GRADUATE COLLEGE DEFENSE NOTICE
Neuroscience Graduate Program

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“Inflammation-Induced Plasticity in Micturition Reflex Pathways.”

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ABSTRACT

Although a seemingly basic and simple behavior, micturition necessitates precise integration and coordination of multiple divisions of the nervous system: visceral sensory, somatic motor, sympathetic, parasympathetic, as well as voluntary control from higher brain/brainstem centers. When coordination of this circuitry falters, the consequences can be devastating and include severely decreased quality of life and substantial economic burden. This dissertation project investigates the potential role(s) of inflammatory mediators in bladder sensory physiology with the long term goal of elucidating potential targets for intervention. The overall hypothesis is that inflammatory-induced changes in the urinary bladder or afferent projections ultimately lead to dysfunctional micturition symptoms. Using a rodent model of cyclophosphamide (CYP)-induced bladder inflammation, we examined the expression and function of the chemokine/receptor pair, CXCL12/CXCR4, and the activated (phosphorylated) form of ubiquitous signaling molecule, AKT using a multidisciplinary approach that includes: immunohistochemistry, protein and transcript quantification techniques, and in vivo bladder physiology studies combined with pharmacological tools.

Peripheral chemokine levels are elevated in patients with various chronic pelvic inflammatory/pain syndromes including IC/BPS and are implicated in numerous inflammatory and mechanical pain models in rodents. However studies had not previously shown a direct functional role for chemokine signaling in micturition. We hypothesized that CXCL12 and CXCR4 would increase in the urinary bladder with CYP-induced bladder inflammation and that CXCR4 receptor blockade with AMD3100 would reduce CYP-induced bladder hyperreflexia. ELISA, immunohistochemical and qRT-PCR experiments demonstrate duration-dependent increases in CXCL12 and CXCR4 protein and transcript expression in specific tissue compartments of the urinary bladder, mainly the urothelium. In vivo studies provide evidence of a role for chemokine signaling in the mediation of micturition function. Intravesical infusion with AMD3100, a CXCR4 receptor antagonist, significantly reduced CYP-induced bladder hyperreflexia as evidenced by increased bladder capacity, intercontraction interval and decreased voiding frequency.

AKT is a putative cellular survival signal however recent studies also implicate the signaling molecule in the induction and maintenance of pain processes, development of long term plasticity (e.g. LTP and central sensitization) and visceral inflammation. Functional studies addressing the contribution of pAKT in micturition had not been performed. We hypothesized that increasing pAKT levels would contribute to CYP-induced bladder hyperreflexia. Western blot and immunohistochemical studies demonstrate that phosphorylation of AKT increases in the whole urinary bladder with CYP-induced bladder inflammation in a tissue compartment- and time-dependent manner. Intravesical infusion with inhibitors of AKT phosphorylation, AKT Inhibitor IV and deguelin, significantly improved symptoms of CYP-induced bladder hyperreflexia suggesting a functional role for pAKT in bladder physiology.

These studies demonstrate the functional capacity of inflammatory mediators and inflammatory associated signaling pathways in micturition reflex pathways. Chemokine signaling via the CXCR4 receptor and upstream activators of AKT may provide therapeutic targets with respect to inflammatory-induced bladder sensory physiology dysfunction.