A0769 Therapeutic effects of AF219 on interstitial cystitis/bladder pain syndrome induced by cyclophosphamide and water avoidance stress in rats

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Introduction & Objectives: Using both cyclophosphamide (CYP) and water avoidance stress (WAS) experimental Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) models, we aimed to investigate the role of the purinergic pathway in the development of IC/BPS and the therapeutic effects of the P2X3 receptor antagonist AF219.

Materials & Methods: Sixty-four adult female Wistar rats were used for CYP and WAS (n=32 each) induced IC/BPS. Both models were divided into 4 groups (n=8): Control, Control+AF219, IC/BPS, and IC/BPS+AF219. CYP 75 mg/kg/ml was intraperitoneally administered once a day for 3 days (days 1, 4, and 7). For the WAS protocol, rats were placed on the platform in the center of the plexiglass boxes for 1 hour per day for 10 days. The effects of IC/BPS on nociception and anxiety were evaluated with behavioral experiments. The severity of inflammation in the bladder was scored by histopathological examination. Bladder contraction and relaxation responses were assessed in in-vitro isolated organ-baths. Protein levels of P2X3, P2X7, Trk-A, TRPV1, and TRPA1 in bladder tissue were analyzed by Western blot.

Results: IC/BPS groups had shorter response times to noxious stimuli, more anxiety-like behaviors, and higher inflammation-based histological scores than controls in both models ($p<0.05$). Both behavioral test results and histological scores in the IC/BPS+AF219 groups did not differ from controls ($p>0.05$). IC/BPS groups of both models had increased contractile responses to Carbachol, ATP, and Electrical Field Stimulation (EFS) in in-vitro bladder strip experiments compared to controls ($p<0.05$). However, at cumulative concentrations of Carbachol and ATP and increased frequencies of EFS, IC/BPS+AF219 did not differ from the controls ($p>0.05$). Furthermore, when the bladder strips of both models were incubated with AF219, there was no difference in EFS contraction responses between the groups ($p>0.05$). P2X3, P2X7, Trk-A, and TRPV1 protein levels were higher in the IC/BPS groups than in the controls ($p<0.05$). In the CYP model, P2X3, Trk-A, and TRPV1 protein levels were significantly higher in the IC/BPS+AF219 group compared with the control ($p<0.05$), while no difference was observed in P2X7 ($p>0.05$). But, in the WAS model, no significant difference was observed between the IC/BPS+AF219 and the control in P2X3, P2X7, Trk-A, and TRPV1 ($p>0.05$). Also, in the WAS model, the P2X3 and P2X7 protein levels were significantly lower in the IC/BPS+AF219 compared with the IC/BPS ($p<0.05$).

Conclusions: IC/BPS increases nociceptive responses and causes changes in bladder histology and function in CYP and WAS models. The purinergic pathway activated by P2X3 is responsible for changes in bladder contractile responses and nociception, and this pathway may regulate the expression of other proteins involved in afferent pathway sensitization. Finally, AF219 was able to improve these findings.