β-3ADRENERGIC RECEPTOR ACTIVATION CAUSES HYDROGEN SULFIDE PRODUCTION VIA CYSTATHIONINE γ-LYASE IN HUMAN UROTHELIUM

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Introduction: Lower urinary tract symptoms (LUTS) are a common age-related condition in men characterized by a complex of symptoms that may belong to obstructive, irritative or postmicturition domains. Even if most of LUTS in men are secondary to benign prostatic hyperplasia (BPH), recent evidence suggests that LUTS may be a non-sex specific and a non-organ specific group of symptoms. In parallel, a relationship between erectile dysfunction (ED) and LUTS have been documented. LUTS are common in men with ED and there is a strong correlation between the severity of LUTS and the degree of ED suggesting a causal relationship or the presence of common pathogenetic pathways. In this scenario, a role of hydrogen sulfide (H_2S) in the control of bladder tone and erectile function has been shown. It is endogenously generated mainly by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) from L-cysteine. Considering that β-3receptor activation relaxed human corpus cavernosum (HCC) strips through a mechanism cGMP and H_2S dependent here we have investigated the contribution of H_2S in β-3adrenoceptor activation-induced relaxing effect in human bladder.

Materials and methods: Full thickness bladder samples (detrusor plus urothelium) were obtained by prostatectomy from male patients affected by BPH. H_2S production was measured by using a colorimetric assay in human urothelium tissues incubated with BRL-37344, a β-3adrenergic selective agonist,(0.1,1, 10 and 100 μM); in another set of experiments samples of detrusor muscle were incubated with BRL (10 μM) at different time. On a stable contraction of bladder strips induced by carbachol, in presence or in absence of urothelium, a curve concentration effect of BRL-37344(0.1μM-300 μM) was performed. In order to evaluate the contribution of H_2S a pharmacological modulation was operated.

Results: The β-3receptor activation with BRL-37344of human detrusor muscle did not affect the H_2S production. Conversely, the human urothelium stimulated with BRL-37344caused a significant (*$p<0.05$) increase in H_2S production compared to vehicle. The inhibition of CSE and the blockade of the β-3receptor reverted the increase in H_2S production (*$p<0.05$). The β-3relaxant effect was higher in presence of urothelium (***$p<0.001$) compared to those without urothelium. The CSE inhibition but not CBS inhibition significantly reduced the BRL-37344-relaxing effect (***$p<0.001$). The BRL-37344relaxing effect was not modified in human bladder strips denuded from the urothelium in presence of CSE or CBS inhibitor.

Discussion and conclusion: The activation of β-3adrenergic receptor in human urothelium bladder promoted the H_2S production through CSE enzyme causing the detrusor muscle relaxation. This finding opens new perspective in the pathophysiology of LUTS and further supports the therapeutic use of mirabegron, a β-3adrenergic receptor agonist, for overactive bladder. In addition, considering the fact that i) β-3adrenergic receptors are localized in both HCC and human bladder ii) H_2S is involved in β-3relaxing effect iii) H_2S relaxes both HCC and human bladder strips the use of mirabegron could be effective in patient with LUTS associated to ED.