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Author(s)	ORINO, Kouichi
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action is unique compared to other G-quadruplex compounds : that is, 5'-end modification of G-rich ODNs enhanced stability, ability of forming a hyperstructure and capability of binding to gp120, resulting in interference with the binding of virus to receptors. Thus, I concluded R-95288 as a unique G-quadruplex agent with potent anti-HIV-1 activity.

The results in this thesis demonstrate that the short modified ODN compound exhibit potent

anti-HIV-1 activity in vitro by specific interaction with the V3 region and CD4 binding site region of HIV-1 gp120. Inhibitors of virus adsorption or entry to host cells are attractive combination candidates. Taken together, 5'-modified G-rich ODN may provide a new class of HIV chemotherapy for HIV infectious disease, therefore I will expect it as new combination partner in chemotherapy for AIDS.

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## BIOCHEMICAL STUDIES ON BOVINE FERRITIN

Kouichi Orino

*Laboratory of Biochemistry,  
School of Veterinary Medicine and Animal Sciences,  
Kitasato University, Towada, Aomori 034-8628, Japan*

Ferritin (Ft), an iron-storage protein, is an intracellular protein with a molecular weight of 480 kDa, but also present in serum. Serum Ft level reflects the amount of iron stored in the body, and increases in inflammatory and malignant diseases. The fetal serum Ft level gradually increases as gestation progresses. The aims of this study are to clarify the molecular structure of bovine Ft and to assess the pathophysiological significance of the serum Ft. The results are summarized as follows :

1) To clarify what causes the reversed mobility of bovine Ft H(earth)- and L(iver)-subunits (H : 18 kDa, L : 21 kDa) compared to other mammalian Ft subunits by SDS-PAGE, the cDNA clones for bovine Ft H- and L-subunits were isolated from a bovine spleen cDNA library and sequenced. The bovine H and L chains were composed of 180 and 174 amino acid residues with calculated molecular weights of 20,920 and 19,856, respectively. The amino acid sequence of bovine H

and L chains shows high homologies with those of the corresponding chains of the other mammalian Fts. These results suggest that the much slower mobility of bovine L chain compared to other mammalian L chains on SDS-PAGE may result from significant differences in the binding affinity of SDS to these L chains.

2) To access clinical significance of measurement of serum Ft in bovine serum, a highly sensitive ELISA for bovine serum Ft was developed using avidin-biotin complex technique. Serum Ft levels of cows with leukemia, inflammatory diseases, and theileriasis were significantly higher than those of nonpregnant cows. These results suggest that bovine serum Ft may be inflammation and malignant markers and that high Ft levels of theileriasis caused by *Theileria sergenti* result from the activation of reticuloendothelial system.

3) To elucidate physiological roles of serum Ft in bovine fetal circulation, the levels of Ft and its iron in fetal bovine sera were estimated. In 13

lots of commercial fetal bovine sera, the Ft levels ranged between 800 and 6,000 ng/ml. The serum Ft iron concentration ranged from 0.16 to 0.96  $\mu$ g/ml, and the iron content of Ft was about 20% regardless of serum Ft concentration. The percentage of Ft iron to total serum iron ranged from 8.8 to 28.5%, and correlated significantly with Ft concentration. There was a significant correlation between serum Ft concentration and transferrin saturation. These findings demonstrate that bovine fetuses have the elevated iron stores.

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### Adrenergic Regulation of Glucose Utilization and Glucose Transporter in Rat Brown Adipose Tissue

Hideki Nikami

*Laboratory of Animal Experiment,  
Institute of Immunological Science,  
Hokkaido University, Sapporo 060, Japan*

Brown adipose tissue (BAT) is known to be the major site of nonshivering heat production during cold acclimation and spontaneous overfeeding. The metabolic activation and subsequent heat production in BAT are primarily controlled by sympathetic nerves distributed abundantly to this tissue. Although the main substrate for BAT thermogenesis is fatty acids derived from intracellular triglyceride, glucose metabolism in BAT is also activated by the sympathetic nerves. In order to clarify the regulatory mechanism of BAT glucose metabolism, in this study, I examined the effects of cold exposure and adrenergic stimulation on tissue glucose utilization and glucose transporter both *in vivo* and *in vitro*.

Exposure of rats to a cold environment at 4°C for 10 days increased the glucose uptake remarkably in BAT. In parallel with tissue glucose utilization, the protein and mRNA levels

of an insulin-responsive glucose transporter GLUT4, which is the major glucose transporter in rat adipose tissues, were also increased. These stimulative effects of cold exposure were completely abolished when sympathetic nerves into BAT had been surgically severed, but were mimicked when noradrenaline was administered continuously for 10 days at 24°C. Continuous administration of a  $\beta$ -adrenergic agonist (isoproterenol) was as effective as noradrenaline, whereas an  $\alpha$ -adrenergic agonist (phenylephrine) showed no effect. In contrast to BAT, in other insulin-sensitive tissues neither cold exposure nor adrenergic agonist-treatment showed noticeable effects on tissue glucose utilization and GLUT4. From these results, it was concluded that the stimulative effect of cold exposure on glucose utilization in BAT is based on the increased synthesis of GLUT4 protein evoked by the  $\beta$ -adrenergic action of noradrenaline released