BASIC RESEARCH

Toxic cations could be the root cause of interstitial cystitis

Cationic metabolites in the urine of patients with interstitial cystitis (IC) might be responsible for initiating the process that ultimately leads to bladder pain symptoms, according to C. Lowell Parsons and his team at the University of California, San Diego, USA.

Although the cause of IC remains unknown, the 'leaky bladder' theory has gained support in the urological community. This theory states that dysfunction of the mucus layer of the transitional epithelium causes a change in its permeability that enables irritative substances to reach the bladder wall. Parsons and colleagues set out to identify the origin of bladder epithelial dysfunction, and urinary factors were an obvious place to start; dietary and inflammatory factors in urine have been implicated in the pathogenesis of IC.

Researchers focused their efforts on previously identified urinary factors that bind to heparin and kill cultured urothelial cells, suggesting that they are cationic

and toxic, respectively. The mucus layer is anionic, providing a potential mechanism of attack, and an anionic molecule (Tamm-Horsfall protein) has been associated with protection against IC.

“...a balance between urinary cations and anions is crucial for the maintenance of a healthy bladder...”

Cations were isolated from fresh urine specimens collected from 62 women with IC (defined as a minimum score of 15 on the Pelvic pain, Urgency and Frequency [PUF] questionnaire and ≥ 1 year of continuous bladder symptoms) and 33 controls (PUF scores of 1 or 0 and no history of IC or related conditions) using solid-phase extraction.

Using mass spectrometry, 20 metabolites were identified in IC urine, at various concentrations. Higher levels of modified nucleosides, amino acids and

tryptophan derivatives were isolated from women with IC than controls. Individual metabolites were tested for cytotoxicity in HTB-4 urothelial cells; five of the most toxic factors (5-methylcytidine, 1-methyladenosine, 1-methylguanine, N²,N²-dimethylguanosine and L-tryptophan) could be neutralized by Tamm-Horsfall protein.

The investigators propose that a balance between urinary cations and anions is crucial for the maintenance of a healthy bladder, and IC can result from either an increase in toxic cations or a decrease in protective anionic activity. Future therapeutic strategies could be based on the neutralization of cationic factors, using molecules similar to heparin or Tamm-Horsfall protein.

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