Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmacology 577 (2007) 150–155
www.elsevier.com/locate/ejphar

Human epididymal and prostatic tracts of vas deferens: Different contraction response to noradrenaline stimulation in isolated organ bath assay

Nicola A. Colabufo [a,*], Vincenzo Pagliarulo [b,*,1], Francesco Berardi [a], Marialessandra Contino [a], Roberto Perrone [a], Mauro Niso [b], Giancarlo Albo [b], Gaetano de Rienzo [b], Arcangelo Pagliarulo [b]

[a] *Dipartimento Farmacochimico, Facoltá di Farmacia, Università degli Studi di Bari, via Orabona 4, 70125 Bari, Italy*
[b] *Dipartimento Emergenza e Trapianti d'Organo, Sezione di Urologia, Università degli Studi di Bari, Piazza G. Cesare 11, 70124 Bari, Italy*

Received 18 May 2007; received in revised form 11 August 2007; accepted 28 August 2007
Available online 11 September 2007

Abstract

In the present study epididymal and prostatic portions of human vas deferens were separately isolated and stimulated with exogenous noradrenaline to study their contractile properties. The results displayed that the epididymal tract produced a phasic–tonic response, while the prostatic strip produced only a phasic response suggesting a different functional role of each vas deferens segment. Moreover, it has been verified if α_1-adrenoceptor antagonists doxazosin, alphuzosin and terazosin could differently block the noradrenaline response in each segment.

Doxazosin, the most potent antagonist, displayed similar potency in epididymal and prostatic tract ($pA_2=8.51$ and 8.42, respectively). Analogously, alphuzosin, although less potent than doxazosin, displayed in the same tracts a superimposed potency ($pA_2=7.25$ and 7.30, respectively). In contrast with doxazosin and alphuzosin, terazosin displayed higher potency in blocking the contractile response in prostatic tract ($pA_2=7.67$) than in epididymal segment ($pA_2=6.43$).

These results showed that α_1-adrenoceptor antagonists doxazosin and alphuzosin, although with a different potency, did not discriminate between epididymal and prostatic segment while terazosin showed high potency in prostatic tract and only a moderate activity in epididymal section. Moreover, the biological model employed in our experiments could be a valid screening method to test the potential interferences of drugs indicated for bladder outlet obstruction with the peristaltic activity or the global tone of the human vas deferens.

Keywords: Human vas deferens; α_1-Adrenoceptor antagonist; Doxazosin; Alphuzosin; Terazosin

1. Introduction

Under physiological conditions in human males the spermatozoa are stored in the seminal tract and rapidly released in the urethra during ejaculation. Although seminal vesicles were supposed to be the reservoir, more recent data attribute this function to the coda epididymis (Jones, 2004). When ejaculation occurs, the spermatozoa are transported from the epididymis to the pre-prostatic segment of the vas deferens, where they are released mixed to prostate and seminal vesicles secretions (Amann, 1981; Johnson and Verner, 1988).

In ejaculatory disorders, anejaculation had always been thought to be caused by bladder neck relaxation. Recent *in vitro* researches (Grasso et al., 2006; Tambaro et al., 2005) on rats deferent ducts have suggested that the ejaculatory disorder would be secondary to anomalies in sperm progression due to the alteration in the contractile mechanism of the vas deferens.

Moreover, observations conducted on specimens of human vas deferens, mostly obtained at vasovasostomy after vasectomy, have shown that the smooth muscle coat of the human vas deferens receives a dense noradrenergic innervation, and the contraction is mainly mediated by neurally released noradrenaline and stimulation of postjunctional adrenoceptors (Sjöstrand, 1965; Alm, 1982; McConnell et al., 1982). Although previous workers have reported the existence of a complex neurochemical coding of nerve fibres innervating this organ, as yet, few attempts have been made to determine the contraction effect by noradrenaline stimulation in the

* Corresponding author. Tel.: +39 080 5442727; fax: +39 080 5442731.
E-mail addresses: colabufo@farmchim.uniba.it (N.A. Colabufo), vpagliarulo@urologia.uniba.it (V. Pagliarulo).
[1] Tel.: +39 080 5478741; fax: +39 080 5478741.

0014-2999/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2007.08.038

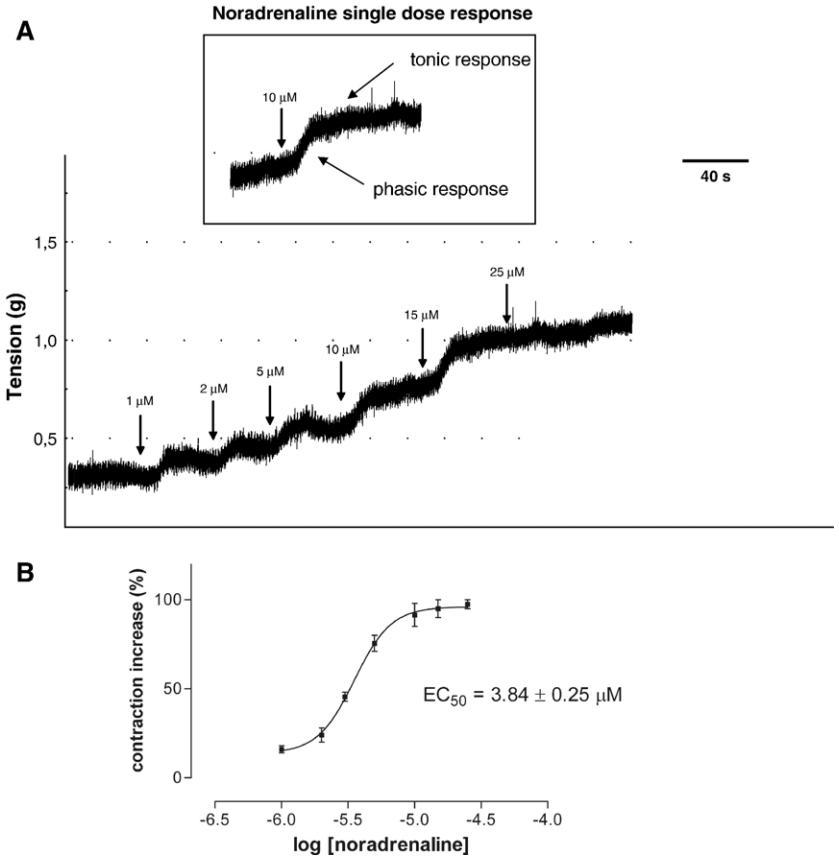

Fig. 1. (A) Single dose–response at 10 μM noradrenaline stimulation (insert) and representative cumulative dose–response curve of noradrenaline on human vas deferens (epididymal tract). (B) Dose–response curve of noradrenaline on epididymal human vas deferens tract (by phasic component measurement). EC_{50} is the mean ± SEM of three experiments with each dose ($P < 0.0001$ *vs* basal).

different segments of the vas deferens (Sjöstrand, 1965; Alm, 1982; McConnell et al., 1982; Tainio, 1995). Moreover, ejaculatory disorders have been reported in patients treated with α_1-adrenoceptor antagonists, and this adverse effect is corroborated by the presence of α_{1A} adrenoceptors in the vas deferens duct.

In the present work epididymal and prostatic portions of human vas deferens were separately stimulated with exogenous noradrenaline in order to attempt a better understanding of their specific contractile properties. In particular, it has been investigated if there was a difference in these two segments to noradrenaline stimulation consistent with their specific functions (Prins and Zaneveld, 1980). Moreover, a second aim of the present work was to verify if α_1-adrenoceptor antagonists differently blocked the contractility of epididymal and prostatic tracts induced by exogenous noradrenaline. For this purpose, we selected, among α_1-adrenoceptor antagonists, doxazosin, alphuzosin and terazosin, which are involved in retrograde ejaculation, traditionally attributed to bladder neck relaxation (Hampel et al., 2002; Giuliano et al., 2004).

2. Materials and method

2.1. Patients and sampling technique

Specimens of human vas deferens were obtained from 6 patients undergoing radical cystoprostatectomy for muscle invasive bladder cancer. The mean age of the patients was 64 years (range 52–79). Preoperatively, all patients referred to be fertile men, and were never under therapy with α_1-adrenoceptor antagonists or 5-α reductase inhibitors, as well as drugs interfering with peripheral noradrenaline responses. The present study was approved by the institutional review board and patient informed consents were obtained previous to surgery in all cases.

About 10 mm of vas deferens segments closest to the prostate were left with the bladder specimen for pathologic evaluation. The remaining intra-abdominal segments were bilaterally dissected up to the internal inguinal ring, clipped, and incised. Connective tissue and blood vessels were removed and the specimens cut transversely into rings (circular muscle preparations; 2 cm of length), in order to separate a prostatic and an epididymal segment. Final pathologic examination excluded in all cases vas deferens involvement by bladder or prostate cancer.

2.2. Human vas deferens epididymal and prostatic strips preparation

Sections of 2 cm in length of human vas deferens were quickly washed in a Krebs solution (118 mM NaCl, 4.75 mM KCl, 2.45 mM $CaCl_2$, 1.71 mM $MgCl_2$, 25.0 mM $NaHCO_3$, 0.93 mM KH_2PO_4, 11 mM glucose) and placed in 20 mL organ baths containing Krebs solution at 37.0 °C and bubbled with a 5% CO_2 and 95% O_2 gas. The strip was placed under a 1 g load