α -Adrenoceptor-mediated Penile Erection in Dogs: *In vivo* and *in vitro* Observations

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Abstract

We have evaluated the role of adrenergic components in the pelvic splanchnic nerve on the erectile function in the dog. Electrical stimulation of pelvic splanchnic nerves increased blood flow in the internal pudendal artery and also elevated the cavernous pressure. These increases were blocked in part by phentolamine or methylene blue, but not by propranolol or atropine. The effects of cholinergic and adrenergic agonists and antagonists on mechanical responses were also examined in muscle strips obtained from various arteries in the intrapelvic region including the internal pudendal artery. Norepinephrine induced contraction in the iliac artery and relaxation in the internal pudendal artery, and both the contraction and relaxation responses were blocked by phentolamine but not by propranolol. These findings suggest that in the dog, α -adrenergic components projected through the pelvic splanchnic nerve may contribute to penile erection, together with cyclic GMP-mediated mechanisms.

Key words: Internal pudendal artery, Penile cavernous pressure, α -Adrenoceptors, Erectile function

Introduction

The mechanism of penile erection remains unclear, even though increased arterial flow with relaxation of the cavernous smooth muscle and restriction of the cavernous outflow are functionally important (Steers, 1990; Andersson, 1993). Vardi & Siroky (1990, 1993) demonstrated that stimulation of the pelvic splanchnic nerve (PSN) increased the arterial flow into the cavernosum, implying that sacral parasympathetic nerve excitation induces penile erection. However, PSN contains not only a parasympathetic component but also sympathetic and somatic components (Morita *et al.*, 1984; Kihara *et al.*, 1993). It is therefore reasonable to

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speculate that multiple factors are involved in the nervous control of penile erection.

The present *in vivo* and *in vitro* experiments were carried out to investigate the factors involved in the neural control of erection in the dog. The blood flow in the internal pudendal artery and the cavernous pressure were measured directly *in vivo*. Mechanical responses of arterial smooth muscle to norepinephrine and other antagonists were measured *in vitro* using isolated arteries from the intrapelvic region. The results indicated a possible role of α -adrenoceptors in the PSN stimulation-induced increases in the cavernous inflow in the dog.

Materials and Methods

Animals

Thirty male mongrel dogs, weighing between 16 and 20 kg, were used. All animals were treated ethically according to the rules of the Animal Use and Care Committee settled in The Tokyo Medical and Dental University. Anesthesia was induced with pentobarbital sodium, 30 mg/kg, i.v.. An endotracheal tube was placed to facilitate free ventilation with room air. The femoral vein was cannulated via a polyethylene catheter for hydration with lactate Ringer's solution at 125 ml/h. Anesthesia was maintained with additional doses of 15 mg/kg/h throughout the experiments via the femoral catheter. Systemic blood pressure was monitored via a polyethylene catheter placed in the internal carotid artery. Drainage of the urinary bladder was achieved by placement of a 16 Fr cystostomy tube.

Exposure of intrapelvic arteries and autonomic nerves

The abdomen was opened through the midline and the abdominal aorta and its branches extending to the intrapelvic arteries exposed as depicted in Figure 1. In addition, bilateral sympathetic nerve trunks under the caudal mesenteric nerves, the lumbar splanchnic nerves, the hypogastric nerves and the pelvic splanchnic nerves were exposed (Fig. 2).

Pelvic splanchnic nerve stimulation

A pair of electrodes were placed around the pelvic splanchnic nerve (PSN) bundles bilaterally at the proximal region of the junction with the hypogastric nerves (Fig. 2). PSN stimulation (unidirectional square wave stimulation, 2 ms duration, 8–16 V intensity, 10 Hz frequency) was delivered for approximately 25 s using an electric stimulator (SEN-3301, Nihon Kohden, Tokyo, Japan). These stimulus parameters were chosen because they produced reproducible responses during the experiments. The stimulus voltage was chosen so as to produce a submaximum response.

Arterial flow measurement

An appropriately sized blood flow probe (SP-2204, Nihon Kohden, Tokyo, Japan) was placed around the internal pudendal arteries bilaterally (Fig. 1) and connected to a blood flow meter (MFV-2100, Nihon Kohden, Tokyo, Japan). When blood flow in the internal pudendal artery was measured, the prostatic artery was tied to convert the internal pudendal artery into an end artery supplying the cavernosum penis. Blood flow in the internal iliac artery or

Fig. 1. Schematic representation of the intrapelvic arteries. CMA, caudal mesenteric artery; EIA, external iliac artery; MSA, median sacral artery; UA, umbilical artery; IIA, internal iliac artery; 7th LA, 7th lumbar artery; IPA, internal pudendal artery; ILA, iliolumbar artery; CrGA, cranial gluteal artery; CaGA, caudal gluteal artery; PA, prostatic artery. Arteries drawn in gray (CMA, EIA, IIA, IPA and GA) were used in *in vitro* experiments for measurement of muscle contraction.

Fig. 2. Schematic representation of the intrapelvic autonomic nerve branches. LSN, lumbar splanchnic nerve; ST, sympathetic trunk; HGN, hypogastric nerve; PSN, pelvic splanchnic nerve. Arrows show the areas where the nerve was cut and electrical stimulation applied on the distal side.

external iliac artery was also measured using blood flow probes.

Corpus cavernosum pressure measurement

Intracavernous pressure was measured with an 18-gauge needle placed directly into the

appropriate corporal space, and connected to a pressure transducer (P50, Statham, USA).

Muscle strip study

Helically cut strips of muscle, 2 mm wide and 10 mm long, were dissected from the abdominal aorta, the caudal mesenteric artery, the external iliac artery, the internal iliac artery, the proximal region of the internal pudendal artery, the distal region of the internal pudendal artery and the prostatic artery (see shaded regions, Fig. 1). The strips were mounted in a 3 ml chamber containing modified Krebs solution of the following composition (in mM): NaCl 133.6, KCl 4.7, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 1.9, $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 1.2 and glucose 8.3. The solution was aerated with 95% O_2 and 5% CO_2 at 37°C (pH = 7.4). One end of the muscle strip was connected with 4-0 silk thread and connected to the hook at the bottom of the chamber while the other end of the strip was connected to a force transducer (UC-2, Statham, USA) mounted on a movable slide assembly. Muscle strips were stretched to the length of optimum tension development and equilibrated for 60 min prior to the start of experiments. Resting tension at this length ranged from 90 to 110 mg, with a baseline tension of 100 mg maintained throughout the experiments. Functional data were expressed as grams of force change per cross-sectional area in mm^2 . The cross-sectional area was calculated as $\text{weight/length} \times 1.05$ (where 1.05 is the assumed density of the muscle).

Drugs

Carbamylcholine chloride (carbachol), norepinephrine hydrochloride, propranolol hydrochloride, phentolamine hydrochloride, atropine sulfate and methylene blue trihydrate (Sigma) were used.

Statistics

Statistical analysis on the data of *in vivo* experiments was evaluated using the Student's *t*-test to compare between measurements made both before and after stimulation of the pelvic splanchnic nerve or of drug administration. Statistical analysis on the data in muscle strip experiments was performed using a non-paired *t*-test of the absolute (raw) value measurements. Probabilities less than 5% ($P < 0.05$) were considered significant.

Results

Measurements of blood flow in the internal pudendal artery and of cavernous pressure

Neurotomy of sympathetic trunks, lumbar splanchnic nerves or hypogastric nerves affected neither the blood flow in the internal pudendal artery nor the systemic blood pressure. Neurotomy of one side of the pelvic splanchnic nerves (PSN) decreased the blood flow of the internal pudendal artery on the ipsilateral side, with associated increase in the flow of the contralateral internal pudendal artery. Bilateral neurotomy of the PSN caused a bilateral decrease in the blood flow of the internal pudendal arteries.

When one of the PSN was stimulated distally, the flow of the internal pudendal artery increased immediately on both sides followed by an increase in the cavernous pressure on both

Fig. 3. Representative tracings of cavernous pressure (CP, upper trace) and the flow of the internal pudendal artery (IPA flow, lower trace) elicited by electrical stimulation of the right pelvic splanchnic nerve (rt PSN stimulation), measured on the right (rt) and left (lt) sides.

Table 1. The flow of the internal pudendal artery (IPA) and the cavernous pressure (CP) measured on the right (rt) and left (lt) sides, before and during electrical stimulation of the right pelvic splanchnic nerve (PSN). The flow (ml/min) and pressure (mmHg) are expressed as the mean $\pm$ s.e.m. ($n=8$ dogs).

	rt IPA flow (ml/min)	rt CP (mmHg)	lt IPA flow (ml/min)	lt CP (mmHg)
before PSN stimulation	15.4 $\pm$ 3.2	2.4 $\pm$ 0.2	15.4 $\pm$ 2.6	2.2 $\pm$ 0.1
rt PSN stimulation	48.3 $\pm$ 10.8	22.5 $\pm$ 6.3	22.0 $\pm$ 8.2	12.0 $\pm$ 4.2

sides approximately 10 s after initiation of PSN stimulation. The increases in the flow of the internal pudendal artery and of the cavernous pressure were approximately two times greater on the ipsilateral side than on the contralateral side (Fig. 3, Table 1). PSN stimulation did not significantly alter the systemic blood pressure or the flows of the internal and external iliac arteries. The increases in the flow of the internal pudendal artery and of the cavernous pressure induced by PSN stimulation were not altered by cutting either the sympathetic trunks, the lumbar splanchnic nerves or the hypogastric nerves. Intravenous administration of 0.1 mg/kg phentolamine 2 min before nerve stimulation significantly reduced the PSN stimulation-induced increases in the flow of the internal pudendal artery by 50–80% and the increases in the cavernous pressure by 10–70% (Fig. 4, Table 2). Methylene blue (0.2 mg/kg) injected into the abdominal aorta also reduced the PSN stimulation-induced increase in the flow of the internal pudendal artery and of the cavernous pressure by approximately 30%. Systemic blood pressure was not altered by injection of 0.1 mg/kg phentolamine or 0.2 mg/kg methylene blue. The increases in the flow of the internal pudendal artery and of the cavernous pressure elicited by stimulation of the PSN were not altered by i.v. administration of 0.05 mg/kg atropine or 0.1 mg/kg propranolol.

Fig. 4. Effects of phentolamine on the right cavernous pressure (rt CP, upper trace) and the flow of the right internal pudendal artery (rt IPA flow, lower trace) evoked by stimulation of the right pelvic splanchnic nerves (rt PSN stimulation). Phentolamine 0.1 mg/kg, i.v. was applied at the arrow.

Table 2. Effects of intravenous administration of 0.1 mg/kg phentolamine on the flow of the right internal pudendal artery (IPA) and on the right cavernous pressure (CP) evoked by electrical stimulation of the right pelvic splanchnic nerves (PSN). The nerves were stimulated 120 s after i.v. administration of phentolamine, and the flow (ml/min) and pressure (mmHg) were expressed as the mean $\pm$ s.e.m ($n=6$ dogs).

	rt PSN stimulation before administration of phentolamine	rt PSN stimulation 120 sec after administration of phentolamine
rt IPA flow	52.6 $\pm$ 8.2 ml/min	24.4 $\pm$ 5.1 ml/min
rt CP	21.8 $\pm$ 4.2 mmHg	12.0 $\pm$ 4.1 mmHg

Muscle strips

Carbachol (10^{-6} – 10^{-4} M) did not produce any detectable mechanical response in the arterial muscle strips isolated from any region. Norepinephrine (10^{-6} – 10^{-4} M) elicited contraction or relaxation of the muscle, depending on the origin of the artery. Figure 5 shows the distribution of the responses of arterial muscle to norepinephrine in peripheral arteries of the dog. Norepinephrine produced relaxation in the proximal and distal regions of the internal pudendal artery and to a lesser extent in the prostatic artery. Contractions were elicited by norepinephrine in the internal and external iliac arteries and in the caudal mesenteric artery. The contractions in muscle strips from the caudal mesenteric and internal iliac arteries were significantly smaller than those in strips from the external iliac artery.

In the proximal and distal internal pudendal arteries, the relaxation produced by norepinephrine was antagonized by phentolamine, but not by propranolol (Fig. 6). The contractions of

Fig. 5. Schematic representation of the intrapelvic arteries, in which the responses of the arterial muscle strips (gray regions) to 10^{-4} M norepinephrine are shown by arrows (upward arrow, contraction; downward arrow, relaxation). Muscle responses are represented as force (mg) per cross-sectional area (mm²) of muscle with the mean $\pm$ s.e.m. (n=6-8). CMA, caudal mesenteric artery; EIA, external iliac artery; IIA, internal iliac artery; Prox-IPA, proximal region of internal pudendal artery; DisIPA, distal region of internal pudendal artery; PA, prostatic artery.

Fig. 6. Norepinephrine-induced relaxation and its inhibition by phentolamine but not by propranolol in arterial muscle strips of the proximal (Prox) and distal (Dis) internal pudendal arteries (IPA). Carbachol, norepinephrine, propranolol (10^{-5} M) and phentolamine (10^{-5} M) were added cumulatively.

the internal and external iliac arterial smooth muscle produced by norepinephrine were again antagonized by phentolamine but not by propranolol (Fig. 7).

Fig. 7. Mechanical responses produced by cumulative application of carbachol, norepinephrine, propranolol and phentolamine in muscle strips obtained from the internal and external iliac arteries (IIA and EIA, respectively).

Discussion

In laboratory animals, electrical stimulation of the pelvic plexus and of the cavernous nerves elicits erection, whereas stimulation of the hypogastric nerves or sympathetic trunks causes detumescence, implying that sacral parasympathetic input is responsible for tumescence (Vardi & Siroky, 1990, 1993; Lue, 1992). Cholinergic innervation is considered to be involved in penile erection, and this is supported by the transient increase in intracavernous pressure that occurs when acetylcholine is injected directly into the canine corpus cavernosum (Stief *et al.*, 1989). A reduced erectile response to nerve stimulation is also reported to occur after intracavernous injection of atropine (Trigo-Rocha *et al.*, 1993). However, Brindley (1986) reported that intracorporeal injection of atropine or of neostigmine had no effect on human penile erection. An intravenous or intracavernous injection of atropine again fails to prevent the erection induced by electrical nerve stimulation (Carati *et al.*, 1987; Stief *et al.*, 1989), indicating that a cholinergic mechanism alone may not be responsible for the erection. Patients with sacral spinal cord injury often retain psychogenic erectile ability even after reflexogenic erection had been lost (Lue, 1992). Thus, the role of acetylcholine in the relaxation of vascular smooth muscle during erection is controversial (Steers, 1990). In the dog, electrical stimulation of the pelvic splanchnic nerve (PSN) increases the blood flow in the internal pudendal artery with an associated elevation of cavernous pressure, and these responses are not attenuated by intravenous injection of atropine (Kihara *et al.*, 1993). These results suggest that unidentified factors may be involved in the nerve-mediated erection, in addition to the parasympathetic innervation.

Andersson and Wagner (1995) report that a high dose of atropine (1 mg/kg, i.v.) inhibits the erectile response measured as an increase in penile volume. The present experiments show that in the dog, atropine does not abolish the increase in the flow of the internal pudendal artery and in the cavernous pressure elicited by PSN stimulation. The reason for this discrepancy

remains unclear. It is reasonable to speculate that the concentration of atropine administered in the present study (equal to 0.05 mg/kg) was not sufficient to block functional muscarinic receptors. However, this would seem to be unlikely since this concentration of atropine definitely diminishes salivary excretion (Kihara *et al.*, 1993). Possible involvement of factors other than cholinergic components must be considered, as low frequency stimulation of PSN induces an effective inhibition of urinary bladder activity in spinal (S_3) injured men (Schmidt *et al.*, 1988).

Penile erection is caused in part by the increase in arterial flow to the cavernosum. The present experiments indicate that the increases in IPA flow and in CP induced by PSN stimulation are antagonized by phentolamine, an α -adrenoceptor antagonist, but not by a β -adrenoceptor antagonist. As sympathetic nerve fibers are contained in the PSN (Kihara *et al.*, 1993), our findings indicate a functional role of α -adrenoceptors in the PSN-induced penile tumescence.

Intracorporeal injection of phentolamine induces penile erection in men (Blum *et al.*, 1985). The human penile erection induced by local α -adrenoceptor blockade may be not due to an increased flow in the internal pudendal artery, but due to an increase in the volume of the corpus cavernosum, because strips of corpus cavernosum contract with α -adrenergic stimulation (Saenz de Tejada *et al.*, 1989). The absence of any effect of the administration of phentolamine on the flow of the internal pudendal artery is also confirmed in the present experiments. Partial inhibition (40%) of the effects of PSN stimulation on the flow of the internal pudendal artery and on the cavernous pressure by phentolamine support the proposal that non-adrenergic non-cholinergic (NANC) nerve components may be involved in the nerve-mediated erection, in addition to adrenergic nerve components (Rajafer *et al.*, 1992). Phentolamine completely blocks (100%) the relaxation of the internal pudendal artery elicited by norepinephrine, which supports the concept that the receptors involved are mainly α -adrenoceptors.

Regional differences in the response of arterial smooth muscles to α -adrenergic stimulation may suggest that blood inflow to the cavernosum during erection is controlled locally by changing the distribution of blood supply in the pelvic region. This idea may be supported by evidence that PSN stimulation increases the systemic blood pressure with no significant increase in the blood flow in the internal and external iliac arteries. The fact that systemic blood pressure in the dog is not significantly decreased following administration of 0.1 mg/kg phentolamine, also supports the proposal that the effects of administration of phentolamine occur mainly in the internal pudendal artery.

α -Adrenoceptor stimulation induces arterial relaxation in the porcine pulmonary artery, mainly through activation of α_2 -adrenoceptors (Pepke-Zaba *et al.*, 1993). The relaxation produced by α -adrenoceptor agonists may be mediated by the release of endothelium-derived nitric oxide and a rise in cyclic GMP (Palmer *et al.*, 1987; Ignarro *et al.*, 1987). The present experiments demonstrate that norepinephrine relaxes the muscle of the internal pudendal artery supplying the penis and contracts the muscle in the abdominal aorta and of both the external and internal iliac arteries. Although the possible involvement of endothelial factors in the norepinephrine-induced muscle responses has not been tested in the present experiments, the attenuation of the increased flow pressure induced by PSN stimulation of the internal

puddendal artery and of cavernous pressure caused by the injection of methylene blue (a guanylyl cyclase inhibitor) may support the hypothesis that the relaxation induced by α -adrenoceptor stimulation is mediated by cyclic GMP.

The neurotransmitter substances responsible for the nerve-mediated erection remain unclear. Cholinergic nerves have been demonstrated within the human cavernous smooth muscle and surrounding penile arteries (Leu, 1992). The cavernous smooth muscle has been shown to have a specialized vascular bed that responds to nerve stimulation by relaxation, which is assumed to be in response to NANC neurotransmission (Rajfer *et al.*, 1992). Vasoactive intestinal polypeptide (VIP) may be one of the transmitters responsible for the erection (Steers *et al.*, 1984; Juenemann *et al.*, 1987). Other possible neurotransmitters are calcitonin-gene related peptide (CGRP) and prostaglandins (Stief *et al.*, 1990). The present experiments also suggest an involvement of cyclic GMP in the increase in flow of the internal pudendal artery.

It is generally accepted that sacral parasympathetic input is mainly responsible for penile tumescence (Andersson, 1993). It is also reported that psychologic erection can be induced via the thoracolumbar sympathetic pathway in the rat, if the sacral parasympathetic centers are injured (Paick & Lee, 1994). These reports imply the possible existence of several nerve pathways which can bring about erectile function in these animals. The present experiments suggest that the increase in the flow of the internal pudendal artery through stimulation of α -adrenoceptors is one of the mechanisms responsible for penile erection.

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