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Interstitial cells of Cajal in the urethra as effectors of the nitric oxide action through the cyclic GMP pathway

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Background

Specialized cells similar to the interstitial cells of Cajal (ICC) of the gut have been described in the urethra where they seem to act as pacemakers of contractility [1]. Furthermore, nitric oxide (NO) is the main transmitter involved in relaxation of the urethra during micturition [2]. Here we show that urethral ICC are preferential targets of the NO action by the production of cyclic GMP (cGMP) in response to both exogenous addition or endogenous release of NO.

Materials and methods

Under isometric recording of contractile tension, norepinephrine-precontracted preparations from female lambs and rats were subjected to either electrical field stimulation (EFS, 2 Hz for 4 min) or S-nitrocysteine (SNC, 10 mM for 2–10 min) addition, in the continuous presence of cGMP-phosphodiesterase inhibitors. Unstimulated pre-contracted preparations served as controls. Some preparations were pre-treated with the guanilate cyclase inhibitor ODQ (10 mM) for 30 min. Samples were fixed in 4% paraformaldehyde and processed for cGMP immunohistochemistry. Double immunolabelling cGMP-vimentine, cGMP-neuronal NO synthase (nNOS) and cGMP-Protein gene product 9.5 (PGP 9.5, neuronal marker) were also performed.

Results

cGMP-immunoreactivity was intense in dense networks of ICC localized at the serosal, muscular and sub-urothelial layers in sheep and rats preparations exposed to either SNC or EFS (Fig. 1). Reactivity was markedly reduced in control preparations and almost disappeared in ODQ-treated preparations, showing a basal activity stimulated by SNC and EFS. cGMP positive ICC were also vimentine positive. Double labellings cGMP-(nNOS) and cGMP-PGP 9.5 showed no co-localization but close structural relationship between ICC and nerve terminals.

Conclusion

These findings suggest that ICC may play an intermediary role in the urethral nitrergic neurotransmission, as effectors of the NO action, which in turn would induce muscular relaxation by means of unknown mechanisms.

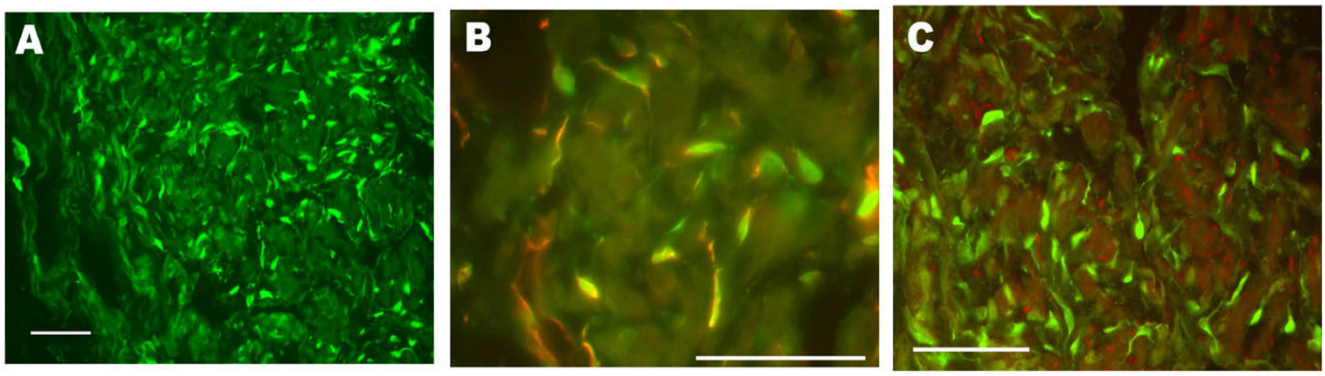

Figure 1
A. cGMP immunoreactive ICC in the smooth muscle layer of the rat urethra exposed to SNC. **B**. cGMP positive ICC are also reactive to vimentine (red). **C**. cGMP ICC (green) did not co-localize with nNOS (red) which is present in adjacent intramural nerves in urethra from sheep. Bar = 30 μm.

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