



Title	Anti-obesity effects of selective agonists to the $\alpha$ -3-adrenergic receptor in dogs
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from sympathetic nerve entering to this tissue.

To confirm the above results obtained from the *in vivo* experiments and to investigate the molecular mechanism of the  $\beta$ -adrenergic action on BAT glucose utilization, next, some *in vitro* experiments were performed using a primary culture system of brown adipocytes. When confluent precursor cells of cultured brown adipocytes were treated with dexamethasone (DEX), mRNAs for GLUT4, hormone-sensitive lipase, and C/EBP  $\alpha$  were increased remarkably, indicating a predominant effect of DEX on the terminal differentiation of the cultured cell. BAT has an adipocyte-specific  $\beta$ -adrenoceptor ( $\beta_3$ ) in addition to  $\beta_1$ - and  $\beta_2$ -adrenoceptors.

In the cells,  $\beta_1$ - and  $\beta_2$ -adrenoceptor mRNA remained constant regardless of DEX-treatment, while  $\beta_3$ -adrenoceptor mRNA was present only in DEX-treated differentiated cells. To assess the metabolic response mediated by  $\beta_3$ -adrenoceptor, glucose transport into the cells was estimated. Noradrenaline enhanced glucose transport in DEX-treated differentiated cells, but not in undifferentiated cells.  $\beta_3$ -adrenergic agonists mimicked completely the stimulatory effect of noradrenaline at lower concentrations. These results suggest that the  $\beta_3$ -adrenoceptor plays a significant role in the response of glucose transport to adrenergic stimulation.

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### Anti-obesity effects of selective agonists to the $\beta_3$ -adrenergic receptor in dogs

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Obesity is the most common nutritional disorder in small animal practices, as in humans. Current treatment of obesity in dogs mostly relies on reducing energy intake by low calorie diet or fasting. It is known that in rodents and humans that the  $\beta_3$ -adrenergic receptor ( $\beta_3$ -AR) is present primarily in adipocytes and plays a significant role in the adrenergic stimulation of lipolysis and heat production. The aim of this study was to evaluate the effectiveness of  $\beta_3$ -AR agonists for the treatment and prevention of obesity in the dog without any side effects.

1) The acute lipomobilizing effects of  $\beta_3$ -AR-selective agonists were examined in the dog

*in vivo*. When a selective  $\beta_3$ -AR agonist, CL316,243 (CL), was infused intravenously into dogs, the plasma level of free fatty acid increased in 30 min and persisted at higher levels for several hours. ICI D7114, another  $\beta_3$ -AR agonist, also showed a similar lipomobilizing effect, but with two order of lower potency.  $\beta_3$ -AR agonist infusion also increased the plasma insulin level, and heart rate. Thus, the lipomobilization effect of the  $\beta_3$ -AR agonist may be due to a direct action on the  $\beta_3$ -AR in adipocytes. These results suggested that functional  $\beta_3$ -AR is present in adipose tissues of the dog and that it is effective for *in vivo* lipomobilization.

2) The chronic anti-obesity effects of CL were examined, because CL was more effective than ICI D711 when given acutely at the same dose. When CL (0.1 mg/kg) was given orally to adult beagles every day for 5-7 weeks, body weight and girth were decreased compared with control placebo-treated dogs. The mean food intake of drug-treated dogs was reduced as compared to the placebo treated dogs, although the change was not statistically significant. There was no significant difference in blood biochemistry data before the experiment and at the end of the first or second phase of the experiment. In postmortem examinations, no apparent difference in gross appearance of individual organs, except fat pads, was found between the two groups. The fat pads of various sites of drug-treated dogs were small and the adipose tissue was composed of multilocular cells containing smaller amounts of triglyceride. Immunohistochemical examination of this adipose tissue showed a remarkable increase in brown adipocytes expressing a thermogenic protein, uncoupling protein (UCP). The increased expression of UCP and its mRNA in drug-treated dogs was also confirmed by Western blot and reverse transcription polymerase chain reaction (RT-PCR) analyses. It was concluded that treatment with a  $\beta$ 3-AR agonist stimulates UCP

expression, which may lead to an increase in energy expenditure, and thereby is useful for the treatment and prevention of obesity in the dog.

3) To clarify the molecular structure of dog  $\beta$ 3-AR, its cDNA was cloned by RT-PCR method and the nucleotide and deduced amino acid sequences were determined. A  $\beta$ 3-AR cDNA fragment (650bp) was obtained by amplifying RT-PCR of RNA extracted from dog white adipose tissue. The nucleotide sequence of the fragment was 81.9-91.1% homologous to the corresponding region of  $\beta$ 3-AR cDNA of other species so far reported. The deduced amino acid sequence (206 amino acid residues) was also highly homologous (87.4-89.8%) to other species, while it showed low sequence homologies (about 50%) compared to the  $\beta$ 1- and  $\beta$ 2-ARs. Thus, it is likely that the cDNA fragment obtained in this study was the dog  $\beta$ 3-AR. The tissue distribution of dog  $\beta$ 3-AR mRNA was studied using RT-PCR. Abundant expression of  $\beta$ 3-AR mRNA was found in subcutaneous and visceral adipose tissues. Unlike in rodents, a weak but apparent expression of  $\beta$ 3-AR mRNA was found in lung, liver, kidney and spleen. Thus, the tissue distribution of  $\beta$ 3-AR in the dog is a little different from these in rodents, and this may explain why the  $\beta$ 3-AR agonists induce tachycardia as well as lipomobilization in the dogs.

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