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Relaxation of Isolated Corpus Cavernosum Induced by Smooth-Muscle Relaxant Drugs

A Comparative Study

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Summary. Intracavernous injection of vasoactive substances are used in the treatment and investigation of impotence. We studied the effects induced by some pharmacological agents on strips of human erectile tissue. Specimens of corpus cavernosum were obtained from 16 men undergoing cystectomy or penectomy for bladder or penile malignancy. Strip preparations were mounted in thermostically controlled baths containing Krebs solution. Pharmacologic effects were monitored by means of an isotonic transducer. Papaverine was shown to be the substance able to cause the biggest relaxation effect. The authors compared the action of other drugs having a relaxant effect, studied the antagonist effects of epinephrine and dopamine on the pharmacologically relaxed preparations, and stressed that the relaxation of the erectile tissue has a determinant role in the appearance and maintenance of erection.

Key words: Erectile dysfunction – Intracavernous therapy – Smooth muscle relaxant drugs – Isolated human corpus cavernosum

Introduction

The physiology of the erectile mechanism is still the subject of numerous studies [2, 8]. The presence of multiple nerve endings and the knowledge of their role in the tumescence-detumescence phenomenon leads us to believe, that smooth muscle tissue plays a determining role in erection [1, 3, 4, 8].

Intracavernous administration of drugs has proved to be therapeutically efficacious in the treatment of patients with abnormal erectile function [5, 12–14, 16]. In the search for a "pharmacological prosthesis" the Authors compared the effects of several drugs with a relaxant action on smooth muscle tissue by using samples of human cavernous tissue in vitro.

Materials and Methods

Thirty-two samples of cavernous tissue were removed from 16 patients between the ages of 42 and 68 (average 55.4) during radical cystectomy for bladder carcinoma (13 patients) or during total or subtotal penectomy for carcinoma. (3 patients). Before surgery the patients were evaluated by means of a series of noninvasive screening tests that included, history, physical examination, screening for hormonal imbalance with measurements of serum levels of testosterone, prolactin, follicle-stimulating hormone, luteinizing hormone and estradiol, evaluation of the penile arteries by Doppler study with calculation of the penile-brachial index (at rest and after exercise) and determination of the bulbo-cavernous reflex latency time. Only those patients with normal sexual activity, normal serum levels of sex hormones, with a penile-brachial index greater than or equal to 0.9, and with a bulbo-cavernous reflex latency times less than 35 ms were admitted to the study.

After removal, the strips of cavernous tissue, with dimension of approximately 1 × 3 × 5 mm, were immediately placed in Krebs solution at 4 °C. The samples were mounted in an organ bath containing Krebs solution at 37 °C bubbled with O_2 (95%) and CO_2 (5%). The solution was administered by a Watson Marlow pump at a flow rate of 12 cc/min. The two ends of the strips were attached to the bottom of the basin and to a Harvard isotonic transducer connected to a RDK continuous pen recorder. To balance the traction exerted by the fragment, a 0.65 gm weight was attached to the opposite extremity of the transducer (Fig. 1).

An interval of one to two hours was necessary from the moment of assembly to the beginning of the drug administration in order for the spontaneous contractions to begin. To provoke this phenomenon the administration of potassium chloride was necessary in only six cases.

The Krebs solution, prepared on the day of the experiment, had the following composition (mM): NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3^-$ 25, NaH_2PO_4 1.2, glucose 11.5. The high potassium solution (124 mM) used to stimulate the appearance of the contractile activity was obtained with the equimolar exchange between Na and K in the Krebs solution.

The drugs used were administered by a Watson Marlow pump at 0.2 cc/min for one minute and included: papaverine hydrocloride, phentolamine mesylate, tolazoline hydrocloride, aminophylline, pentoxiphylline, isoxsuprine hydrochloride, nitroglycerin, dihydroergotamine mesylate, carbachol, histamine, 5-hydroxytryptamine, atropine, epinephrine and dopamine. The Krebs solution as well as the solutions containing drugs were prepared by adding double distilled water.

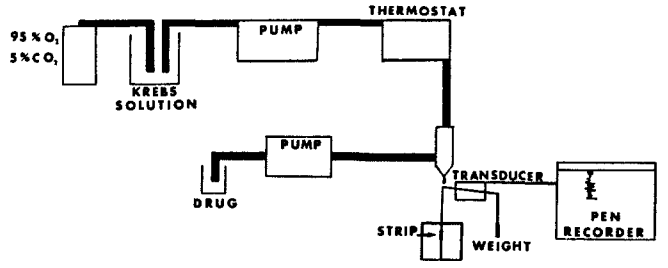

Fig. 1. Experimental set-up

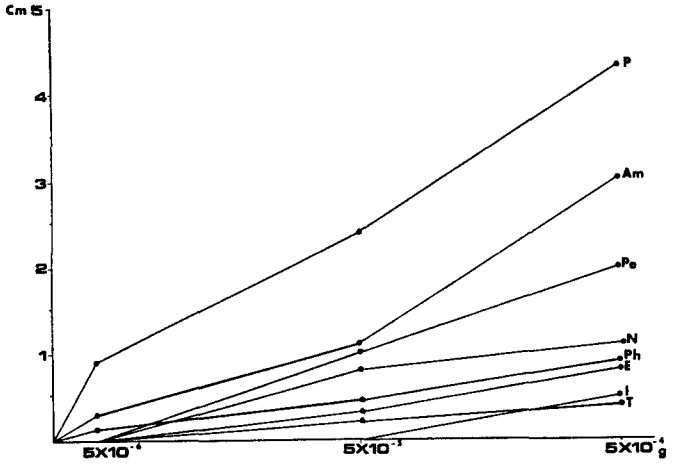

Fig. 2. Relationship between dose and amplitude of relaxant effect of aminophylline (*Am*), pentoxiphylline (*Pe*), isoxsuprine (*I*), tolazoline (*T*), phentolamine (*Ph*), nitroglycerin (*N*), ergotamine (*E*) and papaverine (*P*) (mean values)

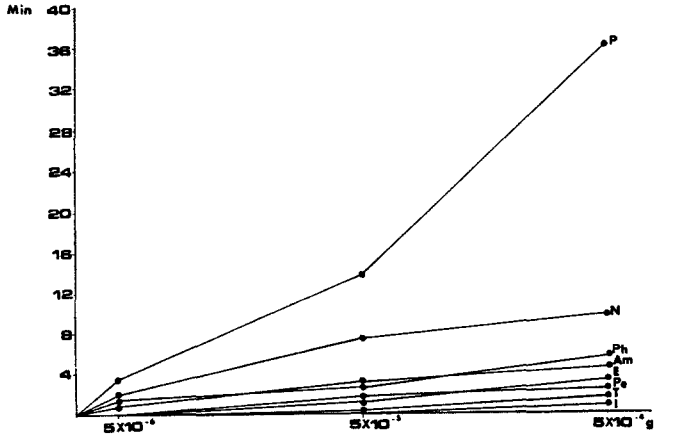

Fig. 3. Relationship between dose and duration of relaxant effect of aminophylline (*Am*), pentoxiphylline (*Pe*), isoxsuprine (*I*), tolazoline (*T*), phentolamine (*Ph*), nitroglycerin (*N*), ergotamine (*E*) and papaverine (*P*) (mean values)

Results

The parameters considered to evaluate the effect of the drugs were amplitude and duration. Amplitude was considered to be the deviation from the base line. Whereas, the duration was the time interval from the onset of the deflection from the base line to the appearance of the contractile activity (Figs. 2, 3).

Papaverine (5×10^{-6}–5×10^{-4} gm) (1.09×10^{-6}–1.09×10^{-4} M/lt) ($n = 8$) had a marked dose-dependent effect (Fig. 4A–C). The drug action was only temporarily antagonized by the additions of epinephrine (5×10^{-6}–5×10^{-4} gm) (1.87×10^{-6}–1.87×10^{-4} M/lt), of dopamine (5×10^{-6}–5×10^{-4} gm) (2.16×10^{-6}–2.16×10^{-4} M/lt) and of potassium chloride (3×10^{-5}–3×10^{-3} gm) (3.3×10^{-5}–3.3×10^{-3} M/lt) (Fig. 4D, E). In fact, after the contraction induced by the addition of one of these drugs the cavernous tissue returned to the state of relaxation which had been caused by the papaverine. Atropine and ergotamine did not show any antagonistic action. The amplitude and duration values were respectively 4.3 ± 1.79 cm and 36′31″ ± 2′36″ at the maximum dose of 5×10^{-4} gm. Phentolamine (5×10^{-6}–5×10^{-4} gm) (1.09×10^{-6}–1.09×10^{-4} M/lt) ($n = 7$) had an action similar to that of papaverine but the apperance of the relaxation effect was faster and the amplitude and duration were minor at equal doses (Fig. 5A–C). At the maximum dose of 5×10^{-4} gm the amplitude was 0.85 ± 0.16 cm and duration 5′48″ ± 33″. The relaxation effect was definately inhibited by the addition of epinephrine and dopamine (Fig. 5D).

The relaxant effect of aminophylline (5×10^{-6}–5×10^{-4} gm) (9.75×10^{-7}–9.75×10^{-5} M/lt) and pentoxiphylline (5×10^{-6}–5×10^{-4} gm) (1.48×10^{-6}–1.48×10^{-4} M/lt) with respect to amplitude was inferior only that of papaverine ($n = 7$).

Moreover, like papaverine, their action was totally inhibited by the administration of epinephrine or of dopamine. At the maximum dose of 5×10^{-4} gm, the amplitude and duration values were respectively 3.02 ± 0.67 cm and 4′31″ ± 28″ for aminophylline and 2.01 ± 0.15 cm and 3′18″ ± 7″ for pentoxiphylline (Fig. 6A, B).

Nitroglycerin (5×10^{-6}–5×10^{-4} gm) (1.81×10^{-6}–1.81×10^{-4} M/lt) ($n = 5$) caused a modest relaxation with regards to the amplitude but there was relevant relaxation with respect to the duration (Figs. 2, 3). At the maximum dose of 5×10^{-4} gm the amplitude was 1.03 ± 0.05 cm and the duration was 9′1″ ± 19″ (Fig. 6C).

Ergotamine ($n = 4$), isoxsuprine ($n = 4$) and tolazoline ($n = 4$) provoked only modest relaxation of the cavernous tissue (Fig. 6D–F). Administration of carbachol, histamine, 5-hydroxytriptamine and atropine did not provoke any change in the contractile state of the cavernous tissue.

Discussion

Experimental studies [9, 10] and studies on human volunteers [15] have demonstrated that erection is caused by an increase in the arterial flow, a decrease in the venous flow and the relaxation of the sinusoidal spaces. By increasing our knowledge of the hemodynamic aspects involved, and with the possibility to cause an erection with the intracavernous administration of papaverine and other pharmaceu-

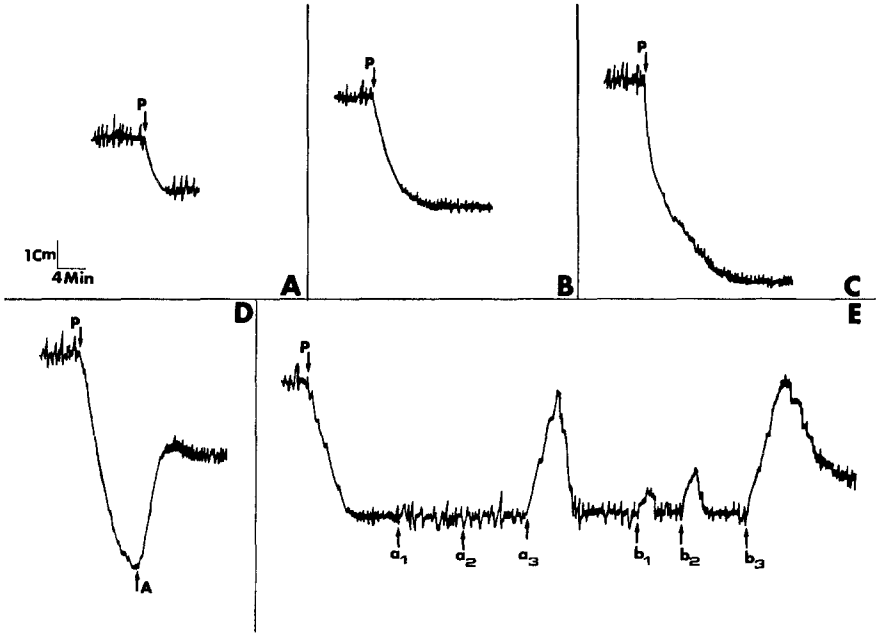

Fig. 4A–E. Relaxant effect of papaverine in isolated preparations of human corpus cavernosum. A (5×10^{-6} gm), B (5×10^{-5} gm) C (5×10^{-4} gm). D Effect of epinephrine (5×10^{-4} gm) on papaverine (5×10^{-4} gm) relaxed preparation. E Effect of KCl ($a_1 - 3 \times 10^{-5}$ gm; $a_2 - 3 \times 10^{-4}$ gm; $a_3 - 3 \times 10^{-3}$ gm) and dopamine ($b_1 - 5 \times 10^{-6}$ gm; $b_2 - 5 \times 10^{-5}$ gm; $b_3 - 5 \times 10^{-4}$ gm) on papaverine (5×10^{-5} gm) – relaxed preparation

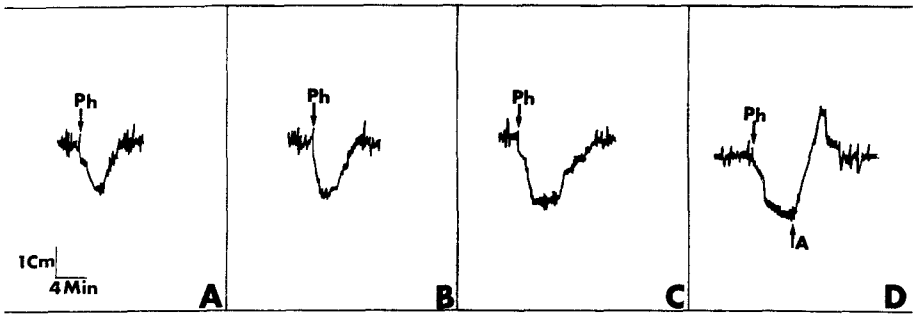

Fig. 5A–D. Relaxant effect of phentolamine in isolated preparations of human corpus cavernosum. A (5×10^{-6} gm), B (5×10^{-5} gm), C (5×10^{-4} gm). D Effect of epinephrine (5×10^{-5} gm) on phentolamine (5×10^{-4} gm)

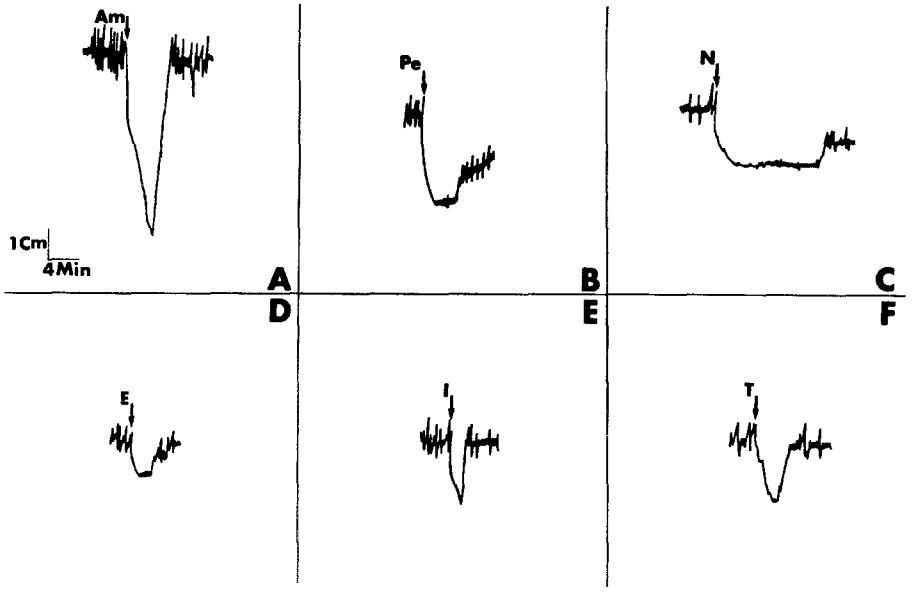

Fig. 6A–F. Relaxant effect induced by 5×10^{-4} gm of: aminophylline (A), pentoxiphylline (B), nitroglycerin (C), ergotamine (D), isoxsuprine (E), and tolazoline (F)

tical agents, it is possible to hypothesize a rapid change in the diagnosis [6] and the treatment of impotence [5, 12–14, 16].

The comparative study of the action of several drugs having a relexant effect on fragments of isolated human erectile tissue in vitro led to several conclusions Papaverine, at equal doses, was shown to be the substance able to cause the biggest relaxant effect with respect to both duration and amplitude. No other drug which we used was able totally to inhibit the action of this drug. This agreed with clinical experience where the appearance of priapism represents the most important limitation to the use of this drug [7, 11]. However, the α-blocking substances, whose action is definitely inhibited by drugs like epinephrine and dopamine, did not show an intensity equal to that of papaverine with regards to the relaxant effect.

The data obtained in the study of nitro – and theophylline derivatives were particularly interesting for an eventual application in clinical use. The relaxant effect of nitroglycerin and theophylline derivatives was shown to be superior to that of phentolamine. The more powerful relaxant effect of nitroglycerin was particularly manifested by greater amplitude and longer duration; whereas theophylline derivatives are more effective than phentolamine only with respect to amplitude. At present the intracavernous administration of papaverine in combination with phentolamine is preferred in the treatment of erectile dysfunction. [12, 16] but according to our results, nitroglycerin and theophylline derivatives might have a significant role in clinical practice in combination with papaverine.

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