Influence of the inhibition of cyclic nucleotide phosphodiesterase type 4 on human detrusor smooth muscle contractions

S. Oger 1, D. Behr-Roussel 1, J. Bernabe 1, P. Denys 2, E. Comperat 3, T. Lebret 4, F. Giuliano 1,2

(1) Pelvipharm, Gif Sur Yvette, (2) Neuro-Urology Unit Dept. of Physical Medicine and Rehabilitation Raymond Poincaré Hospital, Garches, (3) Pitié Salpêtrière Hospital, Dept. of Urology, Paris, (4) Foch Hospital, Dept. of Urology, Suresnes, (5) Raymond Poincare Hospital, Dept. of Neurological Rehabilitation, Garches, France

Abstract

OBJECTIVES

The second messenger, cAMP, controls many physiological processes including smooth muscle relaxation. At the cellular level, the intensity and the duration of the cAMP signal is partly regulated by the phosphodiesterase type 4 (PDE4) enzyme which selectively hydrolyzes cAMP 1. Elevation of cAMP levels by PDE4 inhibition relaxes various types of smooth muscle cells 2, 3, 4.

In human detrusor smooth muscle, the cAMP pathway plays a critical role in mediating relaxation and PDE4 expression has been characterized 5, 6.

The aim of this study was to evaluate the effect of the selective inhibition of PDE4 activity using the archetypal PDE4 inhibitor, rolipram, on human detrusor strips contractions induced by carbachol.

RESULTS

Effect of rolipram on human bladder strips precontracted with carbachol

- The cumulative addition of rolipram induced a significant concentration-dependent inhibition of human detrusor smooth muscle strip contractions elicited by carbachol.

Effect of rolipram on human bladder strips precontracted with carbachol in presence of forskolin

- Forskolin pre-treatment dramatically enhanced the concentration-relaxant effect of rolipram with a significant marked effect at the highest concentrations tested.

CONCLUSIONS

- Selective inhibition of PDE4 activity by rolipram relaxed human detrusor strips precontracted by carbachol.
- The elevation of the intracellular cAMP levels by forskolin strongly strengthened the relaxant effect exerted by rolipram.

PDE4 inhibitors could represent an attractive target for the treatment of overactive bladder although it requires further investigation.

MATERIALS & METHODS

IN VITRO CONTRACTILE EXPERIMENTS

The detrusor strips were progressively stretched to 500 mg. Following an equilibration period, contractile reactivity of the strips was evaluated with an exposure to KCl (100 mM, 10 min) and a priming period was achieved with carbachol (3.10^-5 M, 10 min). Strips were then washed and pre-contracted with a sub-maximal concentration of carbachol (10^-5 M) and allowed to re-equilibrate during 30 min. For the forskolin (a non selective activator of adenylyl cyclase) pre-treatment, the strips were exposed to forskolin (25 min, 3.10^-4 M; i.e. concentration giving 15-20% relaxation, as determined in preliminary experiments, data not shown) or vehicle. Then, concentration-response curves to rolipram or vehicle were performed. At the end of the concentration-response curve, strips were exposed to the maximally-effective concentration of forskolin (3.10^-4 M) to induce maximal relaxation.

Relaxations in response to increasing and cumulative concentrations of rolipram or vehicle were expressed as a percentage of the steady-state tension obtained after the addition of carbachol (10^-4 M, 30 min) considered as the maximal contraction. The amount of relaxation produced by the maximally-effective concentration of forskolin (3.10^-4 M) determined at the end of each experiment and after 30 min of stabilization was taken as 100% relaxation.