequilibrium. The linkage disequilibrium was assessed using HaploReg version 4.1 (Broad Institute, Cambridge, MA, USA). Thus, we can assume that the rs10501089 A-allele (corresponding to the rs728635 T-allele) was associated with elevated BDNF levels and, therefore, the proportion of fast-twitch muscle fibres was compared between carriers of the rs10501089 A-allele (i.e., individuals with A/A or A/G genotypes) and individuals with the G/G genotype. Likewise, the relationship between the *BDNF* gene rs10501089 (G>A) polymorphism and handgrip strength was investigated, and the frequency of the BDNF-increasing allele was assessed in a cohort of elite Russian athletes and controls.

All procedures adopted in this study were conducted ethically according to the principles of the Declaration of Helsinki for research involving human subjects, and were approved by the Ethics Committee of the Physiological Section of the Russian National Committee for Biological Ethics and the Ethics Committee of the Federal Research and Clinical Center of Physical-chemical Medicine of the Federal Medical and Biological Agency of Russia. A written informed consent was obtained from all individuals prior to participating in the study.

Evaluation of the proportion of fast-twitch muscle fibers

The muscle fiber type study involved 164 physically active individuals of both genders (113 men and 51 women). Although not involved in international sports competitions, these individuals are trained in endurance or power activities. Age, height and weight of participants grouped according to gender and training background are presented in Table 1.

TABLE 1 ABOUT HERE

Samples of the vastus lateralis muscle of physically active individuals were obtained with the Bergström needle biopsy procedure with aspiration under local anesthesia with 2% lidocaine solution. Serial cross-sections (7 μm) were obtained from frozen samples using a microtome (Leica Microsystems, Wetzlar, Germany). The sections were thaw-mounted on Polysine™ glass slides and myosin heavy chain (MHC) isoforms were identified by immunohistochemical analysis, as previously described (19). The primary antibodies used were: monoclonal Anti-Myosin (M4276, 1:600) for fast-twitch fibers, and monoclonal Anti-Myosin (M8421, 1:5000) for slow-twitch fibers (Sigma-Aldrich, St. Louis, MO, USA). The secondary antibody (F0257, 1:100) was labeled with a fluorescent probe (Sigma-Aldrich, St. Louis, MO, USA). The immunohistochemically staining tissue section image was captured using a fluorescent microscope Eclipse Ti-U (Nikon, Tokyo, Japan). All analyzed images contained > 100 fibers. Fibers stained in serial sections with antibodies against slow and fast isoforms were considered as hybrid fibers.

Measurement of physical activity

Physical activity of physically active individuals was assessed using a questionnaire. Participants were classified according to their training frequency as mildly active (1-2 training

sessions per week), moderately active (3-4 training sessions per week), highly active (5-7 training sessions per week) and extremely active (two training sessions per day).

Handgrip strength

In addition to the fast-twitch muscle fiber study, 83 physically active individuals (30 women: 9 power-trained and 21 endurance-trained; 53 men: 16 power-trained and 37 endurance-trained) from the initial cohort (n = 164) were enrolled in the handgrip strength study. The hand dynamometer (DK-140, St Petersburg, Russia) was used for the handgrip strength testing. The strength of both the left and right hands was measured thrice each in a standing position (i.e., with the arm in complete extension and without touching any part of the body with the dynamometer), and the best score of the dominant hand (kg) was used in the analysis.

Case–control study

The case-control study involved 686 elite athletes (277 females, 409 males; age 23.7 (4.0) years) and 190 controls (38 females, 153 males; age 45 (4.3) years). The athletes were stratified into two main groups: power or endurance. The power group (n = 508) included 72 sprinters (14 runners (100-400 m), 23 speed skaters (500-1000 m), 3 short-trackers (500-1000 m), 23 swimmers (50-100 m) and 9 sprint cyclists), 90 speed-strength athletes (16 alpine skiers, 5 heptathletes/decathletes, 10 throwers, 22 jumpers, 30 climbers and 7 rhythmic gymnasts), 273 combat athletes (145 wrestlers, 107 boxers, 21 karate athletes) and 73 game players (48 rugby players and 25 football players). All of these athletes have a predominantly anaerobic component in their sports performance. The endurance group (n = 178) included 52 rowers, 8 long-distance runners ($\geq$ 3 km), 32 biathletes, 47 cross-country skiers, 20 long-distance swimmers ($\geq$ 800 m), 8 race walkers, and 11 long-distance speed skaters (5-10 km). All athletes were international-level competitors who represented Russia in international

competitions and have been tested negative for doping substances. The control group included unrelated citizens, without any competitive sport experience.

DNA extraction and genotyping

Genomic DNA was isolated from leukocytes (venous blood) using a commercial kit according to the manufacturer's instructions (Technoclon, Moscow, Russia). Extracted DNA quality was assessed by agarose gel electrophoresis. Genotyping of the rs10501089 polymorphism was performed by genome-wide DNA analysis BeadChips arrays (HumanOmni1-Quad or HumanOmniExpress BeadChips) according to the instructions of Infinium HD Assay (Illumina Inc., San Diego, CA, USA), as detailed previously (32). HumanOmni1-Quad BeadChips were used to genotype 1,140,419 single nucleotide polymorphisms (SNPs) in athletes and controls, and HumanOmniExpress BeadChips were used to genotype > 900,000 SNPs in participants of the muscle fiber study.

Statistical analysis

Differences in the proportion of fast-twitch muscle fibers between groups with different genotypes were analysed using unpaired *t*-tests. In addition, multiple regression was used to determine the association between the *BDNF* polymorphism and phenotypes (percentage of fast-twitch muscle fibers and handgrip strength) adjusted for covariates (age, sex, physical activity, type of training, height, weight). Allelic frequencies between athletes and controls were compared using Fisher's exact test. The Chi-square test (χ^2) was used to test for the presence of the Hardy-Weinberg equilibrium in the genotype distribution, and to evaluate the association between genotypes and athletic status among the main groups of the case-control study (power, control and endurance). *P*-values < 0.05 were considered statistically significant. Bonferroni's correction for multiple testing was performed by multiplying the *P*-

value with the number of tests where appropriate. Statistical analyses were conducted using GraphPad InStat (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Association between the BDNF-increasing allele and the proportion of fast-twitch muscle fibres

Table 2 shows the proportion of fast-twitch muscle fibers between groups based on the rs10501089 G>A genotypes. Both power (P = 0.032) and endurance trained (P = 0.014) male carriers of the minor A-allele (i.e., A/A+A/G genotypes) had significantly higher percentage (13.3-16%) of fast-twitch fibers than individuals homozygous for the major G-allele (all males: 64.3 (7.8) *vs*. 50.3 (15.8)%, P = 0.0015). Although a higher prevalence (e.g., 14.3%) of fast-twitch fibers was also observed in female carriers of the minor A-allele, this comparison did not reach the significance threshold (62.4 (12.5) *vs*. 48.1 (12.2)%, P = 0.114). However, the pooled data of all participants (i.e., male and female participants) confirmed that carriers of the minor A-allele had significantly higher percentage (e.g., 14.5%) of fast-twitch fibers than individuals homozygous for the major G-allele (64.1 (7.9) *vs*. 49.6 (14.7)%, P = 0.0002). The associations remained significant even after the correction for multiple comparisons and after adjustment for sex, age, physical activity and type of training (P = 0.018 for the whole group). Of note, based on our genome-wide DNA analysis, no other SNP in the *BDNF* gene was associated with muscle fiber composition in the participants included in this study.

TABLE 2 ABOUT HERE

Handgrip strength study

We found that the rs10501089 A-allele was significantly associated with greater handgrip strength adjusted for sex, age, height, weight, type of training and level of physical activity ($P = 0.036$) in 83 subjects who underwent handgrip strength testing.

Case–control association study (athletes *versus* controls)

The rs10501089 G>A polymorphism met Hardy-Weinberg expectations (i.e., $P > 0.05$) in all groups. The frequency of the minor A-allele (ranging from 6.3 to 11.6%) was significantly higher in all power subgroups compared to controls (OR > 2.7, $P < 0.0064$), as shown in Table 3. When all power athletes were accounted for, the frequency of the minor A-allele was significantly higher in the power group (e.g., 7.7%) compared to the control (2.4%; OR = 3.4, $P = 0.0001$) or endurance (3.4%; OR = 2.4, $P = 0.004$) groups. All these associations remained significant even after the correction for multiple comparisons. Indeed, individuals with the A/A and A/G genotypes had an increased odds ratio of being a power athlete. The presence of the A-allele (i.e., A/A+A/G genotypes) rather than G/G genotype increased the odds ratio of being a power athlete compared to controls (OR: 3.43, 95% CI: 1.68–7.00, $P = 0.00071$), endurance athletes (OR: 2.36, 95% CI: 1.25–4.45, $P = 0.0081$) or controls + endurance athletes (OR: 2.82, 95% CI: 1.70–4.67, $P < 0.0001$).

TABLE 3 ABOUT HERE

DISCUSSION

This is the first study to demonstrate that the *BDNF* gene rs10501089 polymorphism is associated with muscle fiber composition, hand grip strength and power athlete status. More specifically, we identified a strong association between the rs10501089 A-allele (associated with increased blood BDNF levels) and the prevalence of fast-twitch muscle fibers in the

vastus lateralis muscle of physically active individuals. We further revealed that the BDNF-increasing allele was associated with greater handgrip strength and consistently more frequent in athletes that have a predominantly anaerobic component in their sports performance. This higher prevalence of fast-twitch fibers may be an innate characteristic that predisposes the individual to power-specific activities. Alternatively, carriers of the BDNF-increasing allele may present greater trainability to anaerobic stimuli.

BDNF belongs to the neurotrophin family—a small family of structurally related trophic factors that have a crucial role in differentiation, survival and function of neuronal cells (38). Neurotrophins regulate nearly all aspects of neural circuit development and function, including cell proliferation, axon and dendrite growth, synaptogenesis and synaptic function. There are four neurotrophins in mammals, of which BDNF is the most widely expressed and studied (30). BDNF is modulated by multiple factors, including neuronal activity, stress and exercise. In particular, physical exercise is an interesting strategy to increase circulating BDNF levels (22). Recent meta-analyzes have shown that a single bout of exercise can be an effective stimulus for increasing BDNF levels (11,41), especially in trained individuals (12,41).

The brain is the main source for increased BDNF levels, since the hippocampus and cerebral cortex express BDNF abundantly (33). However, other tissues can also be considered sources of BDNF as they produce and release it, including peripheral blood mononuclear cells, vascular endothelial cells, platelets via the spleen and skeletal muscle (44). Of particular interest, BDNF is secreted from muscle cells in response to contractile activity, where it appears to be mainly involved in autocrine and paracrine signaling (9). Matthews et al. (24) showed that BDNF protein production was increased in human skeletal muscle 24h following

a long-lasting exercise performed on the cycle ergometer at 60% of maximum oxygen consumption. In contrast, there was no statistical difference in *BDNF* gene expression (i.e., mRNA levels), probably due to the fact that the transcript levels demonstrated a marked inter-individual variation with peak mRNA levels between 5 and 8 h for the majority of the participants (24). We speculate that this marked inter-individual variability may be, in part, due to genetic differences, as shown that polymorphisms can affect blood BDNF levels (15). The variability in gene expression can alter fine regulation of the signaling pathway between individuals.

Based on its plasticity, it is not surprising that skeletal muscle is an abundant source of trophic factors. Among the several regulatory genes and proteins that dictate the muscle adaptive response, we explore the theory that BDNF may be one of the key proteins in the gene program of fast-twitch muscle fibers, as recently proposed (10). Muscle-derived BDNF was initially thought to act as a retrograde signaling factor for innervating motor neurons (13). However, there is growing evidence indicating that the primary role of BDNF in mature skeletal muscle is on the muscle progenitor cells, called satellite cells (5,25,26). Based on the skeletal muscle of rats, Mousavi and Jasmin (26) were the first to show that BDNF is expressed in satellite cells. These data were later confirmed in samples of human muscles, where BDNF is supposed to interact with the p75 neurotrophin receptor (p75NTR) to modulate cell proliferation, differentiation and myogenesis (5,6). Recently, McKay et al. (25) evaluated, in humans, the potential role of BDNF in the regulation of satellite cells in response to an exercise-induced muscle damaging protocol. Interestingly, muscle *BDNF* mRNA increased following exercise and remained elevated throughout the 96h post-intervention time-course, and the increase in BDNF levels was associated with satellite cell proliferation/differentiation (25). Although the precise mechanisms are yet unclear, it seems

reasonable to assume that carriers of the BDNF-increasing allele can benefit more from BDNF-mediated processes and as a consequence, have a greater predisposition to power exercises.

In mature muscles, satellite cells are typically in a quiescent state and reside in a niche between the sarcolemma and basal lamina of their associated muscle fiber; however, upon stimulation they activate and proliferate (39). Following proliferation, satellite cells differentiate and fuse with each other forming new myofibers (repairing muscle damage) or fuse to an existing muscle fiber donating their nucleus (supporting muscle hypertrophy) or return back to their quiescent state (self-renewal) (39). The essential role of satellite cells during muscle repair or regeneration is well-established (14), and there are indications that BDNF can contribute. For instance, based on rodent studies, muscle *BDNF* levels were up-regulated in regenerating muscles after cardiotoxin injury (4) or in response to downhill running-induced muscle injury (45). On the other hand, regeneration is delayed in the absence of muscle-derived BDNF (4). Taken together, the regeneration process (undertaken by satellite cells) occurs concomitantly with increases in BDNF levels, suggesting that BDNF is required for the formation of regenerated myofibers following injury or damage (23). Although these studies have been carried out with animals, these data correlate well with human muscle physiology (25,39).

Skeletal muscle fibers are multinucleated, with each nucleus affecting gene products in a finite volume of cytoplasm, referred to as the myonuclear domain (40). Muscle fiber hypertrophy is normally associated with satellite cell-mediated myonuclear accretion to meet transcriptional demands (7). However, the role of satellite cells in fiber size regulation extends beyond providing myonuclei to growing muscle fibers (28). Upon activation, most,

but not all, satellite cells differentiate into myoblasts and fuse with existing myofibers. This means that, after proliferation, a minor population of satellite cells returns to a quiescent state through self-renewal to replenish the available pool, regulating the basal satellite cell content. A common response to strength training (often used by power athletes) is a substantial expansion of the satellite cell pool (28). Training results in an expansion of the satellite cell pool in both slow- and fast-twitch muscle fibers (40), but it is the expansion of satellite cells associated with fast-twitch fibers that is associated with the greatest gains in muscle mass (3). This expansion can occur even without detectable increases in myonuclear number and chronically, the increased satellite cell content could be important in supporting muscle remodeling (8). The expansion of the satellite cell pool mediates proper extracellular matrix remodeling, which appears to allow for continued muscle fiber hypertrophy (16), as well as allows the muscle to resist future damage, such as that caused by high-force eccentric contractions (20). Furthermore, the extracellular matrix facilitates the transduction of mechanical tension sensing to hypertrophy signaling (2). In the absence of satellite cells, there is an excessive production of extracellular matrix components that can lead to muscle fibrosis, limiting long-term hypertrophy and muscle power production (17).

The basal satellite cell pool appears to be an important determinant of hypertrophic potential. Individuals with a greater basal content also demonstrate, with training, a remarkable ability to expand the satellite cell pool and achieve robust muscle growth (31). Petrella et al. (31) suggested that the muscles of these individuals were the most mechanosensitive, leading to superior mitogenic signaling responses. Herein, we speculate that, in part, the rs10501089 A-allele can be an inherent contributor to an increased responsiveness to skeletal muscle hypertrophy, leading to an increase in muscle strength and power. Indeed, when exploring associations from UK Biobank, we found that the rs10501089 A-allele was associated with

increased arm fat-free mass (P = 0.046; n = 354,732) (43). Conversely, the rs10501089 G-allele was associated with longer duration of cardio-respiratory fitness test (P = 0.048; n = 53,998) (43), corroborating recent findings that the loss of BDNF promotes slow contraction velocity and fatigue resistance (i.e., a fast-to-slow transition in glycolytic fibers) (10). Therefore, the BDNF-increasing allele based on its influence on muscle mass and strength can be advantageous for power performance.

It has been well documented that aerobic exercise elevates blood BDNF levels (44). Nevertheless, a recent study showed that an anaerobic stimulus (sprint interval training) can also induce an increase in plasma BDNF levels (34). In fact, the interval training, which consisted of sets of 30 seconds of running at maximum effort, had a greater increase in BDNF levels compared to 30 minutes continuous running (34). It should be noted that, in this study, BDNF levels were assessed in plasma. Whether this occurs within human skeletal muscle still needs to be established, particularly based on the different *BDNF* genotypes. In line with our discussion, it is worth mentioning that sprint interval training is able to activate satellite cells, although for an expansion of the satellite cell pool to occur, an increase in fiber size is required (21). Further molecular studies are required to better determine the role of different *BDNF* genotypes in human skeletal muscle. In this study, we explored the hypothesis that fast-twitch muscle fibers may be more influenced by the polymorphism, which may be relevant to sports performance and clinical phenotypes (1). However, we cannot rule out that the BDNF-increasing allele may also be influencing the release of BDNF in other tissues.

In conclusion, the rs10501089 A-allele (i.e., A/A and A/G genotypes) was associated with increased proportion of fast-twitch muscle fibers and greater handgrip strength in physically active individuals and more prevalent in elite power athletes. The possessing of the BDNF-

increasing A allele, increased the odds ratio of an individual become a power athlete. It is noteworthy that the genetic architecture of sports performance encompasses a number of other variants and complex gene–gene and gene–environment interactions. Furthermore, given that only one cohort of elite athletes from Russia was included in this initial exploratory study, the replication of our findings in independent studies will be interesting.

PRACTICAL APPLICATIONS

The *BDNF* gene rs10501089 polymorphism can be considered a new genetic marker for the prediction of muscle fiber composition, muscle strength and predisposition to power sports, in which the A-allele is preferable for the performance of power athletes.

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