# HORSE BREEDING PROGRAM: BIOCHEMICAL ASPECTS

*MELHORAMENTO GENÉTICO DE EQUINOS: ASPECTOS BIOQUÍMICOS*

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## SUMMARY

In recent years, in Brazil, horse breeding has developed and gained importance in sports and leisure activities. The complex horse agribusiness is relevant on the national scene and the country is an important importer and exporter of horses. The export of racehorses has increased lately and the search for breeding techniques that aim at better sports performance is being sought by breeders, despite their distant relationship with research centers. Scientific studies have been published in various areas of equine production, but when it comes to breeding, heritability values and correlations for traits related to athletic performance of athlete horses, a straightforward selection becomes difficult. The genomic selection can provide the tools necessary to improve horse breeds; although, environmental factors, such as nutrition and sports training can affect horse performance. Horse skeletal muscle is made up by several muscle fibers, whose proportions and types can be modified by specific training. Other phenotypes that can be changed by training are the processes involving acid/base homeostasis mechanisms. ATP is the main fuel supplied for muscle contraction to happen. One of ATP production pathways is anaerobic glycolysis which produces lactate and hydrogen, this one responsible for lowering the pH causing muscle fatigue. Monocarboxylate transporters type 1 (MCT1) and its ancillary protein (CD147) have as function to transport $H^+$and lactate ions from plasma to red blood cells contributing to the maintenance of acid/base homeostasis retarding systemic acidosis and fatigue of glycolytic muscle fibers. Researches are being conducted in order to determine the role of these transporters in muscle and red blood cells, and to seek possible alternatives to improve horse sports performance.


**KEY-WORDS:** Lactatemia. MCTs. CD147. Performance.


## RESUMO

Nos últimos anos, a equinocultura no Brasil se desenvolveu e ganhou importância nas atividades de esporte e lazer. O complexo do agronegócio do cavalo é relevante no cenário nacional e o país apresenta destaque na importação e exportação de animais vivos. A exportação de cavalos de corrida tem aumentado e as técnicas de melhoramento genético visando melhor desempenho esportivo têm sido almejadas por criadores, apesar do distanciamento destes com os centros de pesquisa. Estudos científicos foram publicados em várias áreas da produção equina, porém, quando se trata de melhoramento genético, valores de herdabilidades e correlações para características relacionadas ao desempenho atlético de cavalos de esporte dificultam uma seleção simples e direta. A seleção genômica pode fornecer as ferramentas necessárias para o aperfeiçoamento do melhoramento das raças equinas embora fatores ambientais possam interferir no desempenho dos equinos, como nutrição e o treinamento realizado nos cavalos esportistas. Várias fibras musculares compõem o músculo esquelético dos cavalos. Suas proporções e tipos podem ser modificados conforme o treinamento aplicado. Outros fenótipos que podem ser alterados com o treinamento se referem a processos envolvendo mecanismos de homeostase ácido/base. O ATP é o principal combustível fornecido para que a contração muscular ocorra. Uma das vias de produção de ATP é a glicólise anaeróbia que tem como produto final o lactato e o hidrogênio, este, um dos responsáveis pela fadiga muscular. Transportadores Monocarboxilatos tipo 1 (MCT1), presentes nas hemácias, e sua proteína acessória (CD147) têm como função transportar íons $H^+$ e lactato do plasma para o eritrócito contribuindo para a manutenção da homeostasia ácido/base retardando a acidose sistêmica e a fadiga de fibras musculares glicolíticas. Pesquisas estão sendo realizadas com o intuito de explorar a expressão desses transportadores nos músculos e hemácias de cavalos com o objetivo de buscar possíveis alternativas para melhorar o desempenho de cavalos em esportes.


**PALAVRAS-CHAVE:** Lactatemia. MCTs. CD147. Desempenho.

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## LITERATURE REVIEW

Since the beginning of the country social, economic and political life, when the horse still represented vanity, pride, and was even considered a status symbol in Brazil, the number of horses has grown and their role has changed. The horse that was used to transport cargo and people, as a traction animal to work in the field, and even as transportation means in wars on battlefields; today in addition to its still great importance as a work tool, the horse is also considered a pet and is being widely used in sports and leisure activities (LIMA et al., 2006).

Although horse breeding is currently seen as a leisure activity, trade and business are becoming expressive. Brazil has the fourth largest herd in the world with 5,514,253 million horses (IBGE, 2011), following China, United States and Mexico. The largest number of horses is in the Northeast region (24.8%), followed by Southeast (24.6%) and Midwest (20.4%). The horse breeding business consists of about 30 segments ranging from the manufacture of saddles and equipment, as well as the production of medicines, feeds, accessories, among others. In addition to specialized labor such as veterinarians, trainers and other professionals involved in the entire process of horse rearing, this chain is the basis of the Horse Agribusiness Complex (LIMA et al., 2006), which generates thousands of direct and indirect jobs in our country.

Brazil plays an important role in the international horse business. Brazilian exports of live horses increased 524% between 1997 and 2009, from $702,800 to $4.4 million (MAPA, 2010). The United States was the leading exporter in 2009 (148.472 horses, 48.8% of world trade) and Argentina, the leading exporter in South America, exported almost seven times more than Brazil (4,255 horses), average price per horse was approximately the same (6,800 dollars). In the rank of live horse importers, Brazil occupies the 35$^{th}$ position, while Europe leads (49.8% of world trade) followed by Asia (26%). Mexico, Canada and Italy, individually, are the main importers according to the number of horses.

Race horses are one of the most active segments in international trade. Exports of Brazilian Thoroughbred (Puro Sangue Inglês, PSI) race horses to Dubai, United Arab Emirates, have grown increasingly. From 2002 to 2006, the number of race horses exported jumped from 99 to 314, according to the Brazilian Association of Breeders and Owners of Race Horses (Associação Brasileira de Criadores e Proprietários de Cavalos de Corrida, ABCPCC). Brazil has improved race horse production techniques such as management, pasture and breeding; breeders began importing more often, mares and stallions from the United States and Argentina, which are the two largest PSI breeders in the world. Therefore, the genetic quality of the Brazilian herd has been improving and equine breeding is expanding in the country, which is also observed in the growing number of sporting events.

Thousands of athletes practice the several equestrian sports: Jump, Polo, Enduro, Vaulting, Dressage, Equestrian Tourism, Equitation, Vaquejada, Turf, Three Day Event, 6 beacons, Three Barrels, Rodeo, among others, a horse business segment worth R$705 million that employs around 20,500 people directly, and an estimated 50,000 athletes (LIMA et al., 2006).

Although athlete horse breeders increasingly aim at genetically superior animals, able to perform better in sports events, there is a lack of interest in applying research results and data in the field. Not only in Brazil, but in most countries, there is considerable distance between farmers and researchers. This can be attributed to the fact that for some horse breeders the activity is not the main source of income, but a leisure activity, and thus they see other breeders as potential competitors. Another possible cause for this gap between research and practical application, which prevents consistent and continuous selection programs, is that research institutions, despite depending on the availability and quality of collected information, usually do not consider breeder interests, thus hindering any kind of agreement.

Nevertheless, a breeding and selection program to improve horse breeding has been created and the scientific production in the area has been growing over the last decade, both in Brazil and in countries where horse agribusiness is an important segment of the economy. According to Almeida & Silva (2010), there has been significant increase in publications about horses, reflecting current trends of the equine industry, focusing on sports medicine, neonatology, clinical diagnostic techniques, new technologies of reproduction of stallions and mares, advanced studies on animal health and diseases, as well as research on behavior and welfare of horse production systems.

Animal breeding requires genetic manipulation involving various aspects of living beings. The selection of Quarter Horses for their performance in the 402-m race, or reins and work events; the Mangalarga Marchador, for their riding convenience; the Anglo-Arab, for their lightness to overcome hurdles; and traction animals for their structure and strength, that is, to improve a horse in such a way that it is good at racing or marching, with excellent performance in jumping and dressage tests and maximizing versatility and achievements, is the ultimate dream of horse breeder. However, horse breeding is so complex that improving a horse genetically for either equestrian activities or work is difficult. The difficulty lies in low heritability of athletic performance and genetic correlation values between desired traits in horses. Koenen et al. (1995) estimated heritability values for performance and its correlations with conformation traits in jumping and dressage horses. The results indicated that due to low heritability (0.17 and 0.19 for dressage and jumping, respectively) and genetic correlation values, indirect selection for performance using conformation traits is not adequate. Wallin et al. (2003) while studying the performance of horses at 4 years old and in their competitions over time, also reported low heritability values, ranging from 0.09 to 0.27, for the traits marching, jumping and dressage. Bokor et al. (2005) estimated genetic parameters for horses that race with hurdles using a rank created by mathematical transformation, and reported heritability values of 0.18 for horses from France and 0.06 for horses from the UK and Ireland.

Genetic research is so important that the method and tools developed for the Human Genome Project were also used to study horse genetics. In 1995, 70 researchers from 20 countries started the Horse Genome Project in order to map the genes and complete the genome sequence of the horse. Initial information in the areas of pelage color genetics and hereditary diseases was used for the benefit of horses and their breeders. In January 2007, the sequencing was already complete and today is available online at http://genome.ucsc.edu. The complete genome sequence allows a deep understanding of diseases with simple and complex traits, inheritable or not, that are influenced by many genes, environmental conditions and genetic regulation, in order to improve therapeutic treatments, find cure and enable the breeding of healthy horses. The great attraction of molecular genetics is the direct use of DNA information in the selection to improve breeding, allowing high efficiency, quick genetic gain and low cost compared with traditional selection based on phenotypic data, in addition to being excellent for low heritability traits (RESENDE et al. 2008), such as horse athletic performance. Genomic studies are also focused on aspects related to little known diseases and there is hope that old unknowns related to horse health are going to be unveiled.

However, horse breeding is not only based on genetically controlled traits, there are numerous environmental factors that can influence their performance, such as nutrition, health and training. Athletic horses when subjected to frequent trainings become capable of performing highly intense activities. As an example, horses trained to perform short duration and high intensity exercises develop skeletal muscle fibers suitable for high speed exercises. When the animal starts the exercise, the muscles use energy provided by the body to contract the fibers. During muscle work, adenosine triphosphate (ATP), the main source of energy used in fiber contraction, is hydrolyzed to adenosine diphosphate (ADP) in the skeletal muscle by myosin-ATPase enzyme, releasing inorganic phosphate and energy for muscle contraction. The muscle fiber consists of myofibrils, cylindrical beams, arranged longitudinally that display muscle contractile units, the sarcomeres. The myofibrils differ according to the dominant energy metabolism, their metabolic and functional characteristics, according to histological staining, being correlated with muscle contraction speed and enzymatic activities.

Skeletal muscles of horses are composed of two major fiber types: type I, slow oxidative or red fibers; and type II, fast or white fibers, which are subdivided into types IIA or fast glycolytic-oxidative and IIX or fast glycolytic. Besides these "pure" fibers, Rivero et al. (1996) showed the existence of two types of "hybrid" fibers, which represent an intermediate stage between I and IIA fibers, called type C, and another, IIAX-XA that would be the intermediate between IIA and IIX. It should be noted that type IIB fiber described in the literature (especially related to humans) is not expressed in horses (SERRANO & RIVERO, 2000), and in this species the corresponding fiber is IIX .

Type I fibers exhibit dark red color due to high myoglobin and cytochrome content and vascularization, since they are especially rich in mitochondria, and have relatively smaller diameters which maximize oxygen diffusion to the mitochondria within the cell. Thus, they have high ability to aerobically oxidize carbohydrates and fatty acids to generate ATP. Additionally, they are rich in oxidative enzymes, have slow and prolonged contraction, suffer fatigue more slowly and are used in long lasting activities as posture maintenance (D'ANGELIS et al. 2005).

Type II or white fibers have greater diameter, with a predominance of anaerobic energy metabolism. The muscle comprising such fibers has contraction velocity and maximum tension higher than type I fiber. Type IIA fibers have predominantly anaerobic metabolism, but with higher oxidative capacity, which makes them more resistant to fatigue. They are recruited along with type I fibers, however, as the workload is increased, more tension becomes necessary, and more type IIA fibers are recruited. Type IIX fibers are fast twitch, where energy is obtained almost exclusively by anaerobic glycolysis, using only glucose and glycogen, leading to large accumulation of lactate and hydrogen ions at the end of the exercise. These are easily fatigable fibers with poor energy efficiency found in high proportions in short distance race horses that need very powerful contractions for quick acceleration and strength generation, predominantly found in muscles that move the legs and arms.

All fibers are active in all exercises, but the type of exercise determines specific fiber recruitment. Fiber ratio also depends on genetics, resting time and the type of training to which the horse is subjected. Animals used for endurance sports have higher percentages of low contraction type I fibers compared to racehorses, which have a high percentage of high contraction type IIA and IIB (IIX) fibers, the latter being faster (SNOW & GUY 1980).

The body has one or more systems for energy production that supply the fuel required by the muscle fibers. The only source of energy that can be used as a direct fuel for muscle contraction is ATP. The horse can obtain it by breaking down the creatine phosphate stocks. The other way is through the breakdown of muscle glycogen and conversion of glucose to lactate, and last, by oxidizing carbohydrates and fat and, with smaller contribution, proteins.

When the muscle uses the glycogen reserve to obtain energy as ATP, glucose is converted to pyruvate, and during normal aerobic metabolism pyruvate is then oxidized by molecular oxygen to $CO_2$ and $H_2O$. During intense physical exercise, the oxygen supplied to muscle tissue may not be sufficient to fully oxidize pyruvate (FERRAZ et al. 2009). In these cases, glucose is converted to pyruvate and then to lactate by lactic fermentation pathway, the resulting ATP did not resort to oxygen (NELSON & COX, 2005). Lactate, formed during anaerobic glycolysis, is first produced in the glycolytic fibers and oxidized in the oxidative fibers and heart, and it is also used as a substrate for hepatic gluconeogenesis (BONEN, 2001; FERRAZ et al. 2008). Lactate is removed from the blood at the same rate at which it is produced, so that lactate concentration in the blood of horses remains approximately between 1 and 1.5 mM (HIGGINS & SNYDER, 2006). Concentration in the horse muscles can increase to 23-46 mmol/kg (LOVELL et al., 1987) when performing maximum exercises.

Thus, the anaerobic glycolytic pathway generates lactate and $H^+$ protons accumulation in the muscle and blood, and this is the main cause of muscle fatigue and pain (FITTS, 1994; HOGAN et al., 1995). According to Allen at al. (2008) fatigue may be understood as any decline in muscle performance. The type IIX fibers are those with greater amounts of glycogen and due to glycogenolysis, during intense exercises, higher lactate concentrations are measured in the muscles that recruit large proportions of these fibers (VALBERG et al., 1985). According to Fitts (1994), the low pH determined by the increase of $H^+$ ions can inhibit muscle contraction activity and release $Ca^{2+}$ by the endoplasmic reticulum.

As a defense, cells adapt to physiological stress caused by exercise through a variety of mechanisms to prevent cellular acidosis caused by $H^+$ proton accumulation. In horse muscles, various buffers are used to reduce pH fluctuations in the cells during muscle activity (HYYPPÄ Poso & 1998; FERRAZ et al., 2010). Besides the buffers, there are carrier proteins called monocarboxylate transporters (MCTs) in most tissues and also in the erythrocytes (HALESTRAP & PRICE, 1999). MCTs transport lactate and other anions such as pyruvate, acetoacetate and β-hydroxybutyrate, inside and outside the cell across the plasma membrane. This transport does not require ATP since it is performed together with a proton and is controlled by the hydrogen ion gradient (MEREZHINSKAYA & FISHBEIN, 2009). There are 14 identified MCTs isoforms, most of which do not have specific and determined function, differing according to tissue, species and specific substrate. Among the isoforms already identified, MCT1 and MCT4 are considered the main lactate carrier of the cardiac and skeletal muscles of mammals (BROOKS & MCCLELLAND, 2002; HALESTRAP & MEREDITH, 2004). The MCT1 isoform is prevalent in oxidative fibers and responsible for facilitating lactate absorption, on the other hand, MCT4 is predominantly found on glycolytic fibers and facilitates lactate extrusion (KITAOKA et al., 2010). In many species, MCT1 is the only isoform found in the membranes of red blood cells, but in horses, Koho et al (2002) have reported the expression of MCT2 isoform, which has higher pyruvate affinity, but it is also responsible for facilitating lactate transport when present at low concentrations in the muscle. Koho et al. (2006) studied the location monocarboxylate transporter in horses and found MCT1 and MCT2 isoforms in red blood cells and MCT1 and MCT4 isoforms in muscle cells.

Athlete horses are highly trained to perform high-intensity exercise. One of the most studied and improved horses for speed and endurance competitions, such as running and jumping, is the English Thoroughbred (PSI). These animals have high levels of oxygen and large amounts of glycogen in the muscles. When intense exercises are performed, lactate concentration in the plasma and red blood cells varies considerably and can increase greatly (SNOW & HARRIS, 1988), making them extremely prone to muscle fatigue. This concentration change is due to lactate influx rate into the erythrocytes, which is dependent on the activity of MCTs proteins. Another important consideration is that MCTs need an accessory protein for their correct localization and function in the plasma membrane. The accessory protein of the MCT1 and MCT4 isoforms is a glycoprotein part of the plasma membrane that belongs to the immunoglobulin superfamily, called CD147 (KIRK et al., 2000; GALLAGHER et al., 2007). Because of this, many studies are being conducted to study the number and activity of MCTs and CD147 accessory proteins of horses, in order to improve genetic breeding techniques and make this race increasingly resistant to extreme exercise.

Koho et al. (2006) studied MCTs and CD147 levels in red blood cells and muscles (gluteus medius and cremaster) of English Thoroughbred horses and concluded that MCT1 and MCT4 isoforms were found in abundance in the muscles, while MCT2 isoform was found in the erythrocytes. Training and age increased the amount of MCT4 and correlated positively with CD147. With these findings, the authors reported that as lactate uptake by erythrocyte increases, its plasma concentration decreases, causing lactate efflux from the muscle to the plasma also to increase, thus making the muscle more resistant to fatigue. Because lactate is transported together with $H^+$ ion into the red blood cells, their cytoplasm becomes acidic and hemoglobin oxygen dissociates, promoting greater supply of oxygen to the working muscles.

Kitaoka et al. (2011) while studying PSI horses, reported that the number of MCT1 and MCT4 increased in the *gluteus medius* muscle after 18 weeks of high intensity training and that the increase of MCT1 was maintained for six weeks when the training became moderate.

Reeben et al. (2006) searched for genetic sequences of MCTl and CD147 in Standardbred race horses to examine the differences between horses that had high and low lactate transport activity in their red cells. The authors found polymorphisms in the study (Single Nucleotide Polymorphism - SNP); however, concluded that a correlation with the lactate transport activity was unlikely and suggested further research.

Revold et al. (2010) studied the expression of MCT1 and CD147 in different fibers of the *gluteus medius* muscle (fiber type I, IIA, IIAX, IIX) in

Norwegian-Swedish Coldblood race horses before and after training. The authors reported no significant change in the distribution of MCT1 and CD147 in the membranes of different muscle fiber types, both before and after training. On the other hand, MCT1 and CD147 levels increased in the cytoplasm of fibers type I, IIA and IIAB compared with the reference value of type IIX fibers, which may indicate the presence of these proteins in the mitochondria (BENTON et al. 2004; BUTZ et al. 2004).

Accurate research is very important when the objective is practical application of results. Due to the various segments of the Brazilian agribusiness complex where horses are a large part, the objective and the criteria to be included in breeding programs should be clearly defined. Regarding racehorses, the study of monocarboxylate allied to species breeding can bring significant improvement in the performance of these animals, since these carriers are closely related to performance and muscle fatigue during races. The search for mutations that may influence the correct functioning of MCTs, the study of candidate genes associated with lactate transporters or horse genome sequencing are genomic tools that linked to traditional animal breeding, can provide accurate information to the breeders.

Clearly, the practical application of research in breeding horses is the increasing sales. The efficient use of improvement techniques can reduce the purchase of foreign genetic material, since one of the main reasons to import semen and live animals is related to genetic improvement of broodstock. The number of exported animals can also increase if the herd consists of high quality horses, recognized internationally. When combining health and nutrition with breeding techniques, the expenditure with quarantine, lab tests, veterinarian and treatment of diseases can be reduced.

The business of rearing and using horses occupy prominent position in developed countries and in many developing countries, like Brazil. The various segments that make up the Horse Agribusiness have a fundamental role in the development of the country, mainly by generating income and jobs. Thus, it is clear that breeding techniques applied to genetically improve the Brazilian herd can contribute effectively to the development of our country.

Although horse agribusiness is of great importance to Brazil and numerous studies in many countries are being published in the literature, regarding breeding of horses, breeding programs are not being practiced consistently. This means, in a way, that the majority of research results and data in this area does not generate practical application, and therefore, contributes little to species development. Most often, this fact reflects more the lack of interest from breeders to use research results, than the quality of the research itself (MOTA & REGITANO, 2012). Still, horse breeding is likely to be enhanced due to the excellent herd, the high production potential and the scientific tools available today.

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