β_3 adrenergic receptor activation relaxes human corpus cavernosum via cGMP/ hydrogen sulfide-dependent mechanism

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Human penile erection is a result of several complex neuronal and hemodynamic mechanisms. The balance between contracting and relaxant factors represents the key issue to achieve penile erection. It is now well accepted that nitric oxide (NO) plays a major role in induction and maintenance of erection resulting in sinusoids expansion and increased intracavernous pressure [1,2]. However, alternative relaxing pathways have been widely described [3,4]. Indeed, it has been reported that β_3 adrenoceptorare are expressed in human corpus cavernosum (HCC) and are localized mainly in smooth muscle cells [5]. β_3 adrenoceptor stimulation relaxes HCC strips in a cyclic guanosine monophosphate (cGMP)-dependent and NO-independent mechanism [5]. β_3 adrenoceptors play a physiological role in penile erection, although the mechanism is still unclear. In this scenario, hydrogen sulfide (H_2S) has been suggested as a relaxant signal molecule involved in penile erection [6]. H_2S is endogenously produced from L-cysteine mainly by the action of two enzymes cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE). Both enzymes are constitutively expressed in HCC but CSE rather than CBS is more abundant in human penile tissue [6]. Additionally, it has been demonstrated that H_2S inhibits phosphodiesterase increasing cGMP levels [7]. Therefore a link between cGMP and H_2S exists. Here we have investigated if β_3-induced relaxation involves H_2S signaling in HCC and penile artery. In order to address this issue a relaxation response-curve to BRL37344, a β_3 selective agonist, has been performed either in HCC strips or penile artery rings in presence of D,L-propargylglycine (PAG), a CSE inhibitor. H_2S generation and cGMP content has been measured in HCC and in human penile artery samples incubated with BRL37344, in presence of PAG, KT5823 (a protein kinase G inhibitor) or SR59230A (a selective β_3 antagonist). In order to better define the underlined mechanism, a pharmacological approach has been operated. BRL37344 relaxes in a concentration-dependent manner pre-contracted HCC strips as well as penile artery rings. CSE inhibitor significantly reduces BRL37344-induced effect in both HCC strips and in penile artery rings. β_3 adrenoceptor stimulation significantly increases H_2S production in both HCC strips or penile artery samples. This effect is significantly reduced by either protein kinase G or CSE inhibitor or by β_3 antagonist. As expected the β_3 adrenoceptor incubation cause a significant increase in cGMP level in both HCC strips or penile artery. Finally, the BRL-increase in cGMP is significantly reduced by CSE inhibition. In conclusion, BRL37344-induced relaxation in HCC and penile artery occur by cGMP/H_2S-dependent mechanisms. Thus β_3/H_2S/cGMP may represent an alternative pathway to NO sharing the same final mediator, i.e. cGMP. Betmiga®-mirabegron, a $\beta_3$agonist, has been recently approved by FDA and EMA for lower urinary tract symptoms (LUTS) treatment. LUTS and erectile dysfunction are strongly associated in men and share several possible pathogenetic mechanisms. Therefore, a therapy with β_3 agonists may open new frontiers in the treatment of patients affected by LUTS associated with erectile dysfunction.

References

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