

From Physiological Models to Gene Action

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ABSTRACT

Mathematical models, which are based directly on mechanism of a particular biological process can provide a powerful conceptual link between the gene map and the phenotypic expression of traits. As soon as the physiology of the trait is understood it is possible to express the existing knowledge in terms of non-linear differential equations. These dynamical equations are the body of a physiological model. These mechanistical models are usually formulated in a manner in which the parameters match measurable physiological variables, and thus serve as a mathematical bridge from the genotype to the phenotype.

In the present study we explore the development and ovulation of ovarian follicles in mammals with the help of mathematical modeling and show how this approach has identified a specific gene effect on phenotype.

A dynamic model to describe ovarian follicular development following commitment has been developed [1]. It identifies follicular growth with oestradiol production and assumes that this growth is the result of intra-ovarian stimulation, gonadotrophin stimulation, and inhibitory interactions among the follicles, where larger follicles suppress the growth of the smaller follicles. The parameters of the model are the levels of oestradiol in each follicle at commitment, the rate of change of oestradiol production by individual follicles during follicular development, and the level of oestradiol that will induce a luteinizing hormone (LH) surge.

Generally changes in the parameters of the model could be associated with both genetic and environmental effects. The former assumes that an increase of ovulation rate results from an animal having a different genotype described by the parameters of the model. The model was applied to describe the ovulation response of different breeds of sheep, in particular the difference between the Romney and Booroola breeds. In this case the number of growing follicles per wave and their levels of oestradiol production at the commitment were treated as stochastic parameters; the results of model simulations were compared with the existing statistics of the ovulation rate responses observed in Booroola, Booroola cross Romney and Romney ewes. Although there was no difference in the total amount of oestradiol, which stimulates the pre-ovulatory LH-surge, the amount of oestradiol per ovulatory follicle was much lower in Booroola ewes in comparison with non-carriers. This confirms the biological mechanism of Booroola gene action proposed in earlier studies [2] on the basis of follicle diameters measurements.

The model was applied to describe the ovarian follicles growth and ovulation in gilts, where the ovulation rate varied from 13 to 26. These animals were selected for either the estrogen receptor (ESR) genotype AA or BB, in which B allele is associated with a larger litter size. Neither estrus length nor estrus cycle length was affected by the ESR genotype. No difference in periovulatory hormone profiles between the AA and BB gilts were detected [3]. Furthermore, temporal aspects of these profiles were not different for both genotypes. Subsequent analysis based on measurements only reveals that the difference in litter size is not due to any differences in oocyte maturation [3]. Application the present non-linear model of ovarian follicles development showed that AA and BB gilts were different in the number and size distribution of follicles at commitment. This is a plausible explanation of the action of the ESR gene. Such difference cannot be picked up by routine measurements directly or by classical statistical analysis of data. Then this example demonstrates that the present model not only successfully describes ovarian follicular development but also is a unique and valuable tool in identifying the action of a particular gene.

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