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Metabolic and cardiovascular disorders in highly inbred lines for intensive pig farming: how animal welfare evaluation could improve the basic knowledge of human obesity

Gianfranco BRAMBILLA and Alfredo CANTAFORA

(a) Dipartimento di Sanità Alimentare ed Animale (b) Dipartimento di Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Rome, Italy

Summary. - Intensive pig farming is currently performed with highly inbred lines of animals characterised not only by fast growing and low proportion of back-fat tissue, but also by an impaired development of muscular mass and cardiocirculatory system, and higher susceptibility to oxidative stress. This picture of genetically-determined metabolic alterations suggests the use of these lines as a nice tool for conducting comparative studies with human populations affected by high incidence of obesity and their sequelae, e.g. type 2 diabetes, arteriosclerosis, and cardiovascular diseases. The animal model offers, in fact, the advantages of low genetic variance, homogeneous feeding regime, and the absence of confounding factors typical of humans, such as smoking, alcohol drinking, etc. The similarity of pathological response to high caloric intakes between the two species supports the use of pig model for identifying genes and their variants associated with energy storage defects through the activation of both hormonal and biochemical pathways. To this purpose, the evaluation of animal welfare constitutes a nice opportunity to deepen the matter, through the evaluation of both ethical and physiological needs.

Key words: pig, animal welfare, genetic selection, oxidative stress, obesity, diabetes, cardiovascular diseases.

Riassunto *(Patologie metaboliche e cardiovascolari in suini da allevamento intensivo: come la valutazione del benessere animale contribuisce alla conoscenza di base dell'obesità umana).* - Le linee genetiche ad alta selezione utilizzate oggi nell'allevamento intensivo del suino, sono caratterizzate da indici di accrescimento molto elevati, dalla tendenza ad una scarsa sintesi di lardo, da una sproporzione tra sviluppo delle masse muscolari e del sistema cardiocircolatorio, da una suscettibilità genetica allo stress ossidativo. Questa stretta correlazione tra selezione genetica e alterazioni biochimiche costituisce un interessante modello per uno studio comparato con alcune popolazioni umane nelle quali è riconosciuta l'esistenza di fattori genetici predisponesti all'obesità, con conseguente alto rischio di sviluppo di malattie metaboliche e cardiovascolari , quali il diabete di tipo 2 e l'arteriosclerosi. Perciò lo studio del benessere negli animali da reddito, caratterizzati da una bassa variabilità genetica, da una pressoché omogenea alimentazione, e dall'assenza di fattori di confondenti legati ad abitudini individuali (quali fumo e assunzione di alcolici) può aiutare ad approfondire i fattori genetici alla base dell'obesità umana e la loro correlazione con alterazioni in specifici profili biochimici e ormonali.

Parole chiave: suino, benessere animale, selezione genetica, stress ossidativo, obesità, diabete, malattie cardiovascolari.

Introduction

In pig husbandry, the progressive development of intensive farming has led to the genetic selection of highly inbred lines with extremely fast growth rates (up to 120 kg b.w. within the first six months of life) and reduced fat content [1]. However, the indiscriminate over-selection for these traits has been found to be associated with biochemical disorders [2], which have been addressed in the EU regulation on the welfare of food-producing animals [3].

Some of the metabolic diseases most commonly reported in association with genetic selection are: Mulberry heart disease (MHD), which is caused by extensive oxidative-based cardio-angiopathy [4]; Porcine stress syndrome, characterised by an abnormal accumulation of lactic acid in the muscle cells [5]; and osteochondrosis, which is due to altered bone-growth metabolism [6]. The close correlation between these metabolic alterations and genetic selection provides a good opportunity for studying the function and the regulation of the genes involved in the alteration of metabolic and hormonal profiles underlying the modification of quantitative traits such as muscle-mass development, fat accumulation and feed conversion. This is of particular interest in light of the fact that fast-growing farmed pigs display patterns of genetically-determined pathological alterations that are similar to those observed for human populations recently afflicted by epidemics of obesity [7].

Indirizzo per la corrispondenza (Address for correspondence): Gianfranco Brambilla, Dipartimento di Sanità Alimentare ed Animale, Istituto Superiore di Sanità, V.le Regina Elena 299, 00161 Rome, Italy. E-mail: g.brambi@iss.it

Pig leanness and its biochemical implications

Various biochemical studies have provided hormonal and metabolic profiles of inbred pigs: compared to highly inbred pigs, those that are less inbred have lower growth-hormone expression, thicker back-fat, and a lower ratio of lean meat to fat meat in the carcass [8]. However, the higher levels of growth hormone found in highly inbred pigs increase oxidative metabolism through the formation of free radicals and lipid peroxidation products, which could lead to MHD [9]. The ability to cope with oxidative stress is directly affected by the degree of genetic selection, as demonstrated by the evaluation of oxidative stress on sera of non-inbred swine, such as wild boars from low-inbred Cinta Senese pigs, which reach 120 kg b.w. after around 14 months, and intensively farmed animals from the highly inbred Large White x Landrace lines [1]. In terms of assessing animal welfare, this finding has contributed to discriminating between stress and distress situations, the latter term indicating the lack of an adequate adaptive anti-oxidant response to compensate for free radicals and the formation of their reactive oxygen metabolites, with the distress situation evidently predisposing to degenerative pathological sequels.

Other studies have focused on the correlation between leptin levels and the proportion of adipose tissue and have shown that, in different pig lines, there is a positive correlation between this hormone and average daily gain, fat thickness, and percent fat-free carcass, demonstrating that the differences in leptin levels account for breed-specific traits of growth, leanness, and meat quality. For this reason, leptin levels have been used as a selection criterion for genetically increasing the lean content in pig carcasses [11, 12]. Other efforts have been made to genetically characterise the correlation between pig leptin polymorphisms and economically important traits such as feed intake and growth rate in Landrace animals [13]. In this context, the exogenous administration of porcine recombinant leptin can be used to shift energy away from lipid accretion, directing the metabolism towards lean-meat production [14]. In this way, it could be possible to pharmacologically modulate metabolism through a decreased synthesis of adipose tissue [15].

Why pigs are a good model for studying obesity in humans

Interestingly, current developments in the farming of fast-growing pig lines have created new perspectives for the study of human obesity, which for decades has been a major public-health problem in economically developed countries and which has recently become a serious concern in economically underdeveloped countries [16]. In fact, the increased proportion of obese individuals in the world's population has led to epidemics of type 2 diabetes, which has lost its connotation of adult-onset disease and is turning into the world's leading public-health threat [17]. This simultaneous growth of obesity and type 2 diabetes supports James Neels' "thrifty gene" theory [18], which hypothesises that there exist metabolically thrifty genes that permit a more efficient use of food, fat accumulation, and rapid weight gain during periods characterised by food abundance and subsequent famine. Thus genes that resulted in high levels of insulin and leptin and that were advantageous under the conditions of unpredictably alternating feast and famine typical of past centuries have become a disadvantage in the modern affluent world, causing both obesity and diabetes [17].

The mechanisms of genetic selection for a better utilisation of food are active in feral pigs, as well as in humans. This has been demonstrated in wild pigs from Ossabaw Island (Georgia, USA), which were well adapted to feast and famine but which, when put on a high-fat diet and exercise restrictions, shortly developed traits preceding diabetes and heart disease, such as increased sugar and fat levels, hypertension, and arteriosclerosis [19]. However, this is only a confirmation of previous reports that pointed out similarities between pigs and humans in the genetic control of growth and fat-accumulation traits, suggesting that pigs could be used for studying human obesity [20]. It appears that pigs mimic the health problems of obese humans so well that they could be much more useful in studying diabetes and heart disease [19] than other animal models, such as rodents or fatty worms [21].

In this context, a better understanding of adipogenesis and the regulation of energy metabolism in humans and pigs could be used for two main purposes. The first, typically economic, would be that of using genetic selection to drive metabolism towards the production of the so-called "functional foods" [22], without regard for animal welfare or its ethical importance. The second purpose, which is more promising for its impact on human health, would consist of developing a suitable model for identifying the genes that direct metabolism towards storing any energy excess into adipose tissue with maximum efficiency [16]. That humans and pigs are physiologically and genomically similar seems to favour this second approach, which involves using classical methods for identifying candidate genes, such as quantitative trait loci (QTL) scanning, gene-transcript profiling, and the identification of significant DNA polymorphisms of obesity-related genes in the pig genome that might provide useful targets for the genetic study of human obesity [2].

Candidate genes in the pig model

Among the 130 candidate genes studied in pigs, a very interesting polymorphism has been identified in the porcine *melanocortin-4 receptor (MC4R)* gene [24]. This MC4R type was significantly associated with less backfat thickness, slower growth rate, and lower feed intake that are basically animal wefare parameters easy recordable in field conditions. This association could be useful for studying the physiological relationship between melanocortin signalling and human obesity, given that similar *MC4R* mutations have been found in morbidly obese humans [25].

In recent years, a significant number of QTL have been identified in the pig [25]. The first major QTL for fatness and growth was identified on pig chromosome 4, and comparative mapping between humans and pigs has indicated that the QTL is located in a region homologous to HSA1q [2]. A recent study has also identified a significant QTL for growth and fat-content traits on pig chromosome 7 [26]. The polymorphisms in a candidate gene, *high mobility group A1(HMGA1)*, have been consistently shown to be associated with variations in QTL in other genetically diverse commercial populations. Since the corresponding human and mouse chromosomal region is also known to be associated with obesity [27], the *HMGA1* gene could be important for human obesity and other organism models.

Furthermore, the use of a pig model would be ideal for studying the response to different dietary stimuli (and in general environmental stimuli) by transcriptional profiling, as previously demonstrated in pigs with high and low lean-growth rates, following the collection of tissue samples at different times, with transcriptional profiling achieved through the use of microarrays for human genes [28].

Conclusions

The evaluation of animal welfare in farmed pigs could constitute a very interesting opportunity for better understanding the relationships among the genetic, genomic, and post-genomic factors that regulate energy-balance disorders and their relative metabolic sequels. The comparative genetic analysis of pig strains with marked differences in the utilisation of food energy could allow for the identification of the loci involved in the onset of human obesity, with the advantage of low genetic variance, homogeneous feeding regime, absence of individual habits (such as smoking and alcohol consumption), and the availability of body fluids and tissues. Moreover, the known anatomical and physiological similarities between pigs and humans suggest that the pig is preferable to other more common animal models for studying human obesity and cardiovascular pathologies.

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