"Distribution and function of chemokines/receptors in micturition reflexes and referred somatic pain in urinary bladder inflammation."

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Abstract

Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) is a chronic bladder syndrome with symptoms of urgency, frequency, nocturia, suprapubic and pelvic pain. While some theories exist as to the underlying mechanisms of this syndrome, the etiology remains largely unclear. Studies suggest plastic changes at the level of the urinary bladder, bladder primary afferents and/or central pathways may contribute to symptoms. Emerging hypotheses suggest that inflammatory- or injury-induced immune responses may elicit such plastic changes. The overall hypothesis for this research proposal is that inflammatory-induced plastic changes at the level of the urinary bladder and bladder primary afferent neurons in the lumbosacral dorsal root ganglia result in altered visceral sensation/bladder sensory physiology that results in hyperactive reflexes and hyperalgesia/ allodynia of somatic sites. Chemokines, chemotactic cytokines, are well known mediators of the innate immune response and may serve as a link between the immune response and plastic sensory changes. Chemokine expression has been correlated with severity of visceral inflammation (e.g., colon and bladder) and exaggerated pain behaviors. Additionally, chemokines may assert nociceptive effects through a ubiquitous signaling cascade: PI3-K/AKT. Studies have linked PI3-K/AKT signaling to both nociception and chemokine regulation. Therefore, studies examining chemokine/receptor signaling and downstream targets in the urinary bladder and central and peripheral nervous system components of the lower urinary tract, may provide key insights into potential mediators of bladder dysfunction and associated pain. Specifically, we hypothesize that chemokine signaling via CXCL12 and its cognate receptor, CXCR4 plays a role in the initiation and/or maintenance of urinary bladder hyperreflexia and somatic pain associated with IC/PBS. Using a cyclophosphamide-induced model of bladder inflammation, this research proposal investigates distribution, expression, regulation and function role of the chemokine receptor pair CXCL12/ CXCR4 and potential downstream target, PI3-K/AKT in micturition pathways using a multidisciplinary approach that includes: immunohistochemical, quantitative real-time polymerase chain reaction (qRT-PCR), western blot, and enzyme-linked immunoassay (ELISA) techniques and functional studies using conscious cystometry combined with pharmacological tools. Revealing the roles of these molecules may uncover potential novel targets for therapeutic intervention. Health Impact: Relieving or reducing the symptoms of many who suffer from IC/PBS will reduce the pain of as many as 1 million Americans and reduce the financial health care burden that this syndrome bears. In addition to the potential clinical significance of these studies, the present studies will also contribute to our overall understanding of chemokine/receptor distribution and function in micturition pathways under control and inflamed conditions. Chemokine/receptor signaling is a relatively new frontier in the field of micturition control; therefore, these studies will further our basic understanding of chemokine/receptor signaling in micturition reflex pathways.