Title

Cellular localization of the diazepam binding inhibitor in the mouse gastrointestinal tract and nervous system with special reference to coexistence with fatty acid binding protein

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Citation

Japanese Journal of Veterinary Research, 50(1): 29-30

Issue Date

2002-05-31

Doc URL

http://hdl.handle.net/2115/2933

Type

bulletin

File Information

KJ00002400417.pdf
INFORMATION

Hokkaido University conferred the degree of Doctor of Philosophy (Ph. D) in Veterinary Medicine on March 25, 2002 to 18 recipients.

The titles of theses and other information are as follows:

Cellular localization of the diazepam binding inhibitor in the mouse gastrointestinal tract and nervous system with special reference to coexistence with fatty acid binding protein

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The diazepam binding inhibitor (DBI), a 10 kDa cytosolic polypeptide, was originally isolated from the brain as an intrinsic ligand of the benzodiazepine binding site on the type-A γ-aminobutyric acid receptor (GABA receptor). DBI has been found in a wide variety of species including yeasts, plants, and mammals with highly conserved structures. It is also shown that DBI is identical with acyl-CoA binding protein, which has the ability to bind long chain acyl-CoA esters with high affinity. Acyl-CoA esters are substrates and intermediates in lipid metabolism to regulate various cellular functions, such as enzyme activities, cell signalings, and gene expressions. Thus, it is expected that the main function of DBI would be related to a fundamental activity of the cell, by regulating the transfer and metabolism of acyl-CoA esters. The present study, using in situ hybridization and immunohistochemistry, revealed the distribution of DBI and its consistent coexistence with fatty acid binding protein (FABP) subtypes, which participate in the metabolic processing of long chain fatty acids, in the gastrointestinal tract and the nervous system of mice.

In the gastrointestinal tract, DBI mRNA and the product were intensely expressed in the spinous layer in the stratified squamous epithelium of the oral cavity, esophagus and forestomach, in surface mucous cells of the glandular stomach, and in columnar (absorptive) cells of the intestinal villi. The neural tissues displayed the definite existence of DBI in non-neuronal supporting cells. In the brain, intense immunoreactivities for DBI were detected in the cerebellar Bergmann glia, olfactory ensheathing cells, subgranular layer of the dentate gyrus, and retinal Müller cells. In the peripheral nervous system, satellite cells in sensory/autonomic ganglia, Schwann cells, and sustentacular cells in the adrenal medulla were immunoreactive to a DBI antibody. DBI always coexisted with FABPs in epithelia throughout the digestive tract, that is, with epidermal (E-) FABP from the oral cavity to forestomach, and with intestinal (I-) FABP in the intestine. The colocalization of DBI and brain (B-) FABP was observed in most of the non-neuronal supporting cells mentioned above. In addition to the gastrointestinal tract and nervous systems, DBI mRNA and the products have also been reported to be expressed in the liver, adipose tissue, heart, and testis, which all contain other types of FABP subtypes. The widespread and consistent colo-
calization of DBI and FABPs suggests that they work together for various intracellular fundamental activities or metabolism. For example, in enterocytes, DBI and I-FABP seem to play an important role in the absorption and transportation of lipids derived from food. DBI and B-FABP may be involved in the energy metabolism in astrocytes and related cells, which are thought to support neuronal development and functions. In addition, the patterns of DBI/FABP colocalization indicate that the specialization of their cooperative functions is decided by the tissue-specific expression of FABP subtypes.


Novel methods for diagnosis and treatment of obesity in dogs

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Obesity is the most common nutritional disorder and the risk factor for a number of diseases in small animal practice. During the last decade, there has been a great advance in our understanding on human obesity, especially on some obesity-related molecules. For example, an adipocyte-derived peptide, leptin, was discovered as a key blood hormone for the regulation of food intake and energy expenditure. Alternatively, mitochondrial uncoupling protein (UCP) has been expected as a target for prevention and treatment of obesity, because this molecule has been proved in rodents to dissipate excess fat energy as heat. On the basis of such recent knowledge, in the present study, I have tried to develop novel and reliable methods for diagnosis and treatment of obesity in the dog.

1. Serum leptin was assayed in beagles under various physiological and pathological conditions using an enzyme-linked immunoassay specific to canine leptin. The serum leptin concentration was decreased during starvation, but increased after food intake and administration of insulin or dexamethasone. The serum leptin concentration was positively correlated with body fat content, and was higher in experimentally developed obese beagles. Elevated serum leptin concentration was also confirmed in clinically obese dogs with higher body condition scores regardless of their breed, age and sex. These results indicate that serum leptin is a good biochemical index of adiposity and useful for diagnosis of obesity in the dog.

2. To evaluate visceral and subcutaneous fat contents separately in beagles, computed tomographic analysis (CT) was applied under standard scanning conditions of 120 kV, 200 mAs and 5 mm in slice thickness. Fat area measured at 3rd lumbar vertebra using level detection analysis at -105/-135 HU correlated well with total body fat content. In experimentally developed obese beagles, the total fat area increased as expected, but the ratio of the visceral to subcutaneous fat area tended to decrease.

3. Three isoforms of canine UCP cDNA were cloned by reverse-transcription polymerase chain reaction. Nucleotide and deduced