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Title: YC-1 ENHANCES NO- AND CO-INDUCED RELAXATIONS IN THE FEMALE PIG URETHRA

Aims of the study:

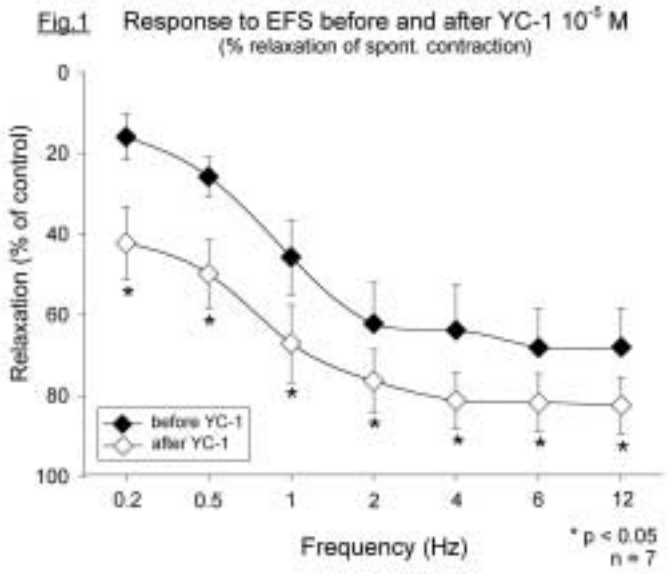
Neurogenic relaxation of urethral smooth is partly dependent on nitric oxide (NO)-induced activation of soluble guanylate cyclase (sGC) [1]. Carbon monoxide (CO) can also activate sGC, but a physiological role for CO in the regulation of urethral tone is not yet established. Probably by allosterical binding to sGC, YC-1 improves the catalytic rate of the enzyme [2]. The aim of the present study was to investigate if YC-1 can modulate the relaxant responses of the isolated female pig urethra to electrical field stimulation (EFS) and exogenous administration of CO and NO.

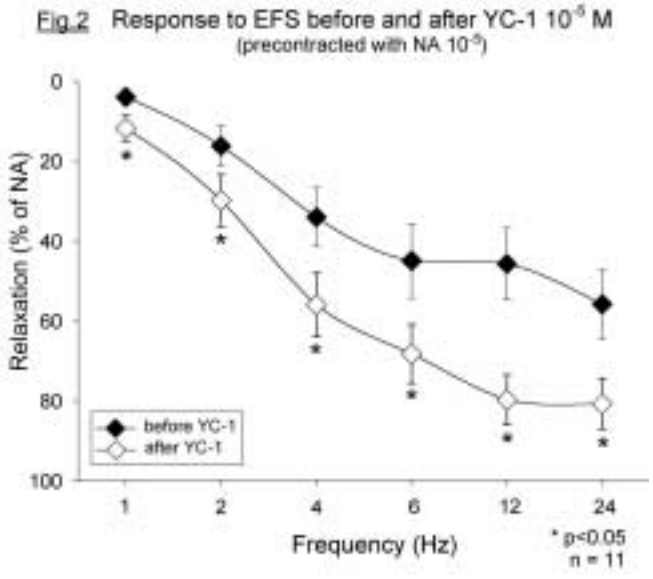
Methods:

In spontaneously active and noradrenaline (NA)-precontracted preparations of isolated pig urethra smooth muscle, relaxant responses were evoked by EFS before and after incubation with YC-1 (10^{-5}M for 30 min). Then some of the preparations were repetitively stimulated after the sGC-inhibitor ODQ (10^{-6} M) or the nitric oxide synthase (NOS)-inhibitor L-NNA (10^{-4}M) were added. In addition, the concentration response curves (CRC) for NO and CO were investigated in NA-precontracted strips before and after incubation with YC-1 (10^{-5}M for 30 minutes).

Results:

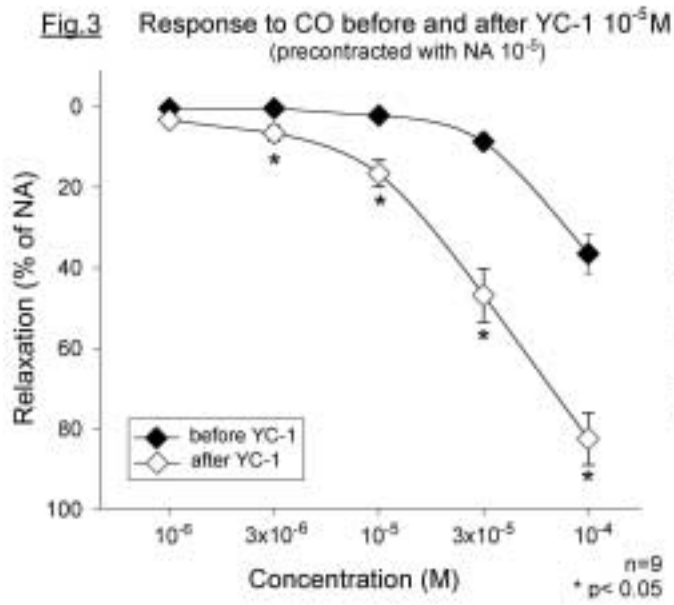
There was a significant enhancing effect of YC-1 on the relaxations evoked by EFS under spontaneous and NA activated tension for all frequencies tested (see fig. 1 and 2). Incubation with YC-1 increased the amplitude of the induced responses by an average of 151±19% (range 120-260%) in the spontaneously active and 190±23 (301-151%) in the NA activated preparations (fig. 1 and 2). ODQ 10^{-5} M or L-NNA 10^{-4}M abolished the relaxations evoked by EFS after incubation with YC-1 10^{-5}M.

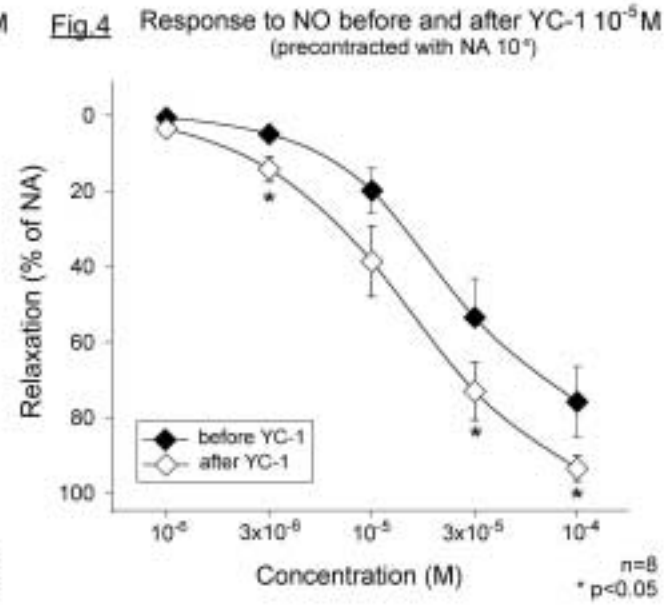




At CO concentrations higher than 10^{-6}M, preincubation with YC-1 significantly enhanced the CO-induced

relaxant responses by 1038±374% (262-2404%) (see fig. 3). The relaxant response to NO was significantly enhanced after incubation with YC-1 at $3x10^{-6}$, 10^{-5}, and $3x10^{-5}$M. YC-1 (10^{-5}M) increased the response to NO by 263±81% (130-566%) (see fig. 4).





Conclusion:

1 potentiates nerve-induced and NO/cGMP-dependent relaxant responses of the female pig urethra in vitro. The finding that the weak response to CO was greatly enhanced after sensitising the sGC, suggests a cGMP-mediated mechanism for CO-induced relaxation in the urethral smooth muscle.

Sources of funding:

Swedish Medical Research Council, grant no. 6837

References:

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