

The search for canine obesity-related genes and the effects
of genetic mutation on metabolism in dogs

Abstract of Doctoral Thesis

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Obesity is a condition that the energy intake exceeds energy expenditure, and excessive fat is accumulated in white adipose tissues. Many kinds of genes are reported as obesity-related genes in rodents and human beings, however, there is no report about that in dogs. In the present study, we focused on the G-protein coupled receptor (GPR) 120 and beta-3 adrenergic receptor (ADRB3) as representative ones, and analyzed the relationship between their genetic polymorphism and body condition scores in dogs.

In chapter 1, we cloned canine GPR120 cDNA and revealed the tissue distribution. We have analyzed GPR120 genomic sequences of 141 dogs, and found 5 synonymous and 4 non-synonymous SNPs. Gene frequency of c.595C>A (p.Pro199Thr) was significantly higher in overweight and obese dogs than that in normal dogs.

In chapter 2, We have analyzed ADRB3 genomic sequences of 160 dogs, and found 5 synonymous and 7 non-synonymous SNPs. Gene frequency of c.749C>T (p.Ser250Phe) was significantly higher in overweight and obese dogs than that in normal dogs. Furthermore, gene frequency of c.1121C>G (p.Pro374Arg) was significantly higher in underweight dogs than that in normal dogs.

In chapter 3, we have developed a cell expression system of the cADRB3 mutants. Three kinds of mutants (Ser250Phe, Pro374Arg, Pro395Gln) and wild type (WT) canine ADRB3 were expressed on HEK293 cells. These cells were stimulated with adrenergic agonists (adrenaline, noradrenaline, CL316,243, IBMX and RO20-1274) and intracellular cyclic-AMP (cAMP) concentrations were measured after 30 minutes-incubation. Adrenaline, noradrenaline and CL316,243 raised intracellular cAMP, but other agonists did not. The raise of cAMP in the cells expressing Ser250Phe or Pro395Gln mutants tended to be lower than that with WT.

These mutants may be related to obesity in dogs. In particular, c.749C>T (Ser250Phe) mutant of ADRB3 showed higher frequency in obese dogs epidemiologically, and lower cAMP production *in vitro* study suggestive of that the dogs with this mutation are easy to get weight when compared to dogs without them. They are available for gene screening items for treatment and prevention of obesity in dogs.