Infections/Inflammation of the GU Tract: Kidney & Bladder
Podium
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CYSTITIS AND NOCICEPTION IN MICE LACKING ESTROGEN RECEPTORS

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Introduction and Objective: The incidence of painful bladder disorders such as interstitial cystitis is much greater in women than in men. It has been suggested that estrogen and its receptors (ER-α and ER-β) play a role in inflammation and pain. Cyclophosphamide (CYP) is metabolized by the liver to acrolein, and excretion of acrolein causes cystitis. We investigated CYP-induced cystitis and pain sensation in ER-α (αERKO) and ER-β (βERKO) knock-out mice. Methods: Cystitis was induced by injection of CYP (150 mg/kg, i.p) in adult male mice or by intravesical instillation of acrolein (1 mM, 200 μl) in adult female mice. 24 hours later, tissues were collected for analysis of histology and mRNA expression. Peripheral sensitivity to thermal stimulus was evaluated prior to and 30 minutes after injection of a selective P_2X_3 agonist (α,β-meATP; 1 nmol) into hind paw prior to sacrifice. Results: The bladders of all animals demonstrated histological evidence of inflammation. Mean wet bladder weights (mg/g body weight, 24 h after acrolein) were 2.5 ± 0.3 (WT), 3.1 ± 0.3 (αERKO) and 3.2 ± 0.5 (βERKO), n=6, $p > 0.05$. Basal thermal sensitivity was virtually the same in WT and KO mice and was not altered 24 hours after acrolein. Injection of α,β-meATP did not produce significant changes in thermal sensitivity before induction of cystitis. 24 hours after acrolein, injection of α,β-meATP significantly reduced thermal sensitivity latency (s) of the hind paw in WT (basal: 11.7 ± 0.7; α,β-meATP: 8 ± 0.6, n= 6, $P<0.005$.), but not in αERKO (basal: 10.7±0.7; α,β-meATP: 10.8±1.1; n =6). In βERKO, the latency was reduced from 11.1 ± 0.9 to 8.8 ± 1.5, n= 6, but this decrease was not statistically significant. Expression of inflammation/pain-related neuropeptides (SP and CGRP) and receptors (TRPV1 and P_2X_3) was similar among KO and WT mice. Cystitis caused a 2-fold increased in COX-2 mRNA in urothelium from WT and βERKO, but not αERKO mice. Conclusions: CYP or acrolein induced cystitis in both WT and KO mice. Acrolein-induced cystitis enhanced peripheral thermal sensitivity after ATP receptor activation in WT and βERKO, but not αERKO mice. Our data indicate the lack of ER-α or ER-β does not seem to alter bladder inflammation but ER-α contributes to subsequent changes in peripheral pain perception. Prostaglandin E_2, a product of COX-2, greatly augments the effect of α,β-meATP in the paw (Br J Pharmacol 126:326-332, 1999) and increased expression of COX-2 may play a role in enhanced thermal sensitivity mediated by ATP after cystitis.

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