Sildenafil effect on the human bladder involves the L-cysteine/hydrogen sulfide pathway: a novel mechanism of action of phosphodiesterase type 5 inhibitors

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Several studies have documented a relationship between male sexual dysfunction and lower urinary tract symptom (LUTS) (Speakman MJ, 2009). LUTS are common in men with ED and there is a strong correlation between the severity of LUTS and the degree of erectile dysfunction in all age groups, which suggests a causal relationship or, more possibly, the presence of common pathogenetic pathways (Speakman MJ, 2009). Phosphodiesterase type 5 inhibitors (PDE5-Is), commonly used in ED therapy, were recently found to be effective in the treatment of LUTS (?ckert S et al., 2011) although their mechanism of action is still unclear. PDE5-Is cause bladder smooth muscle relaxation through a mechanism partially independent from nitric oxide (Oger S et al., 2010). Hydrogen sulfide (H_2S) is a newly discovered gas-transmitter with myorelaxant properties. It is synthesized predominantly from L-cysteine (L-cys) by the enzymes cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) (Wang R, 2012). The aim of our study was to evaluate whether L-cys/H_2S pathway is involved in the effect of sildenafil on human detrusor dome. In this study have been used samples obtained from patients undergoing open prostatectomy for benign prostatic hyperplasia and bladder outlet obstruction. The expression of CBS, CSE was evaluated by western blot analysis. CBS and CSE activity was detected measuring H_2S production by a colorimetric assay in basal and stimulated conditions with L-cys (Stipanuk MH et al., 1982). The effect of sildenafil (1, 3, 10, and 30μM), 8-bromo-cyclic guanosine monophosphate (8-bromo-cGMP; 100 μM) and dibutyryl-ciclic adenosine monophosphate (dibutyryl-cAMP; 100 μM) on H_2S production was also evaluated. The relaxation-response to L-cys (0.1μM to 10mM), sodium hydrogen sulfide (NaHS, 0.1μM to 10mM) and sildenafil (0.1 μM to 10 μM) was assessed on carbachol pre-contracted detrusor strips. CBS and CSE inhibitors were used to demonstrate the involvement of H_2S signaling in sildenafil effect. We found that human bladder expresses CBS and CSE and that tissue homogenates significantly convert L-cys into H_2S. NaHS or L-cys relaxed in a concentration-dependent manner the human bladder strips. Sildenafil caused a relaxation of pre-contracted bladder dome strips in a concentration-dependent manner and this effect was significantly reduced by CSE and CBS inhibition. In addition, sildenafil caused a concentration-dependent increase in H_2S production in human tissue. Similarly, both 8-bromo-cGMP and d-cAMP caused an increase in H_2S production. In conclusion we have shown that L-cysteine/H_2S pathway has a functional role in human bladder representing a new therapeutical target in LUTS. At last but not least, sildenafil effect involves H_2S signaling trough cGMP and cAMP. This evidence may clarify the beneficial effect of PDE5-Is either in LUTS or ED treatment.

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