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Nutritional state regulates IRS-1 and SHC tyrosine phosphorylation and expression in vivo in chickens. J. Dupont, M. Derouet, M. Taouis (Station de recherches avicoles, Inra, Tours, 37380 Nouzilly, France)

Upon insulin binding and its autophosphorylation, the insulin receptor (IR) phosphorylates various endogenous substrates such as IRS-1 (Insulin Receptor Substrate-1) and SHC (Src Homology and Collagen protein). IRS-1 (180 kDa) is considered as the major IR substrate in mammalian species. The tyrosine phosphorylation on specific motifs (YXXM, YMXM), allows IRS-1 to interact with several proteins through their SH2 domains such as PI-3 kinase, Grb2, SHPTP2. In mammals, SHC (66, 52 and 46 kDa) are encoded by the same gene. IRS-1 and SHC are involved in metabolic and mitogenic effects of the IR. We have recently partially or totally cloned and sequenced the coding region of chicken SHC and IRS-1, respectively. These genes are highly conserved when compared to mammals. In the present study, we have characterized and studied the expression and tyrosine phosphorylation of IRS-1 and SHC in vivo in chicken muscle and liver. Thirty 9-week-old chickens were subjected to three nutritional states (ad libitum, fasted for 48 h, and refed for 30 min after 48 h fast). By using differential immunoprecipitation of liver and muscle materials with specific antibodies directed against SHC or IRS-1, we have demonstrated that these two substrates are expressed in chicken. We have also shown that IRS-1 and mainly the 52-kDa SHC isoform are associated to the IR. The levels of tyrosine phosphorylation of IRS-1 and SHC are dependent upon the nutritional state with a decrease in phosphorylation in the fasted state which is restored after 30 min of refeeding. Their phosphorylation is well correlated with plasma insulin levels. Finally, IRS-1 and SHC mRNA levels have been examined in the three nutritional states using RT-PCR techniques. Fasting increased IRS-1 mRNA expression in the liver but not in the muscle. In conclusion, SHC and IRS-1 are expressed and associated with IR in chicken liver and muscle. Their tyrosine phosphorylation is regulated by the nutritional state.

GENERAL CONCLUSIONS

Session 1: Regulation of digestive events

(Dr C.H. Malbert and Dr T. Studzinski)

It is now impossible to differentiate the age versus diet related influences on digestive secretions.

The MMC pattern quantitatively and qualitatively modulates pancreatic secretion in calves.

Histamine increases pancreatic secretion primarily via H2 and partially via H1 receptor activation. The role of physiological histamine needs to be further defined.

CCKB receptors present on the acini themselves modulate acini secretion in the absence of intrinsic or extrinsic regulatory pathways.

CCKA receptor activation partially determines postnatal small intestine mucosal development in calves.

Nitrates may change the myoelectric activity of the fed rat stomach. More data are needed in order to clarify their effect in the fasted state.

Starch is an excellent example of a nutrient that requires a careful ratio between degradability and digestion capacity for optimal utilisation.

Soyabean protein, regardless of antigenicity, negatively affects jejunal morphology and enzymatic activities.

Variations in pea digestibility in chickens might relate to the huge differences in the

digestibility of the protein sources present in this diet.

Suggestions for the future

Digestive secretions have been extensively described. It is now time for looking at the neurohumoral regulation especially around birth.

The extrinsic and intrinsic interactions at the secretory cell level must be emphasized in the future.

The morphological and histological characteristics of the mucosal cell must be related to their neuropeptidergic contents as well as their surface receptors.

The secretory events must be related to other physiological events in an integrative form such as the work described by Dr Lesniewska.

A clear distinction must be performed between pharmacology and physiology especially for the relationship between CCK activity and CCK receptor expression.

The experiments dealing with mechanisms at the cell level must take into account the in vivo physiological reality.

If possible, each species must be treated separately and interspecies comparisons must be performed with great care.

Session 2: Lipid metabolism

(Dr D. Bauchart, Dr J.F. Hocquette and Dr A. Orzechowski)

There are interspecies-, interbreed-, food- and age-related differences in lipid metabolism in terms of activities of the enzymes regulating lipogenesis and lipolysis, as well as fatty acid oxidation.

Among them, carnitine palmitoyltransferase I (CPT I) controls the transfer of fatty acids (FA) into mitochondria. The lower sensitivity of CPT I to metabolites derived from FA in piglet than in rat muscle is an example.

The levels of activity of several enzymes such as lipoprotein lipase (LPL) and CPT I are considered in most situations, but not all, as rate-limiting steps for FA uptake and catabolism in muscles.

To some extent, utilization and distribution of lipids result from variations in very-low density lipoprotein (VLDL) formation in the liver, which depends on dietary and physiological conditions.

Phytoestrogens exert a significant effect on lipid metabolism since they enhance lipolysis and suppress lipogenesis.

Lipids are vulnerable to the action of radicals. TBARS, CD, and more recently found isoprostanes were therefore elected as markers of oxidative stress. Some antioxidants (tocopherols) as well as unknown substances of plant origin (evening primrose) limit the extent of lipid peroxidation

Session 3: Tissue growth

(Dr J. Simon and Professor T. Motyl)

The maintenance of a dynamic equilibrium between cell replication and apoptosis at the physiological level is crucial for proper tissue growth and remodelling, and thereby for the development and health of each multicellular organism. Bcl-2-related proteins establish an important checkpoint in the regulation of programmed cell death in normal, transformed and neoplastic cells. They are also involved in the regulation of mammary gland remodelling.

Endo-, para- and autocrine regulation of tissue growth occurs:

– throughout the expression of early response genes and the activation of enzymes involved in the signal transduction pathway (ODC, MAP, p90RSK and p70S6 kinases);