AGOUTI RELATED EFFECTS

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SUMMARY

The *Agouti* locus is usually recognised for effects on coat colour and in sheep the problem of black lambs initiated molecular genetic investigations. However, there are other recognised affects of this locus and the independent *Agouti Related Transcript* locus that may have commercial relevance in sheep or other livestock. This paper reviews knowledge generated from rodents and humans.
Keywords: Agouti locus, related affects

INTRODUCTION

The *Agouti* locus is usually known for effects on coat colour. In sheep white coat is considered to have a phaeomelanin (tan/yellow) background from the dominant *Agouti* allele (A^{Wt}), on which interacting white spotting genes limit pigmentation, while black lambs arise from lower alleles (Sponenberg *et al.* 1996; Parsons *et al.* 1997). Adult-onset obesity, elevated insulin levels, reproductive limitations and susceptability to tumors are characteristics of some mice bearing yellow coats determined by the *Agouti* locus (Wolff and Bartke 1966; Silvers 1979; Wolff *et al.* 1986). However, these pleiotropic traits are not dependent on phaeomelanin since recessive yellow coat determined by the *Extension* locus has no similar effects (Silvers 1979). The relationship with diabetes in the mouse aided identification of the human homolog of the murine *Agouti* gene as no colour effects were evident. The human agouti gene was found to map close to (but is not the candidate of) the locus *MODY1* for maturity on-set diabetes of the young (Kwon *et al.* 1994; Wilson *et al.* 1995).

BASIS OF AGOUTI EFFECTS

The murine *Agouti* locus encodes a signal protein (ASP) of 131 amino acids (Bultman *et al.* 1992) that blocks some melanocortin receptors. In the case of melanocytes, the receptor (MC1-R) determined by the *Extension* locus (Cone and Mountjoy 1993; Robbins *et al.* 1993) conveys a signal via increased cAMP stimulating eumelanin (dark) pigment production in response to binding by alpha melanocyte stimulating hormone (MSH). Production of ASP in the skin tissue inhibits MSH binding to MC1-R and leads to phaeomelanin production in melanocytes (Lu *et al.* 1994; Blanchard *et al.* 1995; Wilson *et al.* 1995; Graham *et al.* 1997). ASP also affects melanogenesis independent of MC1-R receptor (Hunt and Thody 1995; Graham *et al.* 1997) through inhibiting MSH induced expression of tyrosinase, tyrosinase-related proteins (1 and 2) and the microphthalmia gene involved in melanoblast differentiation (Sakai *et al.* 1997; Aberdam *et al.* 1998; Furumura *et al.* 1998).

In humans, ASP is normally produced in adipose tissue (Kwon *et al.* 1994), whereas in mice it is 'usually' expressed primarily in skin epidermis and hair follicles. In yellow mice, there is variable ectopic expression in other tissues (Miller *et al.* 1993; Duhl *et al.* 1994 a,b; Klebig *et al.* 1995, Wolff *et* *al.* 1998). Agouti-induced obesity in some yellow mice involves fat-cell enlargement (rather than increased fat cell numbers), elevated lipogenic and decreased lipolytic rates, and marked accumulation of triglycerides. Affected individuals eat more than normal and show increased insulin resistance and occasionally become diabetic (Wolf *et al.* 1986; Perry *et al.* 1994; Yen *et al.* 1994; Mynatt *et al.* 1997). Transgenic mice with expression of ASP in adipose tissue, like humans do not become obese, but injection of insulin increased weight gain. These results suggest that insulin triggers the onset of obesity and that *Agouti* expression in adipose tissue potentiates this effect (Mynatt *et al.* 1997). The proliferation of insulin producing (β) cells in the pancreas preceeds elevated insulin production and weight gain in obese yellow agouti mice (Warbritton *et al.* 1994). Hypothalmic dysregulation through ectopic expression of ASP is a possible initiating basis for increased food consumption, weight gain, obesity and elevated insulin levels (Miller *et al.* 1993; Warbritton *et al.* 1994). The *obese* gene in mice is responsible for production of the protein leptin secreted from adipose tissue and is thought to bind to receptors in the hypothalamus encoded by the *diabetes* locus that controls food intake. In obese yellow agouti mice, expression of the *obese* gene in adipose tissue is continually elevated, while in lean mice, expression is reduced by fasting and elevated by glucose or insulin injection (Mizuno *et al.* 1996; Hayase *et al.* 1996). Agouti antagonism of melanocortin receptors of the central nervous system inhibits the anorexic effects of leptin, whereas in adipose tissue leptin expression is up-regulated serving to limit the magnitude of agouti-induced obesity (Zemel 1998). Other evidence shows that ASP can increase directly lipogenesis and fat storage in adipocytes mediated through an increase in intracellular calcium (Zemel *et al.* 1995; Jones *et al.* 1996; Kim *et al.* 1996, Zemel 1998). Genomic scans for loci linked to percentage body fat in humans revealed leptin receptor and agouti-signal protein as potential candidate genes as well as other unrecognised markers (Norman *et al.* 1998).

Expression of ASP in the ovaries of adult mice has been compared with the finding of reduced out-of-season lambing in white or tan Icelandic sheep (Drymundson and Adalsteinsson 1980; Wilson *et al.* 1995) and may be related to a marked reduction in fertility due to selective fertilisation or selective embryonic mortality (Adalsteinsson 1970). However, the *lethal yellow* agouti allele (A^y) results in embryonic loss (Wolff and Bartk 1966) associated with the coincidental partial deletion and disruption of an adjoining gene named *Raly* that normally produces a RNA-binding protein expressed in the pre-implantation embryo (Silvers 1979; Duhl *et al.* 1994b; Michaud *et al.* 1993 1994).

AGOUTI RELATED TRANSCRIPT

Melanocortin receptors MC3-R and MC4-R appear to be important in the control of feeding. MC3-R is produced primarily in the hypothalamus and thalamus, and MC4-R is expressed more widely through the brain and spinal cord. ASP is an antagonists of MC1-R and MC3-R but not MC4-R. Mice lacking MC4-R produce an obese phenotype and antagonists of MC3-R and MC4-R increase feeding (evidence cited by Shutter *et al.* 1997). MC5-R is produced in the brain, adipose tissue and skeletal muscle and, together with MC4-R, evidence of linkage has been found with genomic scans for human obesity (Chagnon *et al.* 1997). Affects on other behaviour (eg. activity, aggression and ease of handling) associated with the *Agouti* locus in mice and rats may also involve neural melanocortin receptors (Hayssen 1997). A recently identified gene related to *Agouti*, named the *Agouti-related Transcript* (ART*)*, is expressed primarily in the adrenal gland, subthalamic nucleus and hypothalamus of mice and humans and appears to have a key role in the neural control of feeding. ART was mapped to human chromosome 16 and mouse chromosome 8 (Shutter *et al.* 1997) while *Agouti* is on human chromosome

20 (Kwon *et al.* 1994; Wilson *et al.* 1995) and mouse chromosome 2 (Siracusa *et al.* 1996). The elevated expression of ART in the hypothalamus of mice with other obesity gene effects (*obese* and *diabetic*) supports a central role in the neural regulation of feeding (Shutter *et al.* 1997; Ollman *et al.* 1997). A fragment of ART, when administered intracerabroventricularly to rats, increased feeding with long lasting effects, inhibited the action of MSH (Rossi *et al.* 1998) and involved antagonism of MC3-R and MC4-R receptors (Rossi *et al.* 1998; Ollman *et al.* 1997). Several other genes are identified that affect obesity in mice and humans (Yen *et al.* 1994; Naggart *et al.* 1997; Chua and Leibel 1997) and seem likely to have homologs in livestock species that may be of commercial relevance.

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