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Supersensitivity of muscarinic receptors in rat isolated detrusor smooth muscle (DSM) after chronic nitric oxide inhibition

Fabiola Mónica*[1], Gilberto de Nucci[1], Alice Bricola[2], Angelina Zanesco[3], Catarina Porto[4], Fernando Abdalla[5], Leandro Freitas[6], Maria Aparecida Teixeira[7] and Edson Antunes[1]

Address: [1]Department of Pharmacology, Faculty of Medical Sciences, University of Campinas, Campinas (SP), Brazil, [2]Department of Pharmacology, Pontifical Catholic University of Campinas, Campinas (SP), Brazil, [3]Department of Physical Education; Institute of Bioscience, Paulista State University, Rio Claro (SP), Brazil, [4]Section of Experimental Endocrinology, Department of Pharmacology, UNIFESP (SP), Sao Paulo, Brazil, [5]Pharmacology Laboratory, Butanta Institute (SP), Sao Paulo, Brazil, [6]Departament of Clinical Pathology, University of Campinas, Campinas (SP), Brazil and [7]Faculty of Medicine, Pontifical Catholic University of Campinas, Campinas (SP), Brazil

Email: Fabiola Mónica* - fabiolamonica@terra.com.br

* Corresponding author

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Background

It has been suggested that disturbance of the NO-cGMP pathway lead to impaired relaxation of the urethral outflow region, increased bladder afferent activity and overactive bladder, but the precise role of NO in regulating the detrusor smooth muscle (DSM) functions remains to be determined.

Purpose

Our present work aimed to examine the functional and biochemical alterations of rat DSM after chronic NO blockade.

Methods

Male Wistar rats were treated orally with L-NAME (20 mg/rat/day) for 30 days. Age-matched control animals received tap water alone. Concentration-response curves to full agonist carbachol (CCh, 1 nM-30 μM) in the DSM were obtained. The values of potency (pEC_{50}) and maximal responses (E_{max}) were calculated. The IP_3 accumulation and the nitric oxide synthase (NOS) activity, as well as morphometric analyses were evaluated in the urinary bladder of control and L-NAME-treated rats.

Results

L-NAME-treated rats presented a marked arterial hypertension (ctrl:124 ± 2 vs treated: 198 ± 1 mmHg) and a reduction of 86% in the total NOS activity in the isolated rat bladder. Four-weeks treatment with L-NAME increased by 5-fold the CCh potency (6.09 ± 0.02 vs 6.82 ± 0.06), without modifying the E_{max} (ctl: 3.50 ± 0.10 vs treated: 3.40 ± 0.07) (Figure 1A). Incubation of urinary bladder with CCh (10^{-9}–10^{-3} M) concentration-dependently increased the total [^{3}H]-inositol phosphates in rat urinary bladder that was markedly higher in L-NAME-treated rats compared with control animals (Figure 1B). The measurement of the thickness of rat isolated bladder revealed that L-NAME treatment for 30 days caused no alterations in the thickness of submucosa and muscular layers of the DSM when compared with control animals. However, in the trigone smooth muscle (TSM), L-NAME treatment significantly increased the thickness of the muscular layer without changing the thickness of the sub-mucosa layer (Table 1).

Conclusion

Our findings show that long-term NO inhibition significantly increases the sensitivity of DSM for the muscarinic

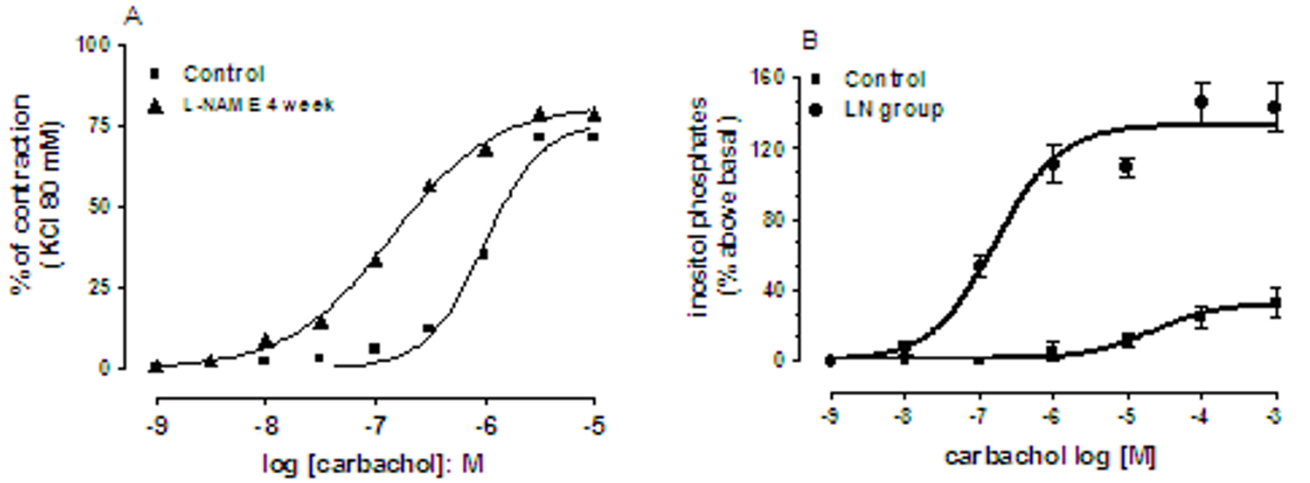

Figure 1
(A) Concentration-response curve to carbachol in rat DSM from control and L-NAME-treated rats in 30 days (n = 6–8, p < 0.05). **(B)** Effects of carbachol on total [^{3}H]-inositol phosphate accumulation in both control and L-NAME-treated group in 30 days (n = 3–6, P < 0.05).

Table 1: Morphometric analyses in isolated rat detrusor and trigone smooth muscle in control and L-NAME-treated groups in 30 days. *p < 0.05.

	Detrusor (μm)		Trigone (μm)	
Layers	Control	L-NAME	Control	L-NAME
Total	1194 ± 73.09	1098 ± 67.72	705 ± 19.56	861 ± 21.85*
Muscular	610 ± 37.18	658 ± 32.24	526 ± 24.29	677 ± 30.49*
Serosal	547 ± 66.36	494 ± 56.15	176 ± 12.47	183 ± 17.11

agonist carbachol via accumulation of IP_3, suggesting that NO exerts a modulatory effect on the contractility mediated by muscarinic receptors.

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