ELSEVIER

Livestock Production Science 93 (2005) 15–21

LIVESTOCK PRODUCTION SCIENCE

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Molecular genetics of behaviour: research strategies and perspectives for animal production

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Abstract

Genetic factors are undoubtedly involved in inter-individual variability of the behaviours that may be important for livestock production, as shown by pedigree studies, comparison of genetic stocks raised in the same environment, and selection experiments. The knowledge of gene polymorphisms responsible for genetic variability would increase the efficiency of selection, as shown for instance by the identification of the ryanodine receptor gene that harbours the mutations responsible for the porcine stress syndrome, that allows the eradication of the susceptibility allele. One strategy is to screen systematically the genes that are known to be involved in regulation of behaviour (functional candidate genes). This strategy is however very difficult for most behavioural traits, since behaviour is an emerging function from the whole brain/body and the molecular pathways involved in genetic variability are very poorly understood. Another strategy is to investigate linkage between trait variation and genetic markers in a segregating population (usually an intercross or backcross between two strains or breeds contrasting for the trait under study). It allows the detection of genomic regions influencing that trait (quantitative trait loci or QTL), and further investigation aims at the identification of the gene(s) located in each of these regions and the molecular polymorphisms involved in phenotypic variation. Although many QTL have been published for behavioural traits in experimental animals, very few examples are available where strong candidate genes have been identified. Further progress will be very much dependent upon the careful definition of behavioural traits to be studied (including their importance for animal production), on the reliability of their measurement in a large number of animals and on the efficient mastering of environmental factors of variability. The fast increase in the knowledge of genome sequence in several species will undoubtedly facilitate the application to farm animal species of the knowledge obtained in model organisms, as well as the use of model organisms to explore candidate genes detected by QTL studies in farm animals.

Keywords: Behaviour; Molecular genetics; Quantitative trait loci; Gene polymorphism

1. Introduction

Behaviour is an integral part of biological regulations and an important factor in animal production

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doi:10.1016/j.livprodsci.2004.11.002

and welfare. General locomotor activity, emotional/stress reactivity, redirected behaviours (feather pecking, tail biting, etc.), social interactions and aggressive behaviours, reproductive behaviours (oestrus, maternal, brooding, etc.), feeding behaviours have all been shown to be heritable to various degrees (Jones and Mormède, 1999; Beaumont et al., 2002). Behavioural traits are complex and individual variability usually results from the influence of numerous genes interacting with each other and with environmental factors. Therefore, it would be of interest to define the genetic variation responsible for different behaviour. This would improve the efficiency of selection for desirable traits or to eliminate unwanted phenotypes, to study biological systems involved in trait variation and to investigate its relationships with other phenotypes such as production traits. However, deciphering the genetics of complex traits requires specific approaches (Andersson and Georges, 2004).

1.1. Behaviour genetics

Genetic mechanisms are basic to the process of domestication (Price, 1998, 1999; Mignon-Grasteau et al., in press). The domesticated phenotype refers to a number of different behavioural and biological traits that facilitate the adaptation of domestic animals to their environment, including a reduced behavioural reactivity towards humans and ease to handling, reduced aggressive behaviours (towards humans as well as intraspecific), as well as attenuated emotional/stress responses. Genetic influences on the domestic phenotype may result from variation in brain neurochemistry, such as in the serotonergic and catecholaminergic systems (see, for instance, Naumenko et al., 1989; Nikulina, 1990; Popova et al., 1991). All these traits are important components of animal welfare. Although these phenotypes respond quickly to genetic selection (Belyaev, 1979), a very large variability is still present in domesticated animals.

For instance, domesticated behaviour is highly variable among breeds of sheep (Lankin, 1997) and in other species (Lankin and Bouissou, 2001). Human–animals interactions show a wide range of diversity and heritability estimates vary widely, depending on the genetic stock and the behavioural measure (Grandin and Deesing, 1998; Boissy et al., 2002). Both behavioural and neuroendocrine stress responses are influenced by genetic factors (Mormède et al., 2002a), as shown for instance in pigs (McGlone et al., 1998; Mercat and Mormède, 2002), ruminants (Boissy et al., 2002), poultry (Mignon-Grasteau and Faure, 2002) and fishes (Vandeputte and Prunet, 2002).

A common challenge to behavioural genetic studies is the definition of phenotypes. Indeed, large concepts like emotionality, anxiety, fearfulness and aggressiveness cover a wide range of psychobiological processes that are difficult to translate into operational terms. Many different behavioural tests have been designed for the study of emotional behaviours and extensive studies in laboratory rodents show that the range of variation in behavioural responses to environmental challenges cannot be described along a single vector from low to high 'emotionality', for instance, but rather by combined variations along different independent dimensions (Ramos and Mormède, 1998). Indeed, this result from experimental psychology experiments is coherent with the data obtained by clinical psychologists studying personality in humans, who describe a limited (although variable) number of dimensions subsuming individual variations in temperament and personality that have been tentatively related to specific neurochemical functions (see Cloninger, 1994; Digman, 1997). These concepts have given a framework to genetic studies of inter-individual variability (Nigg and Goldsmith, 1998; Bouchard and Loehlin, 2001).

There is ample experimental evidence that the same concepts can be applied to the study of psychobiological reactivity in animals (Ramos and Mormède, 1998). However, data available for livestock species are still scarce. The goal here is to find behavioural or biological traits stable across situations, and that describe at best individual characteristics of temperament that would be amenable to genetic analysis. Many studies have used exposure to a novel environment, a test widely used in experimental psychology and behavioural genetics in laboratory rodents, and known as the open field. Tonic immobility in birds has been used as an index of fearfulness and submitted to multifactorial and genetic analysis (Mills and Faure, 1986, 1991; Jones et al., 1994; Mignon-Grasteau et al., 2003). The same test, named backtest, was used in pigs by Hessing et al. (1993) and stimulated many

experiments exploring its psychobiological significance and its relevance to animal production and welfare. Forkman et al. (1995) compared the behaviour of piglets in a number of social (rank order, social dependence, aggression) and non-social tests (novelty extinction, backtest) and used principal component analysis to study the relationships between these different measures. The analysis suggested three independent personality traits: aggression, sociability and exploration, confirming the multidimensional nature of behavioural responses to social and non-social challenges. Further exploration of the structure of temperament in farm animals, its experimental analysis, the relevance of its components for animal production and welfare, and the influence of genetic factors in individual variability would give a firmer basis to the exploration of molecular mechanisms underlying genetic variability and their use in selection.

2. Molecular genetics

We can learn from research in laboratory animals and humans, and from the study of other complex traits in farm animals the strategies to uncover the genes and their polymorphisms involved in genetic variation of behavioural traits (Ramos and Mormède, 1998; Jones and Mormède, 1999; Belknap et al., 2001; Mormède et al., 2002a; Andersson and Georges, 2004).

2.1. Candidate genes

One approach is to explore genes, of which the products are known to be involved in the biological pathways underlying the process under study (functional candidate genes). In humans for instance, the genes encoding the enzymes and receptors involved in the main neurochemical pathways are systematically screened for polymorphisms that may be associated with the clinical condition. Most studies are based on single gene polymorphism, but a multigene approch is better suited to behavioural or psychopathological phenotypes (see, for instance, Comings et al., 2000a, b; Cravchik and Goldman, 2000). This approach is based on previous knowledge in behavioural biology, such as the role of serotonergic systems in aggressive behaviour (Nelson and Chiavegatto, 2001). Such a candidate gene approach has been used by Kim et al. (2000) to demonstrate the association between a mutation in the melanocortin-4 receptor gene, implicated in the regulation of feeding behaviour and body weight in humans and mice, and food intake, backfat and growth rate in pigs.

2.2. The quantitative trait loci approach

The quantitative trait loci (QTL) approach investigates linkage between trait variation and genetic markers in a segregating population (usually an intercross or backcross between two strains or breeds contrasting for the trait under study). It allows the detection of genomic regions influencing that trait, and further investigation aims at the identification of the gene(s) located in each of these regions and the molecular polymorphisms involved in phenotypic variation.

This strategy has been successfully used to identify the molecular mechanism of the porcine stress syndrome (PSS), a condition that has dominated stress research in pigs for decades, and that is also known in humans as malignant hyperthermia (MacLennan and Phillips, 1992). By linkage studies in informative families, the gene responsible for this condition was located in the p12–q22 region of pig chromosome 6 (Davies et al., 1988) or the q12–13.2 region of human chromosome 19 (McCarthy et al., 1990). In this region was mapped the ryanodine receptor gene that is involved in calcium movements across sarcoplasmic membranes in muscle, and mutations in this gene were shown to be responsible for predisposition to malignant hyperthermia (MacLennan et al., 1990) or PSS (Fuji et al., 1991). The availability of a molecular diagnosis assay for the causal mutation (Otsu et al., 1992), which allows the detection of heterozygotes as well as homozygotes, makes it possible to eliminate the mutation. However, many producers continue to use boars which carry the ‘stress gene’ because offspring from these boars produce more kilograms of pork at the expense of meat quality (Monin et al., 1981).

Other examples can be found for production-related phenotypes. Although many studies identified chromosomal regions (QTL) influencing production traits, only few causal genes and their polymor-

phisms have been identified (see Andersson and Georges, 2004, for review). It can be noticed that most of these mutations identified so far have a strong genetic effect on the trait they influence (monogenic trait loci).

2.3. QTL and behaviour

As for behavioural traits, available examples in laboratory rodents show that the mode of inheritance is usually complex. In most cases, several QTL are detected and each QTL explains a small part of the total genetic variance of the trait in the segregating population, except when the two parental strains have a close genetic background. For example, we found a strong QTL in rats for the locomotor response to novel environment exposure in the Wistar Kyoto Hyperactive rat, as compared to the Wistar Kyoto rat that is the strain from which the hyperactive rat is derived (Moisan et al., 1996). On the other hand, a given QTL can influence the trait in different directions in the parental strains and in the segregating population, since a strain that was not selected for the trait under study can carry both increasing and decreasing polymorphisms, and different modes of inheritance between males and females are frequent. In an F2 intercross between Spontaneously Hypertensive (SHR) and Lewis rats, Ramos et al. (1999) found two QTL, on chromosomes 4 and 7, influencing activity in the centre of the open field, but in females only. The SHR rats are more active than the Lewis rats in the centre of the open field, the difference being much larger in females (Ramos et al., 1998). In the F2 population, the SHR allele on chromosome 7 increased activity in the centre, but the SHR allele on chromosome 4 reduced activity in females. Indeed, molecular genetics allows further investigation of the trait, since it is possible to sort apart the influence of each QTL on the final phenotype by marker-assisted selection. With this approach, it was shown that the influence of these loci on locomotion in the centre of the open-field reflects their action on general inhibitory processes (Mormède et al., 2002b).

However, the way from the detection of a QTL to the identification of the gene(s) and polymorphism(s) responsible for behavioural trait variability is still long and difficult (Moisan, 1999). Although many QTL have been published for behavioural traits in experimental animals, very few examples are available where strong candidate genes have been identified. Three recent examples come from the study of alcohol-related phenotypes in mice selected for their sensitivity to withdrawal-induced convulsions (Buck et al., 1997; Fehr et al., 2002) and in rats selected for a high voluntary alcohol intake (Carr et al., 1998; Liang et al., 2003), and from emotionality research in mice (Yalcin et al., 2004).

There are only few examples in farm animal species. In ruminants, several QTL have been detected for the reaction to humans (Fisher et al., 2001; Schmutz et al., 2001). In poultry, Schütz et al. (2002) have studied behaviours related to resource allocation and Buitenhuis et al. (2003) mapped QTL related to feather pecking. Our study of reactivity to stress in a F2 population between the Large White and Meishan pig breeds allowed the identification of genetic loci on chromosome 1 related to locomotion in a novel environment and on chromosome 8 related to exploration, as well as a major locus on chromosome 7 related to cortisol levels (Désautés et al., 2002). Candidate genes previously mapped in these loci can be found in silico, in databases dedicated to genetic map and sequence data collected in man, in model species and in domestic animal species (http://www.ensemble.org/ and http://www.ncbi.nlm.nih.gov/). This allowed us to identify *Cbg*, encoding the carrier protein for cortisol in plasma (corticosteroid-binding globulin) as a candidate gene involved in the genetic variability of cortisol levels (Ousova et al., 2004). This strategy is however very difficult for behavioural traits, since behaviour is an emerging function from the whole brain/body and the molecular pathways involved in genetic variability are very poorly understood. In the absence of any strong candidate gene in the locus, the next step is to narrow the size of the QTL through the study of advanced intercross lines and the construction of congenic lines (Moisan, 1999). These approaches are however time- and money-consuming, especially for large species, and very difficult for behavioural traits that are usually very sensitive to environmental influences, so that the effect of a single QTL (that usually explains only a small part of the overall difference between the parental breeds) is difficult to quantify reliably.

The success of these approaches will depend on the careful definition of behavioural traits to be studied (including their importance for animal production), on the reliability of their measurement in a large number of animals and on the efficient mastering of environmental factors of variability. The fast increase in the knowledge of genome sequence in several species will undoubtedly facilitate the application to farm animal species of the knowledge obtained in model organisms, as well as the use of model organisms to explore candidate genes detected by QTL studies in farm animals.

3. Conclusion

The development of behaviour genetics in farm animals and the study of genes and polymorphisms responsible for genetic variation still appears as a far-reaching goal. One reason is that molecular genetic studies of behaviour are difficult, even in laboratory animals in which homogenous, selected and well-characterised inbred strains are available, as well as a conceptual framework for the study of temperament and the relative easiness to produce and study a large number of animals, a prerequisite to linkage analysis. In the species used for production, only few lines selected for behavioural traits are available. In most cases, we have at best divergent breeds, and the genetic architecture of the trait is usually more complex in unselected strains. Furthermore, within-breed (or strain) variation is usually large, and this important background noise reduces the influence of individual loci. However, a major limit to these studies is the limited basic knowledge about psychobiological dimensions underlying behavioural trait variability, and the availability of reliable and meaningful measures of these, that would be as free from environmental influences as possible. It cannot be excluded that a more thorough phenotypic investigation will uncover the influence of major genes on behavioural traits significant for production, product quality and animal welfare, which could be analysed efficiently by molecular genetic techniques. On the other hand, comparative genomics should allow farm animals to benefit from advances made in this field in humans or in model species.

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