British Journal of Pharmacology (1998) 124, 788–794
http://www.stockton-press.co.uk/bjp

Neurogenic contraction and relaxation of human penile deep dorsal vein

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1 The aim of the present study was to characterize neurogenic and pharmacological responses of human penile deep dorsal vein and to determine whether the responses are mediated by nitric oxide from neural or endothelial origin.

2 Ring segments of human penile deep dorsal vein were obtained from 22 multiorgan donors during procurement of organs for transplantation. The rings were suspended in organ bath chambers for isometric recording of tension. We then studied the contractile and relaxant responses to electrical field stimulation and to vasoactive agents.

3 Electrical field stimulation (0.5–2 Hz) and noradrenaline (3×10^{-10}–3×10^{-5} M) caused frequency- and concentration-dependent contractions that were of greater magnitude in veins denuded of endothelium. The inhibitor of nitric oxide synthesis N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME, 10^{-4} M) increased the adrenergic responses only in rings with endothelium.

4 In preparations contracted with noradrenaline in the presence of guanethidine (10^{-6} M) and atropine (10^{-6} M), electrical stimulation induced frequency-dependent relaxations. This neurogenic relaxation was prevented by L-NAME, methylene blue (3×10^{-5} M) and tetrodotoxin (10^{-6} M), but was unaffected by removal of endothelium.

5 Acetylcholine (10^{-8}–3×10^{-5} M) and substance P (3×10^{-11}–3×10^{-7} M) induced endothelium-dependent relaxations. In contrast, sodium nitroprusside (10^{-9}–3×10^{-5} M) and papaverine (10^{-8}–3×10^{-5} M) caused endothelium-independent relaxations.

6 The results provide functional evidence that the human penile deep dorsal vein is an active component of the penile vascular resistance through the release of nitric oxide from both neural and endothelial origin. Dysfunction in any of these sources of nitric oxide should be considered in some forms of impotence.

Keywords: Penile veins; neurogenic stimulation; nitric oxide; noradrenaline; acetylcholine; substance P

Introduction

The venous drainage from the two corpora cavernosa is primarily through the deep dorsal vein (Tudoriu & Bourmer, 1983; Breza *et al*., 1989; Lue, 1992). Relaxation of the arterioles and arteries, increases intracorporeal pressure and reduction of the venous outflow are key factors in the process of penile erection (Lue *et al*., 1983; Lue & Tanagho, 1987). It is generally accepted that reduction of venous outflow is mainly due to a passive mechanism resulting from compression of the subalbugineal venular plexus by engorgement of lacunar spaces (Fournier *et al*., 1987; Wespes & Schulman, 1993; Andersson & Wagner, 1995). With regard to penile arteries, it has been shown that relaxation of bovine (Liu *et al*., 1991), horse (Simonsen *et al*., 1995), dog (Hayashida *et al*., 1996) and human small (Simonsen *et al*., 1997) penile arteries induced by nonadrenergic, noncholinergic nerve stimulation is mainly due to nitric oxide or a nitric oxide-like substance released from perivascular nerve endings. Consistent with these functional observations, immunocytochemical studies have shown the presence of nitric oxide synthase in penile arteries of rat (Burnett *et al*., 1992), horse (Simonsen *et al*., 1995) and man (Burnett *et al*., 1993). The neurogenic relaxation observed in endothelium-denuded corpus cavernosum strips strongly suggests that a nitric oxide-like factor is also released by the penile autonomic nerves (Ignarro *et al*., 1990; Kim *et al*., 1991). These findings imply not only that nitric oxide may be the major mediator of erection but also that some varieties of impotence may result from a dysfunction in the nitric oxide synthase containing neurones.

Characterization of neurogenic responses of human penile veins remains largely unexplored. In human penile circumflex veins, no evidence for a functional nonadrenergic, noncholinergic relaxation is found in response to neurogenic stimulation (Kirkeby *et al*., 1993). This result appears to be in contrast with recent findings showing the presence of neural and endothelial nitric oxide synthase in the rat penile arteries and veins (Dail *et al*., 1995), thus supporting the possibility that the smooth muscle tone of penile veins may also be regulated by nitric oxide synthase vasodilator nerve fibres and by nitric oxide released from their endothelial lining. It is conceivable that the source of nitric oxide, endothelium -or nerve- derived, would be different whether contraction or relaxation of smooth muscle takes place. This issue may be critical in penile veins because of the marked neurogenic changes in diameter size and blood flow which occur during penile erection and detumescence (Andersson *et al*., 1984). The aim of the present investigation was to characterize neurogenic and pharmacological responses of human penile deep dorsal vein and to determine whether the responses are mediated by nitric oxide from neural or endothelial origin.

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Methods

Collection of penile deep dorsal vein

Human penile deep dorsal veins were obtained from 22 multiorgan donors during procurement of organs for transplantation (age range: 17–71 years). The study was approved by the ethical committee of our institution. The veins were immediately placed in chilled Krebs-Henseleit solution, and rings 3 mm long were cut under a dissecting microscope.

Organ-bath experiments

Two stainless steel L shaped pins 100 μm in diameter were introduced through the lumen of the ring. One pin was fixed to the wall of the organ bath, while the other was connected to a force-displacement transducer (Grass FT03). Changes in isometric force were recorded on a Grass polygraph (model 7). Each vein ring was set up in a 4 ml bath containing modified Krebs-Henseleit solution of the following composition in mM: NaCl 115, KCl 4.6, $MgCl_2$ $6H_2O$ 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25, glucose 11.1 and disodium EDTA 0.01. The solution was equilibrated with 95% O_2 and 5% CO_2 to give a pH of 7.3–7.4. Temperature was held at 37°C. In approximately 50% of the venous rings the endothelium was removed mechanically by inserting a roughened stainless steel wire into the lumen and gently rubbing the ring on a wet filter paper. This procedure has been shown morphologically to result in essentially complete removal of the endothelium (Martínez *et al*., 1994; 1995). Functional integrity of the endothelium was confirmed routinely by the presence of relaxation induced by acetylcholine (10^{-7}–10^{-6} M) or substance P (10^{-9}–10^{-8} M) during contraction obtained with noradrenaline (10^{-7}–3×10^{-7} M).

To establish the resting tension for maximal force development, a series of preliminary experiments were performed on rings of similar length and outer diameter which were exposed repeatedly to 100 mM KCl. Basal tension was increased gradually until contractions were maximal. The optimal resting tension was 30 mN. The venous rings were allowed to attain a steady level of tension during a 2–3 h accommodation period before testing.

Electrical field stimulation was provided by a Grass S88 stimulator (Grass Instruments, Quincy, U.S.A.) via two platinum electrodes positioned on each side and parallel to the axis of the venous ring. To assess the nature of the contractile responses and avoid direct stimulation of smooth muscle, frequency-response relationships were determined on a group of veins in the presence and absence of 10^{-6} M tetrodotoxin, following procedures previously described (Aldasoro *et al*., 1993; Martínez *et al*., 1994; 1995). In summary, the protocol was designed to find the optimal stimulation parameters causing a contractile response that was completely eliminated by 10^{-6} M tetrodotoxin. In another series of experiments neurogenic stimulation was performed in ring segments contracted with noradrenaline (10^{-7} M) in the presence of atropine (10^{-6} M) and guanethidine (10^{-6} M) to reveal nonadrenergic, noncholinergic neurogenic relaxation. Stimulation was conducted at 15 V for 15 s at frequencies of 0.5, 1 and 2 Hz. A pulse width of 0.2 ms was used. A period of 10–15 min was allowed between stimulations.

To study the effects of experimental substances on electrical field stimulation-induced responses, we performed the following protocol: after an initial set of stimulations another set of stimulations was given in the presence or absence of either N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME, 10^{-4} M), L-NAME (10^{-4} M) plus L-arginine (3×10^{-4} M), L-NAME (10^{-4} M) plus D-arginine (3×10^{-4} M), tetrodotoxin (10^{-6} M), or methylene blue (3×10^{-5} M). As a control, two or three consecutive sets of stimulations were given to a group of untreated rings at identical intervals. Less than 10% variability in the magnitude of electrical field stimulation-induced contractions was observed for a given ring during three consecutive sets of control stimulations. Antagonists were added to the organ bath chambers 10–20 min before the initiation of a frequency- or concentration-response relationship.

Concentration-response curves for noradrenaline (3×10^{-10}–3×10^{-5} M) were determined in the absence and presence of L-NAME from separate vein preparations with and without endothelium. To study drug-induced relaxation, rings were contracted with 10^{-7}–3×10^{-7} M noradrenaline. After a stable contraction was obtained, concentration-response curves were determined for acetylcholine (10^{-8}–3×10^{-5} M), substance P (3×10^{-11}–3×10^{-7} M), papaverine (10^{-8}–3×10^{-5} M) and sodium nitroprusside (10^{-9}–3×10^{-5} M).

Drugs and chemicals

The following drugs were used: acetylcholine chloride, noradrenaline hydrochloride, tetrodotoxin, guanethidine sulphate, atropine sulphate, N^G-nitro-L-arginine methyl ester hydrochloride, L-arginine hydrochloride, D-arginine hydrochloride, methylene blue, substance P, sodium nitroprusside dihydrate, papaverine hydrochloride and prazosin hydrochloride (Sigma Chemical Co, St. Louis, MO). Drugs were prepared and diluted in distilled water. Stock solutions of the drugs were freshly prepared every day.

Data analysis

All values are expressed as means ± s.e.mean. Contractions are presented as a percentage of response to KCl (100 mM). EC_{50} values (concentrations of noradrenaline producing half-maximal contraction) were determined from individual concentration-response curves by non-linear regression analysis, and from these values the geometric means were calculated. The EC_{50} values were compared by an unpaired t test. Relaxations are expressed as a percentage of the noradrenaline (3×10^{-7} M; EC_{50})-induced contraction. The number of rings taken from each patient varied from eight to sixteen. Concentration-response curves of the tested agonists or frequency-response relationships were performed in rings with or without endothelium obtained from the same patient; the responses obtained in each patient were averaged to yield a single value. Therefore, all n values are presented as the number of individuals from whom the venous rings were obtained. For electrical stimulation experiments, in which the same veins were stimulated in the absence and presence of antagonists, a paired t test was used. Statistical significance was accepted at $P<0.05$.

Results

Neurogenic contraction

Electrical field stimulation of the dorsal vein elicited frequency-dependent increases in tension which were abolished by tetrodotoxin, guanethidine and prazosin (all at 10^{-6} M)

(Figure 1a), thus indicating that increases in tension were associated with the release of noradrenaline from periarterial adrenergic nerves acting on α_1-adrenoceptors.

The electrical field stimulation-induced contractions were of greater magnitude in veins denuded of endothelium (Figure 1b). L-NAME (10^{-4} M) significantly potentiated the response to electrical field stimulation in venous rings with endothelium (Figure 1b). This potentiation was significantly reduced by L-arginine (3×10^{-4} M), but not by D-arginine (3×10^{-4} M). The presence of L-NAME did not influence contractile responses of endothelium-denuded veins (Figure 1b). The contractile response to 100 mM KCl was similar in intact and denuded vessels (38.6 ± 1.9 mN versus 34.0 ± 3.6 mN; $P>0.05$; $n=12$).

Neurogenic relaxation

Nonadrenergic, noncholinergic frequency-dependent neurogenic relaxations were obtained in venous rings contracted with noradrenaline ($10^{-7}-3\times10^{-7}$ M) and treated with guanethidine (10^{-6} M) (to inhibit adrenergic neurotransmission) and atropine (10^{-6} M) (to block muscarinic receptors) (Figure 2a). No significant differences were observed in the mean values of electrical stimulation-induced relaxations between veins with and without endothelium. As shown by the summarized data in Figure 2a, pretreatment with L-NAME (10^{-4} M), practically abolished relaxations in rings with or without endothelium. L-Arginine (3×10^{-4} M), but not equimolar amounts of D-arginine, significantly reversed the inhibitory effects of L-NAME on neurogenic responses. The neurogenic relaxation was greatly reduced ($P<0.05$) by tetrodotoxin (10^{-6} M) or methylene blue (3×10^{-5} M) (Figure 2b).

Effects of noradrenaline

Noradrenaline produced concentration-dependent contractions of the venous rings in all cases (Figure 3). Treatment with L-NAME (10^{-4} M) induced a parallel leftward shift (about 2.3 fold) ($P<0.05$) of the response to noradrenaline in veins with endothelium; this potentiation was completely reversed by L-arginine (3×10^{-4} M) (Figure 3a). L-NAME did not modify significantly ($P>0.05$) the concentration-response curve to noradrenaline in veins without endothelium (Figure

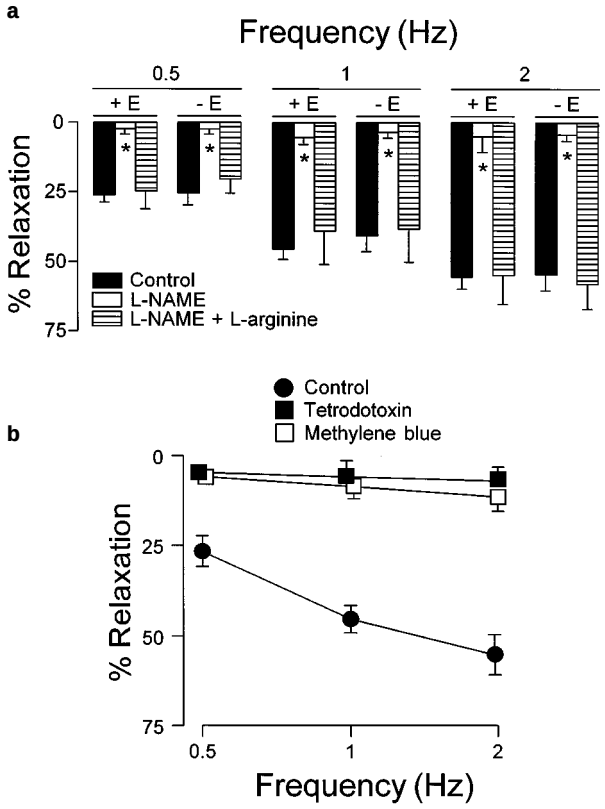

Figure 2 (a) Relaxations to electrical field stimulation in vein rings with (+E) ($n=7$) and without (−E) ($n=7$) endothelium in control conditions and in the presence of L-NAME (10^{-4} M) or L-NAME plus L-arginine (3×10^{-4} M). (b) Relaxation to electrical field stimulation before and after treatment with tetrodotoxin (10^{-6} M; $n=5$) or methylene blue (3×10^{-5} M; $n=5$). Before stimulation all venous rings were contracted with noradrenaline in the presence of guanethidine and atropine. Values are means±s.e.mean. *$P<0.05$ compared with controls.

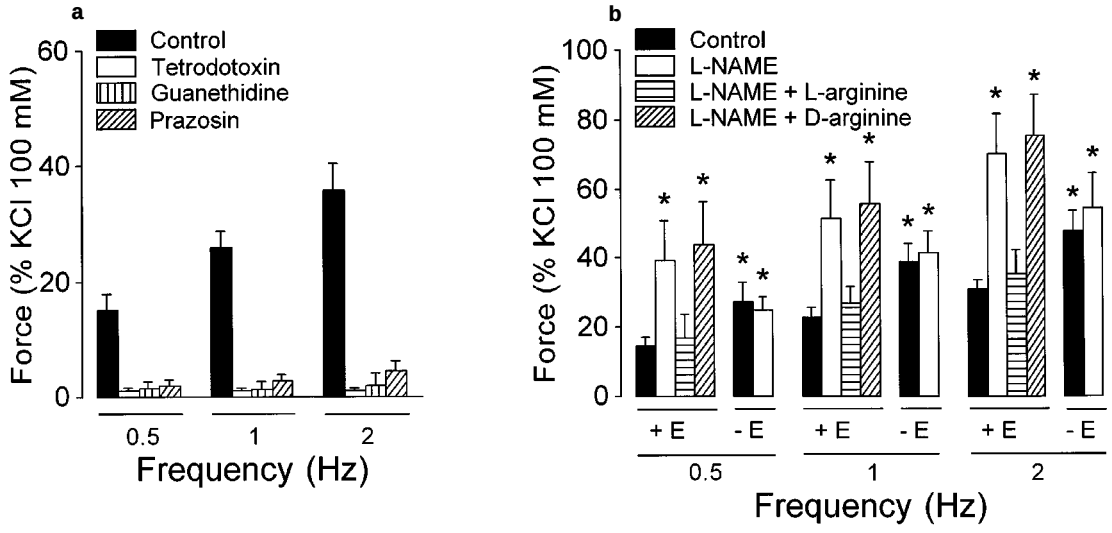

Figure 1 (a) Contractile effects of electrical field stimulation on human deep dorsal vein in the absence (control, $n=7$) and in the presence of tetrodotoxin (10^{-6} M, $n=4$), guanethidine (10^{-6} M, $n=5$) and prazosin (10^{-6} M, $n=6$). (b) Contractile effects of electrical field stimulation in venous rings with (+E) ($n=7$) and without (−E) ($n=6$) endothelium in control conditions and in the presence of L-NAME (10^{-4} M) or L-NAME plus L-arginine (3×10^{-4} M) or D-arginine (3×10^{-4} M). Values are means±s.e.mean. *$P<0.05$, compared with control rings with endothelium.

3b). Table 1 summarizes the geometric mean EC_{50} and maximal contraction values for noradrenaline determined in the absence and in the presence of L-NAME in venous rings with and without endothelium.

Effects of acetylcholine, substance P, sodium nitroprusside and papaverine

The effects of these substances were studied in venous rings previously contracted with noradrenaline (10^{-7} to 3×10^{-7} M). Under these conditions acetylcholine and substance P induced concentration-dependent relaxations in rings with endothelium (Figure 4). Rings without endothelium did not respond to acetylcholine and substance P but did relax in response to sodium nitroprusside and papaverine, indicating that the ability of the vessels to relax was retained. Inhibition of nitric oxide synthase with L-NAME (10^{-4} M) in venous rings with endothelium nearly abolished relaxation in response to acetylcholine and substance P.

Discussion

The present study describes the responses of human penile deep dorsal vein to neurogenic stimulation. We were able to get stable results from veins taken immediately after death and adrenergic constriction as well as nonadrenergic, noncholinergic relaxation was consistently obtained in vein segments from the same donor patient. The neurogenic and pharmacological responses of these veins, which are the main venous drainage from the corpora cavernosa, may represent an active component of the penile vascular bed in the process of erection and detumescence.

The neurogenic contraction observed in the present study is more than 30% (at 2 Hz) of the maximal contraction to KCl. This response is higher than the maximal neural-mediated contraction in human pulmonary (20 ± 3.6% of KCl), mesenteric (7.7 ± 2.0% of KCl) and deferential (10.6 ± 2.7% of KCl) arteries removed at surgery using the same experimental setup (Aldasoro *et al*., 1993; Martínez *et al*.,

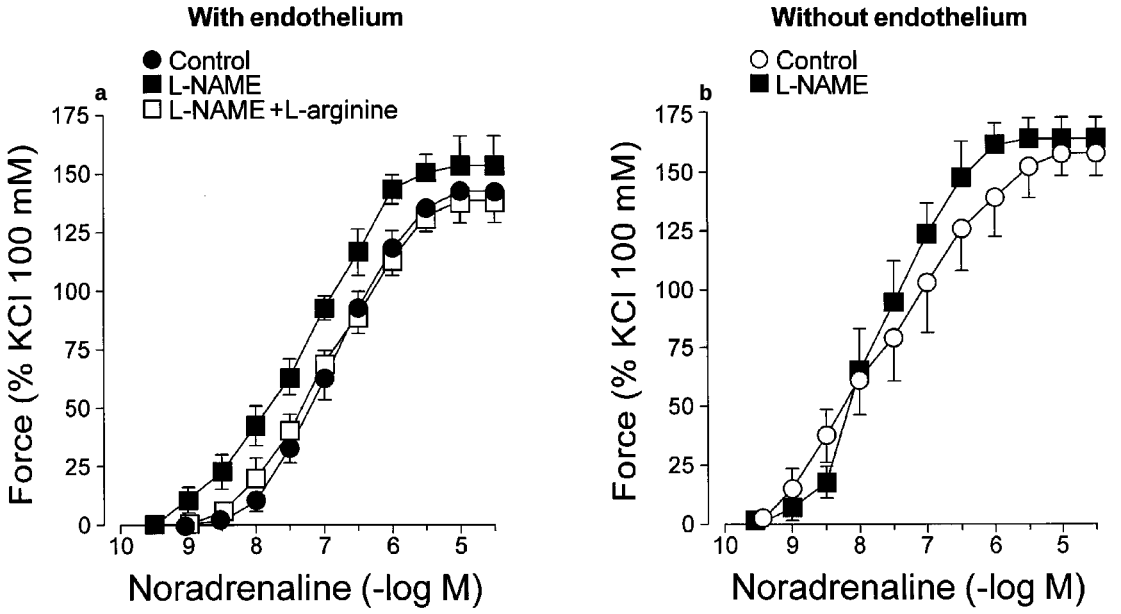

Figure 3 (a) Concentration-response curves for noradrenaline in venous rings with endothelium ($n=7$) and in the presence of L-NAME (10^{-4} M; $n=5$) or L-NAME plus L-arginine (3×10^{-4} M; $n=5$). (b) Concentration-response curves for noradrenaline in venous rings without endothelium in the absence ($n=6$) and in the presence of L-NAME (10^{-4} M; $n=4$). Values are means and vertical lines show s.e.mean.

Table 1 EC_{50} values and maximal responses (E_{max}) to noradrenaline

	EC_{50} (M) (95% confidence interval)	E_{max} (%)
With endothelium		
Control ($n=7$)	1.3×10^{-7} ($0.9-2.0\times10^{-7}$)	142 ± 10
L-NAME 10^{-4} M ($n=5$)	5.7×10^{-8}* ($4.0-8.3\times10^{-8}$)	154 ± 12
L-NAME 10^{-4} M + L-arginine 3×10^{-4} ($n=5$)	1.1×10^{-7} ($0.5-1.3\times10^{-7}$)	139 ± 11
Without endothelium		
Control ($n=6$)	3.1×10^{-8}* ($1.4-7.1\times10^{-8}$)	158 ± 9
L-NAME 10^{-4} M ($n=5$)	2.0×10^{-8}* ($0.7-5.7\times10^{-8}$)	164 ± 9

Maximal contractions are expressed as a percentage of response to 100 mM KCl. *$P<0.05$ compared with control rings with endothelium.

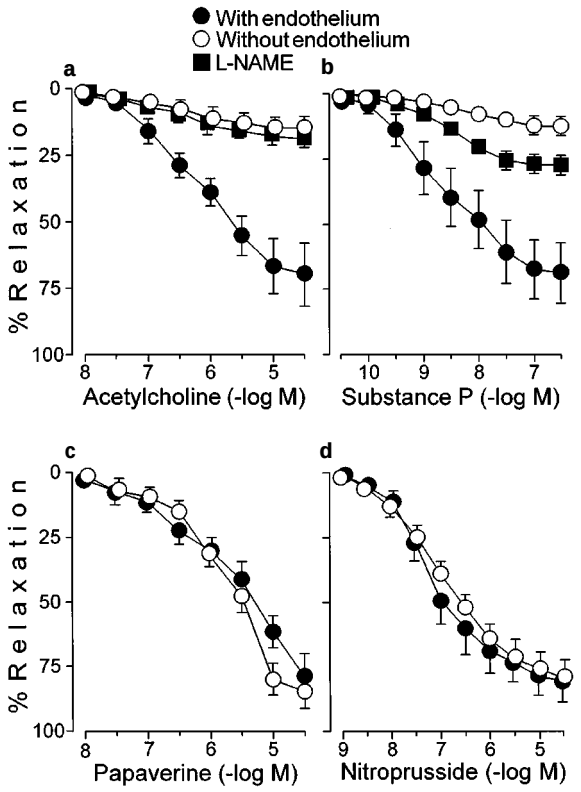

Figure 4 Concentration-response curves for (a) acetylcholine ($n=5$), (b) substance P ($n=5$), (c) papaverine ($n=5$) and (d) sodium nitroprusside ($n=5$) in venous rings with and without endothelium and in the presence of L-NAME (with endothelium; 10^{-4} M; $n=5$). Values are means and vertical lines show s.e.mean.

1994; 1995). The resulting neurogenic contraction is apparently mediated, to a great extent, by the release of the adrenergic transmitter which in turn activates the α_1-adrenoceptors. The evidence for this is that the response is inhibited by guanethidine, a sympathetic neurone blocker, tetrodotoxin, a neuronal sodium channel blocker, or prazosin, an α_1-adrenoceptor antagonist.

The integrity of the endothelium is a widely accepted factor in the regulation of the circulation and it may be of pathophysiological significance in several disease states (Moncada *et al*., 1991). Our present experiments showed that removal of the endothelium significantly enhanced the contractile responses to electrical field stimulation and increased the sensitivity to noradrenaline. This can be attributed to inhibition by endothelium removal of the depressant influence of relaxant factors to oppose the adrenergic vasoconstriction mediated by α-adrenoceptors of smooth muscle.

Nitric oxide (or substance containing nitric oxide) accounts for the powerful vasodilator effects of endothelium-derived relaxing factor (Palmer *et al*., 1987; Moncada *et al*., 1988). Nitric oxide induces vasorelaxation by activating soluble guanylate cyclase and, as a result, increasing the level of 3′:5′-cyclic guanosine monophosphate (cyclic GMP) within vascular smooth muscle (Ignarro *et al*., 1981). The formation of nitric oxide from L-arginine by nitric oxide synthase can be blocked by some analogues of L-arginine such as L-NAME (Rees *et al*., 1990). The existence of such a mechanism in human deep dorsal vein has not been established previously. The results showed that treatment with L-NAME potentiated the responses to field electrical stimulation and noradrenaline in veins with endothelium. In contrast, L-NAME did not affect the contractile responses of endothelium denuded veins. The effects of L-NAME on contractions induced by electrical field stimulation and noradrenaline were reversed by L-arginine (the precursor of nitric oxide production) but not by its inactive isomer D-arginine. The results indicate that nitric oxide released from endothelial cells is responsible for the depressant influence of endothelium on the contractile responses to adrenergic stimulation. Thus our experiments show that human isolated penile deep dorsal vein always responds with contraction when adrenergic stimulation is performed under conditions that allow normal behavior of neurotransmission (without adrenergic and cholinergic blockade). Nitric oxide or a nitric oxide-like substance of endothelial origin, derived from L-arginine, attenuates vasoconstriction whether neurally induced or evoked by exogenous noradrenaline.

The relaxation observed in response to neurogenic stimulation after inhibition of adrenergic and cholinergic neurotransmission and the effective blockade of the relaxation by tetrodotoxin provide the first evidence for a nonadrenergic, noncholinergic neurogenic relaxation in human penile deep dorsal vein. The relaxation appears to be endothelium-independent because mechanical removal of the endothelial layer did not modify the response to neurogenic stimulation. Moreover, the relaxation was markedly reduced by L-NAME and this inhibition was reversed by L-arginine, but not by D-arginine. Taken together the results suggest that nitric oxide (or an intermediate substance) is the nonadrenergic, noncholinergic neurotransmitter released from autonomic nerves. Localization of nitric oxide synthase-containing nerves in the adventitia of penile arteries (Burnett *et al*., 1992; 1993) and penile veins (Dail *et al*., 1995) strongly suggests that nitric oxide is directly released by vasodilator nerves. The marked reduction of neurogenic relaxation observed in our experiments by methylene blue, an inhibitor of guanylate cyclase, suggests that the relaxing response is mediated through an increase in cyclic GMP in vascular smooth muscle. However, this conclusion should be interpreted cautiously since methylene blue also generates superoxide anions (Marshall *et al*., 1988; Wolin *et al*., 1990) and directly inhibits nitric oxide synthase (Mayer *et al*., 1993). We cannot at this point rule out the presence of other inhibitory neurotransmitters such as vasoactive intestinal polypeptide and calcitonin-gene-related peptide that have been proposed as mediators of penile dilatation (Andersson *et al*., 1984; Stief *et al*., 1991).

It is perhaps unexpected that L-NAME did not enhance contractions to field stimulation in endothelium-denuded veins, since neurogenic stimulation would release both motor (noradrenaline) and inhibitor (nitric oxide) transmitters. One possible explanation for this finding is that endothelium-derived nitric oxide could be the main inhibitory factor involved when neurogenic venoconstriction takes place. Apparently the release of nitric oxide from autonomic nerves in quiescent preparations without blockade of adrenergic neurotransmission is too small to attenuate the powerful adrenergic contraction. However, when blockade is present and the veins are contracted, nitric oxide from autonomic nerves is responsible for the nonadrenergic, noncholinergic neurogenic relaxation.

Previous findings suggest that there is no nonadrenergic, noncholinergic neurogenic response in human penile circumflex veins, thus suggesting the lack of an active neurogenic relaxation in these particular veins (Kirkeby *et al*., 1993). However, according to the present results, the neurogenic relaxation found in the deep dorsal vein is similar to that observed in bovine (Liu *et al*., 1991), horse (Simonsen *et al*., 1995), dog (Hayashida *et al*., 1996) and human small

(Simonsen *et al*., 1997) penile arteries. The reason for this discrepancy is not readily apparent. However, important regional variations in the pattern of innervation that have been noted in rat penile veins of different sizes (Dail *et al*., 1995) may account for the different vascular responses. The abundant distribution of nitric oxide synthase fibres in the deep dorsal vein, described in the rat, is consistent with the marked neurogenic relaxation found in the present study. In contrast, the scarcity of nitric oxide synthase in smaller penile veins (Dail *et al*., 1995) suggests that a passive compression by engorgement of cavernous spaces, rather than active neurogenic mechanisms is responsible for variations of venous outflow (Kirkeby *et al*., 1993).

We studied the response of veins to acetylcholine and substance P, two agents that cause endothelium-mediated vasodilator responses (Furchgott, 1983; Luscher *et al*., 1987). The effects of acetylcholine and substance P were compared with sodium nitroprusside and papaverine, two substances that have been used in the treatment of erectile dysfunction. Sodium nitroprusside relaxes smooth muscle by releasing nitric oxide within smooth muscle cells (Ignarro *et al*., 1981), whereas papaverine induces relaxation mainly by increases in cyclic AMP and cyclic GMP (Rüegg, 1992). We observed that the relaxation induced by acetylcholine and substance P was significantly decreased in vessels without endothelium, whereas dilatation in response to sodium nitroprusside and papaverine was similar in control and endothelium-denuded veins. The intervention of nitric oxide in endothelium-dependent dilatation in response to acetylcholine and substance P is indicated by the absence of relaxation in venous rings treated with the inhibitor of nitric oxide synthase L-NAME.

In conclusion, the present experiments indicate that neurogenic regulation of human deep dorsal vein is an active component in the control of venous outflow resistance. Our study provides functional evidence that nitric oxide from both neural and endothelial sources may modulate neurogenic responses. Nitric oxide derived from autonomic nerves is responsible for the nonadrenergic, noncholinergic relaxation, whereas nitric oxide from endothelial origin can actively modulate both sympathetic venoconstriction and the effects of pharmacological agents on the contractile state of venous smooth muscle. The results imply that some forms of erectile dysfunction may result not only from an impairment on the nitric oxide synthase-containing neuronal system but also from an injured endothelium. Endothelial deterioration of penile veins may increase the constrictor response to sympathetic stimulation or blunt the expected relaxant response to those vasoactive agents acting through the release of endothelial nitric oxide. A dysfunction in the peripheral efferent autonomic nerve fibres, the neuronal nitric oxide pathway, may impair the nonadrenergic, noncholinergic relaxation necessary for erection. Impairment of the L-arginine-nitric oxide pathway in penile veins should be taken into consideration in certain forms of impotence in which arterial reconstructive surgery or adequate pharmacotherapy often fails to correct impotence (Krane *et al*., 1989).

This work was supported by the Comisión Interministerial de Ciencia y Tecnología, Ministerio de Sanidad and Generalitat Valenciana.

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(Received February 3, 1998
Revised March 13, 1998
Accepted March 16, 1998)