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MUSCLE POWER AND BLOOD LACTATE KINETICS IN *ACTN3* GENOTYPES

POTENCIA MUSCULAR Y CINÉTICA DE LACTATO EN SANGRE ENTRE GENOTIPOS DE *ACTN3*

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ABSTRACT

In this study, the differences in muscle power and blood lactate concentration ($[LA^-]_b$) kinetics among ACTN3 genotypes were examined during the Wingate anaerobic test (WAnT). Thirty-five healthy and physically active men (18-35 years old) volunteered to participate in the study. Muscle power, $[LA^-]_b$ concentration and Lactate Dehydrogenase (LDH) activity were analysed. ACTN3 gene was determined from white blood cell DNA in peripheral blood. Regardless of the participants' body weight or muscle mass, RR genotype carriers developed greater muscle power during WAnT ($p<0.05$) than RX or XX genotypes, suggesting that RR genotype has greater capacity to use the ATP-PC system during supramaximal exercise. Muscle power and $[LA^-]_b$ kinetics were similar in all genotypes. The WAnT was not sufficient to make muscle damage be detected in LDH concentration.

KEYWORDS: Alpha-actinin-3, lactate dehydrogenase, sport genetics, sport performance, R577X polymorphism.

RESUMEN

En este trabajo se estudiaron las diferencias en la potencia muscular y la cinética de las concentraciones de lactato en sangre ($[LA^-]_b$) entre genotipos de *ACTN3* durante la prueba anaeróbica de Wingate, (PAnW). Participaron 35 voluntarios (18-35 años) masculinos, sanos y físicamente activos. Se analizaron la potencia muscular, las concentraciones de $[LA^-]_b$ y la actividad de la Lactato Deshidrogenasa (LDH). El gen *ACTN3* se determinó a partir de ADN de glóbulos blancos en sangre periférica. Independientemente del peso y masa muscular de los participantes, los portadores del genotipo RR *vs.* RX y XX desarrollaron mayor potencia muscular durante la PAnW ($p<0.05$), lo cual sugiere una mayor capacidad en este genotipo para utilizar el sistema ATP-PC durante un ejercicio supramáximo. La cinética en la potencia muscular y en las concentraciones de $[LA^-]_b$ fueron semejantes entre genotipos. La PAnW no fue suficiente para causar daño muscular observado por la concentración de LDH.

PALABRAS CLAVE: Alfa-actinina-3, lactato deshidrogenasa, genética deportiva, rendimiento deportivo, polimorfismo R577X.

INTRODUCTION

Given the tightness of current elite sport marks, any hundred of a second, additional centimetre or gram that can be moved, thrown or lifted makes the difference between winning and losing. In this context, the identification of genes

and polymorphisms that are involved in the development of physical capacities to high level, advantageous for competitive sport, has become particularly interesting. Sport-related traits like energy metabolism, maximal oxygen uptake (VO_2max), speed, muscle power, maximal heart rate, somatotype or body composition have been reported to be associated with sport training, lifestyle and genetic aspects (Rankinen et al., 2001; Norman et al., 2009).

As regards genetics, the expression of α-actinin-3 (ACTN3) protein gene, one of the four genes composing the α-actinin family, is related with greater anaerobic capacity, muscle strength (Broos et al., 2015), speed (Mikami et al., 2014) and muscle power (Orysiak et al., 2014). By contrast, α-actinin deficiency is associated with reduced muscle mass and strength (Berman & North, 2010). ACTN3 presents R577X polymorphism (North, 2008), and the combination of its R and X alleles generates the genotypes RR, RX and XX. Genotypes RR and RX encode α-actinin-3, while genotype XX does not (MacArthur & North, 2004). Alpha-actinin-3 only expresses in glycolytic or fast-twitch muscle fibers and is located together with the proteins of the sarcomeric Z-line (Beggs et al., 1992). Alpha-actinin-3 is located together with several sarcomeric structural proteins and it was historically conferred the function of maintaining Z-line's structure and integrity, enhancing strength and power of muscle contractions. Nowadays, it is known that it is involved in energy metabolism by indirectly activating glycogen phosphorylase and lactate dehydrogenase (LDH) (Berman & North, 2010), thus providing more glucose to the glycolytic energy system and increasing lactate production. Its absence fosters anaerobic capacity development by increasing the oxidative capacity and the activity of several mitochondrial enzymes, such as nicotinamide adenine dinucleotide tetrazolium reductase, succinate dehydrogenase, cytochrome c oxidase, citrate synthase, hydroxyacyl-CoA dehydrogenase and medium-chain acyl-CoA dehydrogenase, among others (Berman & North, 2010).

Studies conducted in humans on the association between ACTN3 genotypes and physical capacities are scarce, and no conclusive relationships have been established so far. Mikami et al. (2014), Orysiak et al. (2014) and Broos et al. (2016) reported that RR- and RX-genotype carriers were able to generate greater anaerobic power. Besides, MacArthur et al. (2007, 2008) and Yang et al. (2007) observed that athletes with XX genotype generated greater aerobic power. By contrast, Hanson et al. (2010), Ruiz et al. (2010), Bell et al. (2012), Garatachea et al. (2013) and Kikuchi et al. (2014) did not find such effects in a similar population. The analysis of the mentioned studies revealed that the methodologies applied and the samples selected were very different, suggesting the need for standardised processes and protocols in order to reduce controversy. In this regard, the Wingate anaerobic test (WAnT) has been recommended in literature to assess muscle power, especially in a physically active population (Bar-Or, 1996). The percentage of energy obtained from aerobic, alactic anaerobic and lactic anaerobic metabolism during this test was 18.6%, 31.1% and 50.3%, respectively (Beneke et al., 2002).

Thus, given the existing controversy on the participation of ACTN3 genotypes in muscle power, the WAnT was proposed to assess lower-limb muscle power, using $[LA^-]_b$ concentration as metabolic indicator of anaerobic power development and LDH activity as indicator of muscle damage.

MATERIAL AND METHOD

Participants

Thirty-five participants were selected for a cross-sectional observational study according to the following criteria: I. Inclusion criteria: young male adults, aged 18 to 35, non-smokers, not taking medicines or steroids that affected the nervous system or energy metabolism, physically active (doing sport activities three or more times a week). II. Exclusion criteria: to be a competing or high-performance athlete, to present any chronic or acute disease, to suffer from any muscular injury that prevented them from doing strenuous physical exercise. The participants were explained the study procedures and risks and were requested to voluntarily sign an informed consent form. In order to verify the participants' good health status, they were asked to fill in a general health questionnaire (https://github.com/Arnulforam/Formatos.git) and PAR-Q questionnaire (Warburton et al., 2011). The protocol and procedures were approved by the bioethics committee of the Autonomous University of Ciudad Juarez (CIP-ICB-2018-1-01), based on the guidelines provided in the Declaration of Helsinki.

Study Design

All measurements were conducted between 8am and 10am. After having signed the informed consent, the participants were requested to attend the assessment sessions after 8- to 10-h fasting, 72h after having performed any moderate or strenuous physical activity and at least 24h after having drunk coffee, tea or energetic drinks. The first step to determine the genotype and LDH basal enzymatic activity was to collect a venous blood sample. Subsequently, anthropometric measures were conducted to determine fat mass and muscle mass. The WAnT was performed to assess muscle power. In order to determine the effect of the WAnT on $[LA^-]_b$ and LDH concentrations, blood samples were collected again as explained below.

Anthropometric measures

The anthropometric measures were conducted by an experienced anthropometrist according to the protocol published by Güereca et al. (2017) and following the standardised methodology established by the International Society for the

Advancement of Kinanthropometry (ISAK). The body mass index (BMI: weight in kg/height^2 in metres), the fat mass percentage (%F) and the muscle mass (MM) were calculated. Parizkova's (1978) formula was applied to calculate %F: %F = 22.32 x log Σ10 skinfolds – 29, and the weight-height model formula (Eston, et al., 2009) was used for muscle mass: MM (kg) = 0.244 × weight (kg) + 7.80 × height (cm) – 0.098 × age + 6.6 × gender + race – 3.3.

Wingate Anaerobic Test

Prior to the application of the WAnT, every participant was weighed on a digital scale (SECA 876, Hamburg, Germany) wearing only a swimsuit. Subsequently, they were requested to perform a 10-min general warm up, including 5-min pedalling (60-70 rpm) on a cycle ergometer (Monark Ergomedic 884e, Sweden) with 1-kg load. After 10-min rest, the WAnT was conducted with a load equivalent to 7.5% of body weight. The participant was asked to cycle at maximal speed during 5s and then the load was reduced. The participants were verbally encouraged to perform maximally during the 30 seconds of the WAnT (Bar-Or, 1987).

Biochemical Analysis

Genotype Determination

A 4-ml sample of peripheral blood was collected through venipuncture in the median cubital vein and stored at 4ºC in tubes with ethylenediaminetetraacetic acid (EDTA) until their analysis. Genomic DNA was extracted from leukocytes using a MasterPure (Epicentre Biotechnologies, USA) commercial kit. A fragment of ACTN3 gene composed of 291 base pairs was amplified using the polymerase chain reaction (PCR) technique with the following primers: forward primer: 5´-CTGTTGCCTGTGGTAAGTGGG-3', and reverse primer: 5´-TGGTCACAGTAT GCAGGAGGG-3'. Subsequently, enzymatic digestion of every PCR product was conducted using the enzyme *DdeI* (*Desulfovibrio desulfuricans) (*BioLabs, Inc. Beverly, USA). DNA extraction, amplification through PCR and enzymatic digestion were conducted applying the methodology described in an article in press (Güereca et al., 2020).

$[LA^-]_b$ Concentration Analysis

Capillary blood samples were collected from the fingertips under basal conditions, immediately after the WAnT, as well as 3min and 5min after the test. Punctures were performed using commercial sterilised needles after disinfecting and drying the area. $[LA^-]_b$ concentration was analysed by means of a portable lactate analyser and test strips (Lactate Plus, Nova Biomedical, USA). Prior to every assessment, the lactate analyser was calibrated using standard lactate

concentrations of 5 mM (YSI 3005, Yellow Springs, USA). After completing the test, the participant was requested to lie in supine position until all blood samples were collected.

Determination of LDH Enzymatic Activity

In order to determine LDH concentration, the participants were asked to come to the laboratory on three consecutive days, under the aforementioned conditions. Four-ml blood samples were collected under basal conditions through venipuncture in the median cubital vein and stored in tubes with EDTA in three occasions: before the study, 24h and 48h after the WAnT. Plasma LDH concentration was measured by means of kit 03004732122 (Roche, USA), with detection range of 10-1000 IU/L and using a clinical chemistry analyser (Cobas Integra 400 plus, Roche Instrument Center, USA).

Statistical Analysis

The sample size was calculated through the software G*power 3.1.9.2 (Faul, Erdfelder, Lang & Buchner, 2007), using size effect of 0.50, α of 0.05 and power of 0.80. A sample size of 9 participants per group was obtained. Shapiro-Wilk test was used to assess normality and Levene test to determine homoscedasticity. Analysis of variance (ANOVA) and Tukey's *post-hoc* test were conducted to analyse the differences in physical characteristics among genotypes. A repeated measures ANOVA was applied to examine the differences in muscle power and $[LA^-]_b$ and LDH concentrations along time and among genotypes. Time was used as within-subject factor and genotype as between-subject factor, while body weight and muscle mass were included as covariates. Subsequently, the total area under the muscle power, $[LA^-]_b$ and LDH curves (TAUC) was examined through analyses of covariance (ANCOVA), using body weight and muscle mass as covariates. The main effects among genotypes were compared through Bonferroni's test. The total area under the muscle power curve was calculated using the best regression curve for every participant's individual data ($R^2 > 0.95$) and then calculating the definite integral of the time function. The value of α was set at $p<0.05$. The data were analysed using SPSS software, version 22.0.

RESULTS

No significant differences were observed in the participants' physical characteristics among genotypes ($p>0.05$). No differences were found either in muscle power, $[LA^-]_b$ or LDH increases (Δ: final minus initial value) ($p>0.05$, Table 1). Furthermore, the total area under the muscle power curve was larger in those participants with RR genotype compared to RX and XX ($p=0.01$).

Table 1. Participants' physical and physiological characteristics: differences among ACTN3 genotypes.

	RR (n=10)	RX (n=16)	XX (n=9)
Age (years)	25.0 ± 2.4	23.5 ± 2.8	25.4 ± 5.6
Body weight (kg)	80.9 ± 10.1	78.7 ± 13.5	74.8 ± 20.1
Height (m)	1.80 ± 0.06	1.74 ± 0.05	1.73 ± 0.08
BMI (kg/m^2)	25.0 ± 2.8	26.7 ± 4.1	24.6 ± 5.0
Fat mass (%)	15.4 ± 4.7	16.2 ± 5.5	15.5 ± 6.5
Muscle mass (kg)	32.1 ± 4.5	32.9 ± 4.7	31.4 ± 7.1
Muscle power (TAUC)	17136 ± 2944*	14011 ± 2376	14424 ± 3301
Δ Muscle power (W)	-477 ± 97	-406 ± 86	-375 ± 141
Δ $[LA^-]_b$	8.0 ± 1.4	9.5 ± 2.0	9.5 ± 1.7
Δ LDH (IU/L)	4.7 ± 26.5	-3.5 ± 22.6	-14.6 ± 22.4

Values are presented as mean ± SD. TAUC: total area under the curve, BMI: body mass index, $[LA^-]_b$: blood lactate, LDH: lactate dehydrogenase, Δ: difference between final and initial values. *p=0.01 for RR vs. RX and XX.

Muscle power kinetics during the WAnT was similar for the three genotypes (Figure 1A). Nevertheless, RR genotype carriers developed greater muscle power compared to RX and XX genotypes (17,136 arbitrary units, Table 1, Figure 1A; p=0.01). The inclusion of body weight and muscle mass as covariates in the ANCOVA analysis did not affect the results among the three genotypes. $[LA^-]_b$ concentration kinetics during the WAnT was similar for the three genotypes (Figure 1B). No differences among genotypes were found either in LDH concentration in any of the three extractions (0, 24h and 48h; Figure 1C).

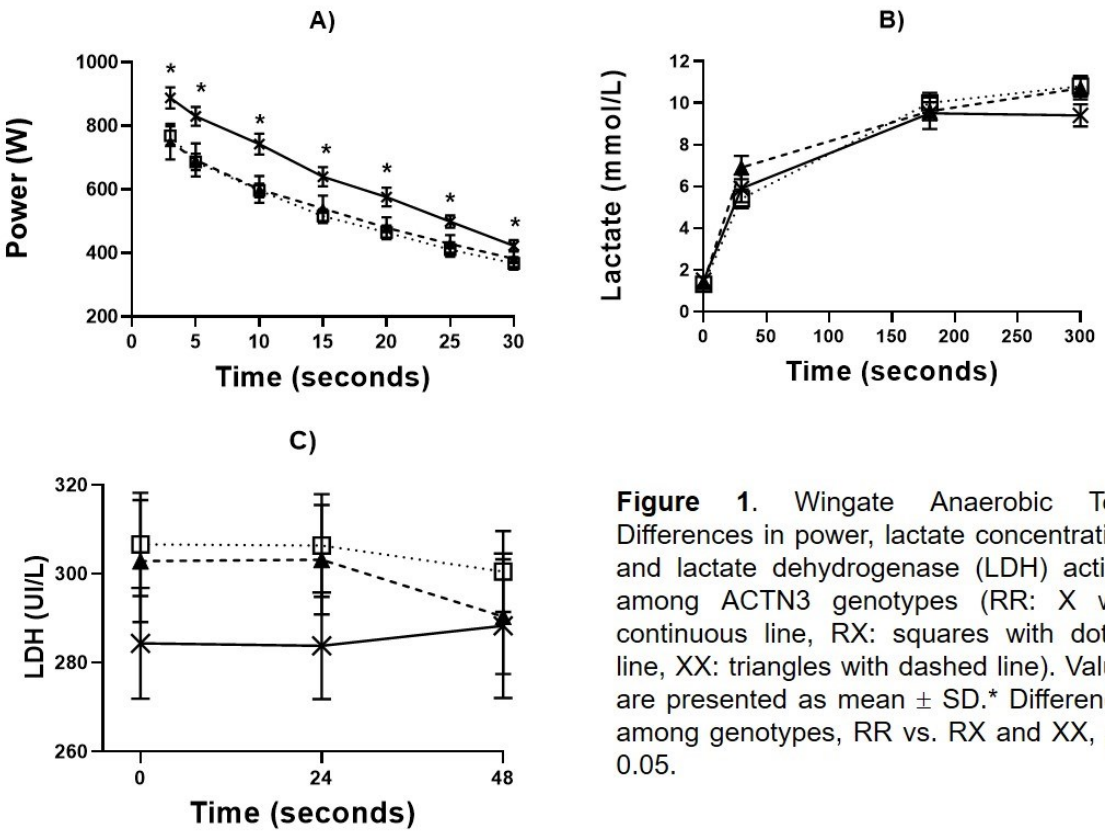

Figure 1. Wingate Anaerobic Test. Differences in power, lactate concentration, and lactate dehydrogenase (LDH) activity among ACTN3 genotypes (RR: X with continuous line, RX: squares with dotted line, XX: triangles with dashed line). Values are presented as mean ± SD.* Differences among genotypes, RR vs. RX and XX, $p < 0.05$.

DISCUSSION

Between 70% and 83% of speed and muscle power capacities have been reported to be inheritable (Costa de Sousa, 2016). In this regard, thanks to the functional or non-functional expression of the sarcomeric protein α-actinin-3, ACTN3 gene RR and RX genotype carriers are considered to present greater anaerobic capacity than XX genotype carriers. By contrast, greater aerobic capacity is associated with XX genotype carriers. Nonetheless, due to the different protocols applied in studies, the results are not consistent. In the present study, the WAnT was used to assess lower-limb muscle power and to examine its association with ACTN3 genotype. The most relevant finding revealed that RR genotype carriers developed greater muscle power compared to RX and XX, measured through the TAUC and regardless of the differences in body weight or muscle mass. Technically, RR and RX genotype carriers encode α-actinin-3 (MacArthur & North, 2004). Nevertheless, it has been reported that RX genotype may express a smaller amount of it in skeletal muscle (Pasqua, Artioli, Oliveira & Bertuzzi, 2011) and, therefore, lead to lower muscle power development. The present findings contradict those reported

by Norman et al. (2009) and Hanson et al. (2010), who did not found differences in power developed during WAnT among the three ACTN3 genotypes. However, Norman et al. (2009) observed a noteworthy increase in knee extensor muscle torque during isokinetic exercise in RR vs. XX genotype carriers. In this regard, Berman and North (2010) explained in their review that a deficiency of α-actinin-3 reduced the activity of glycogen phosphorylase and resulted in a shift towards more oxidative pathways of energy utilisation. This means that RR vs. RX and XX genotype carriers would present more powerful ATP-PC and glycolytic systems (Berman & North, 2010; MacArthur et al., 2008).

Unlike what Norman et al. (2009) and Hanson et al. (2010) reported, in the present study it was verified that all participants presented similar basal levels of fatigue and muscle damage by using creatin kinase (CK) (data not provided) and LDH concentrations: CK<500 IU/L (Sierra et al., 2019) and LDH 240-480 IU/L (Lippi et al., 2008). Furthermore, blood LDH concentration after exercise was confirmed to depend on the exercise duration and intensity (Tesema et al., 2019). In this study, the traditional WAnT was insufficient to generate muscle damage that could be observed in the concentration of these two enzymes, as suggested by Hammouda et al. (2012) and Kim et al. (2017). Nonetheless, a positive and statistically significant correlation (r=0.33, p=0.04) was detected between the TAUC for muscle power and TAUC for plasma LDH concentration (data not provided), deserving specific analyses and further studies.

It is generally agreed in literature that each ACTN3 genotype enhances different physiological or biological mechanisms, concluding that the absence of α-actinin-3 in the Z-line hinders glycolytic metabolism and fosters oxidative metabolism (Berman & North, 2010; MacArthur et al., 2008; Vincent et al., 2007). Besides, it was proved that the presence of α-actinin-3 increases the percentage of type IIx fibers (Broos et al., 2016) and the cross-sectional area of types IIa and IIx fibers (Vincent et al., 2010), both responsible for generating strong muscle contractions by means of anaerobic metabolism. By contrast, muscle fibers where α-actinin-3 is not expressed present a higher percentage of type I oxidative fibers (Ahmetov et al., 2011) and greater muscle damage during strong and long contractions (Seto et al., 2011).

Lastly, $[LA^-]_b$ concentration measured during exercise is an anaerobic activity indicator, so that the higher the exercise intensity, the higher the concentration (Ramos-Jiménez et al., 2013). Since RR genotype carriers developed greater muscle power than XX, they were expected to present higher $[LA^-]_b$ concentrations; however, that was not the case. This may have happened due to three circumstances: 1) the short duration of the WAnT, 2) all participants started with similar relative workload (7.5% of body weight), 3) no associations were observed between muscle power and $[LA^-]_b$ concentration (data not provided).

CONCLUSIONS

RR genotype carriers developed greater muscle power during the WAnT than RX or XX genotypes. This was assessed through both relative and absolute measures, and adjusting muscle power for body weight and muscle mass. These results suggest that RR genotype carriers present greater capacity to use the ATP-PC system during supramaximal exercise. The muscle power and $[LA^-]_b$ curve kinetics was similar in all genotypes. No differences were found in LDH concentration among extractions or genotypes. The latter suggests that the WAnT is not powerful enough to produce muscle damage.

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