LSU Health Sciences Center

Neuroscience Center of Excellence

FACULTY CANDIDATE

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Presenting

Environmental Obesogens: Perturbation of Nutrient Sensor Signaling Pathways and Metabolic Regulation by Pollutants

Normal adaptive physiology maintains the body's metabolic equilibria by integration of gastrointestinal, hormonal, and metabolic signals from the major energy storage and metabolic organs (adipose, liver, and muscle) via a meshwork of CNS feedback networks to effect compensatory changes on food intake, metabolic efficiency, activity, and resource partitioning. Disruption of nutrient sensor pathways or central hypothalamic-pituitary-adrenal (H-P-A) axis signal integration underlie metabolic disease states such as obesity, diabetes, cardiovascular disease and dyslipidemias (collectively termed metabolic syndrome). Enhanced adipogenesis and lipid accumulation is part of the adaptive response to cope with temporary imbalances in the body's energy equation; obesity is the maladaptive consequence when caloric intake chronically exceeds expenditure. Recent epidemiological evidence sugessts other environmental risk factors, besides nutrient dense foods and inadequate physical activity, may be relevant in accounting for the rapid rise in the worldwide incidence of obesity. In particular environmental stressors (nutritional status, pregnancy complications, psychosocial conditions and/or toxic chemical exposure) experienced during fetal development or early childhood have the potential to elicit long term changes in metabolic target organs and adaptive feedback control mechanisms that potentiate metabolic syndrome phenotypes.

The "environmental obesogen" hypothesis proposes that a subset of environmental pollutants disrupts normal development or interferes with the body's homeostatic controls to misregulate critical pathways involved in adipogenesis, lipid metabolism or energy balance. We have identified organotin pollutants, such as tributyltin (TBT), as candidate obesogens that target the nutrient sensing retinoid X receptor-peroxisome proliferator activated receptor gamma (RXR-PPARg) pathway. TBT acts as a dual high-affinity ligand agonist for this permissive nuclear receptor heterodimer to promote adipogenesis and lipid accumulation. Further pleiotropic effects on hepatic, immune and CNS systems are predicted through permissive activation of other metabolic or tissue restricted RXR-heterodimers e.g. RXR-LXR and RXR-NURR1. Organotin toxicity is an informative model system for examining how xenobiotic chemical stressors intersect with multiple regulatory metabolic mechanisms in novel ways to elicit pleiotropic endocrine disrupting effects.

Friday April 18, 2008 11:30am,
8th Floor Neuroscience Center Conference Room,
LSU Lion's Building, 2020 Gravier Street
New Orleans