**DIABETIC UROPATHY PATHOBIOLOGY SITE**

**Focus Area:** Urological Complications of Diabetes and Obesity  
**Research Type:** Translational  
**Funding Source:** NIH/NIDDK

**Description:** The purpose of this project is to define diabetic uropathy in and study the manifestations of diabetes on the lower urinary tract of genetically modified mouse models of diabetes mellitus created in conjunction with the Animal Models of Diabetic Complications Consortium. To accomplish this we have created four specific aims:

- To examine the temporal alterations in the in vivo bladder function by evaluation of 24-hour micturition habits and conscious cystometry at various time points after induction of diabetes.

- To examine the temporal course of morphological changes in neurogenic and myogenic components of bladder remodeling by measuring the changes in bladder tissue components and their contribution to remodeling of the wall and chamber of the bladder, and measuring changes in markers of bladder innervations.

- To examine the temporal alterations in the contractile function of the detrusor by analyzing the contractile responses of the detrusor, the contractile and regulatory proteins of the detrusor, the alterations of the L-type Ca2+ channel, the alterations in the capacitive calcium entry (CCE), the IP3- and RyR-induced calcium release, and the Ca2+ sensitivity in permeabilized detrusor strips.

- To examine the temporal alterations induced by STZ in afferent and efferent autonomic pathways innervating the bladder by assessment of afferent autonomic function by measurement of Current Perception Threshold (CPT), the relative contribution of cholinergic and purinergic components to the contractile response to transmural electrical stimulation, the alterations in ATP-P2X3, VR-1 afferent pathway in the bladder, the alterations in muscarinic receptors (M2, M3) and/or purinergic receptors (P2X1, P2X2), and the connexin 43-containing gap junctions in the bladder.

**MECHANISMS OF NEUROGENIC BLADDER DYSFUNCTION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE) MICE**

**Focus Area:** Neurogenic Bladder  
**Research Type:** Translational  
**Funding Source:** NIH/NIHCD

**Description:** The major goal of this project is to investigate the specific mechanism of neurogenic urge incontinence (NUI) leading to rationale design of preventive and therapeutic interventions. To accomplish this we have created three specific aims:

- To determine the temporal characteristics of the storage and voiding phases of neurogenic bladder dysfunction (NBD) of various clinical scores by simultaneous cystometrogram and electromyogram studies.

- To determine the neuropathological correlates of the storage and voiding phases of NUI as determined in SA#1 by correlating central nervous system histopathology and overall neurologic deficit with defined storage and voiding phases of NBD.

- To determine the contractile responses of the whole neurogenic bladder to in vitro stimuli.
CASE WESTERN RESERVE UNIVERSITY INTERDISCIPLINARY RESEARCH CENTER ON UROLOGICAL COMPLICATIONS OF OBESITY AND DIABETES (UCOD)

Focus Area: Urological Complications of Diabetes and Obesity  
Research Type: Translational  
Funding Source: NIH/NIDDK

Description: The Center consists of a research proposal that functions as the scientific road map for our interdisciplinary work on UCOD; an Administrative Core that plans and implements the short and long term objectives of the Center; and an innovative Enrichment Program that allows us to share our work on UCOD with 50 other junior and established investigators, post-doctoral (PhD and MD) fellows, and students and provide Institutional support for the work of two Research Scholars who spend 12 months in our Center. The goals of the research include the following:

- Characterize bladder and urethral function over time in relation to hyperglycemia and obesity in a mouse model of type-2 diabetes mellitus (T2DM), and in comparison with non-diabetic obese and non-diabetic non-obese controls.
- Study the effects of T2DM and obesity on alterations of the prostate in a mouse model of T2DM, and in comparison with non-diabetic obese and non-diabetic non-obese controls.
- Identify the molecular targets responsible for time-course alterations of the bladder and prostate remodeling and function observed in a mouse model of T2DM by proteomic analysis of cell cycle, inflammatory, and oxidative pathways including systems biology modeling of deregulated protein sub-networks.

MECHANISMS OF DIABETIC BLADDER DYSFUNCTION

Focus Area: Urological Complications of Diabetes and Obesity  
Research Type: Translational  
Funding Source: Juvenile Diabetes Research Foundation

Description: The purpose of this study is to examine the mechanisms of diabetic bladder dysfunction by examination of the relative roles of diuresis, hyperglycemia and oxidative stress on temporal alterations of afferent and efferent autonomic pathways innervation the bladder muscle and urothelium. To accomplish this we have created two specific aims:

- To examine the relative roles of diuresis and hyperglycemia on temporal alterations of afferent and efferent autonomic pathways innervating the bladder muscle and urothelium.
- To examine the role of accumulation of ROS on temporal alterations of afferent and efferent autonomic pathways innervating the bladder muscle and urothelium.