Volume 148 August 1992 Number 2

The Journal of UROLOGY®

Official Journal of the American Urological Association, Inc.
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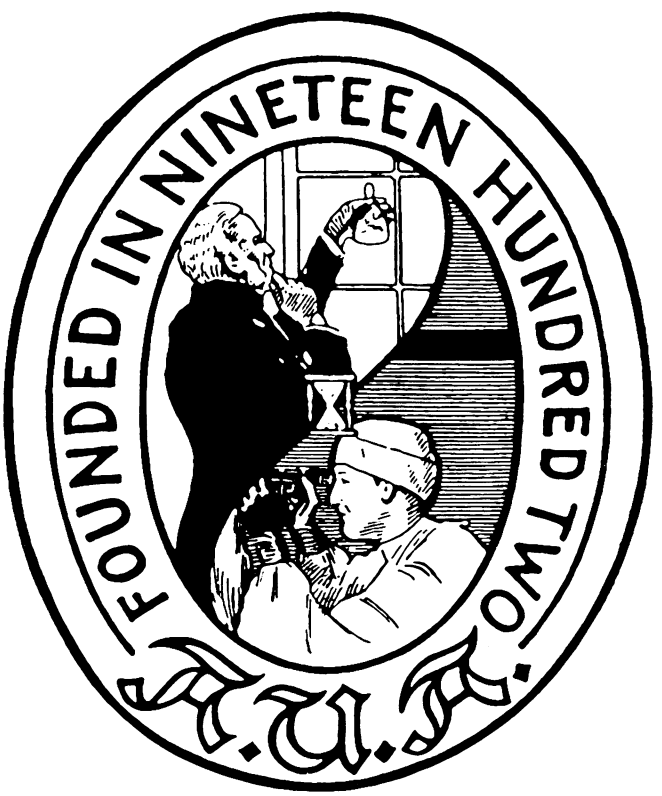

Annual Meeting, American Urological Association, Inc., San Antonio, Texas, May 15–20, 1993

The Journal of
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0022-5347/92/1482-0446$03.00/0
THE JOURNAL OF UROLOGY
Vol. 148, 446-448, August 1992
Printed in U.S.A.

EFFECT OF INTRACAVERNOUS SIMULTANEOUS INJECTION OF ACETYLCHOLINE AND VASOACTIVE INTESTINAL POLYPEPTIDE ON CANINE PENILE ERECTION

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ABSTRACT

We investigated the effects of intracavernous injection of a combination of acetylcholine (ACh) and vasoactive intestinal polypeptide (VIP) on the erectile response in eleven adult male dogs. The minimum dose of ACh which increased the intracavernous pressure in eight dogs varied from 0.2 to 40 μg., and the minimum dose of VIP varied from 0.2 to 5 μg. When the minimum doses of ACh and VIP were injected simultaneously, a strong increase of intracavernous pressure (the mean increase was 102 cm. H_2O from the baseline level) and a sustained erection (mean 5 min.) were observed in all eight dogs. The effect of simultaneous injection of both drugs was not additive but synergistic. Pretreatment with VIP-antibody and atropine intracavernously suppressed the erectile response induced by cavernous nerve stimulation.

VIP may increase the affinity of muscarinic receptors for ACh in canine corpus cavernosum because pretreatment with atropine alone before the simultaneous injection of ACh and VIP completely abolished the effect of the combination. We conclude that ACh and VIP may play a cooperative role in canine penile erection.

KEY WORDS: acetylcholine, vasoactive intestinal peptide, penile erection, canine

There are two types of local control in penile erection: neurological and humoral. In either case, the key event is a relaxation of the smooth muscle of the corpus cavernosum.[1] Neurological control suggests three types of autonomic nervous system effect on the smooth muscle: adrenergic (excitatory), cholinergic (inhibitory) and non-adrenergic non-cholinergic (NANC) (inhibitory). Several groups of humoral agents have been proven to influence the tone of cavernous smooth muscle when injected intracavernously.[2]

The presence of cholinesterase-containing fibers,[3] muscarinic receptors[4] and acetylcholine (ACh) synthesis and release in human corpus cavernosum[5] has been reported. Cholinesterase-positive fibers were also demonstrated around the cavernous arteries and within the cavernous smooth muscle in the canine penis.[6] Vasoactive intestinal polypeptide (VIP)-immunoreactive fibers have been reported to run parallel to cholinesterase-positive fibers in human corpus cavernosum.[7]

Recently it has been found that neuropeptides are often located in the same neurons as ACh.[8] The mechanism of interaction of peptides and non-peptides is better understood in vascular neuromuscular systems.[9] Lundberg demonstrated that VIP increased the affinity of muscarinic receptors for ACh in cat submandibular glands.[10] In this study we investigated the effect of a combination of ACh and VIP in canine penile erection.

MATERIALS AND METHODS

In eleven adult male mongrel dogs (12 to 34 kg.), anesthesia was induced by acepromazine (0.2 mg./kg., B.W.) and ketamine (10 mg./kg., B.W.) subcutaneously. Sodium pentobarbital (45 to 60 mg./hour) was administered intravenously to maintain an adequate level of anesthesia and spontaneous respiration. The animal was placed in a supine position, and the bladder and prostate were exposed through a midline abdominal incision. The cavernous nerves were identified posterolaterally to the prostate and bipolar cuff electrodes (Avery Laboratories, Farmingdale, NY) were placed around them for electrical stimulation. The ipsilateral internal pudendal artery to the cavernous nerves was exposed and an ultrasonic blood flow probe (Transonic Systems Inc., N.Y.) was placed around the internal pudendal artery to measure the blood flow to the penis. The entire penis was denuded, exposing both corpora cavernosa down to the ischial rami. Two 21-gauge scalp-vein needles were inserted into each corpus cavernosum, one proximally for intracavernous pressure (ICP) recording and the other distally for intra-cavernous injection. Systemic arterial blood pressure was monitored via a 16-gauge cannula in the femoral artery. All fluid-filled lines were connected to Statham pressure transducers and a Grass polygraph for recording.

To find the minimum dose that effectively increased ICP, varying doses of ACh and VIP were injected intracavernously while ICP, systemic blood pressure and pudendal arterial blood flow were measured in eight dogs (Nos. 1–8). The doses of ACh injected were: 0.2, 1, 2, 5, 10, 20 and 40 μg. The doses of VIP injected into the same corpus were: 0.2, 0.5, 1, 2, 3, 4 and 5 μg. Between each cavernous injection there were intervals of approximately 15 minutes, which was enough time for ICP to return to the baseline level. Before each injection, one ml. saline was injected intracavernously in order to ascertain the ineffectiveness of previous injection. Then the experimentally determined minimum doses of VIP and ACh were injected simultaneously into the same corpus as before.

Following these studies, we repeated the same injection of the ACh and VIP combination in four dogs in the same corpus (Nos. 1–4). Then, to examine the effect of atropine on the combination, 20 to 50 μg of atropine sulfate was injected two minutes before the ACh-VIP injection was repeated.

To investigate the possibility that ACh and VIP could play a role as neuro-cotransmitters in canine penile erection, the erectile response induced by cavernous nerve stimulation was compared before and after the intracavernous simultaneous injection with atropine (10 to 100 μg.) and VIP-antibody (300 to 500 μg., 1:10 dilution in saline) in six dogs (Nos. 6–11). Neurostimulations were performed every 15 minutes and in each response we measured the peak ICP and the erection time

Accepted for publication February 10, 1992.
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TABLE 1. *Effects of intracavernous simultaneous injection of ACh and VIP on canine penile erection*

Dose of Injection		Baseline	Increase of ICP**			Duration of Plateau
ACh (μg.)	VIP (μg.)	ICP (cm.H_2O)	ACh	VIP (cm.H_2O)	ACh + VIP	(ICP > 80 cm.H_2O) (Seconds)
0.5	3	16	24	16	124	170
20	5	16	4	34	98	126
10	1	36	4	36	104	300
0.2	0.5	10	24	54	96	1200
2	0.2	24	32	24	92	110
0.5	0.5	4	16	28	106	200
40	2	16	20	4	122	330
10	4	30	14	4	70	24
10	2	19	17	25	102	308 (mean)

ICP = Intracavernous pressure, VIP = Vasoactive intestinal polypeptide, ACh = Acetylcholine,**: Increase of ICP means the rise from the baseline level to the peak of ICP.

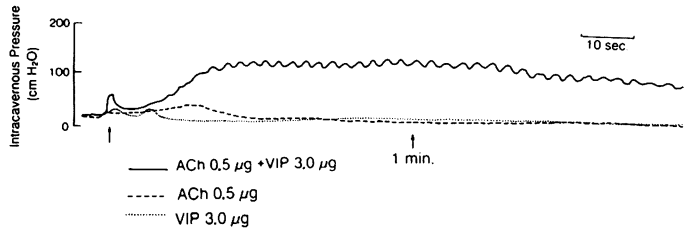

FIG. 1. Representative recordings of erectile response to simultaneous injection of ACh and VIP. Both 0.5 μg. ACh and 3 μg. VIP alone raised ICP slightly. Simultaneous injection of ACh and VIP in same corpus induced an immediate, strong increase of ICP up to 140 cm. H_2O with sustained erection for 1.5 minutes.

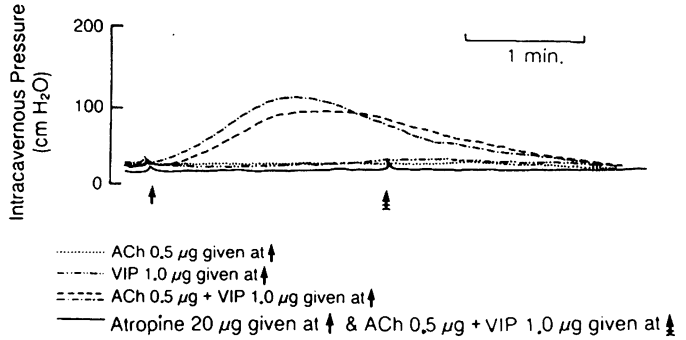

FIG. 2. Representative recordings of ICP induced by ACh and VIP before and after atropine injection. Both 0.5 μg. ACh and 1.0 μg. VIP alone raised ICP slightly. First simultaneous injection of 0.5 μg. ACh and 1.0 μg. VIP increased ICP to 88 cm. H_2O and secondary injection with same doses to 100 cm. H_2O. Following these studies, synergistic effect of ACh and VIP was completely abolished with intracavernous pretreatment with 20 μg. atropine.

(defined as the period when ICP was 60% above the peak ICP induced by the neurostimulation before injection). Drugs used were acetylcholine chloride (Johnson and Johnson Co.), VIP (Sigma), atropine sulfate (LyphoMed., Inc.) and VIP-antibody (Peninsula Laboratories).

RESULTS

The minimum dose of ACh which increased ICP in eight dogs varied from 0.2 to 40 μg. After the injection of ACh, ICP rose 4 to 32 cm. H_2O above the baseline level. The minimum dose of VIP which increased ICP varied from 0.2 to 5 μg. After the injection of VIP, ICP rose 4 to 54 cm. H_2O (mean 25 cm. H_2O). There was no change of systemic blood pressure, but blood flow increased slightly (2–3 ml./minute) with these doses of ACh and VIP. In all eight dogs, the combination of the minimum dose of ACh and VIP induced an immediate, strong increase of intracavernous pressure (mean 102 cm. H_2O from baseline level) and a sustained high pressure (100–140 cm. H_2O) for a mean of 5 minutes (range 0.5 to 20 minutes) with a full erection (table 1). There was no change of systemic blood pressure but a mean 61 percent (range 28 to 100 percent) increase of pudendal blood flow over the baseline level. A representative recording of ICP after the simultaneous injection of ACh 0.5 μg. and VIP 3 μg. is presented in figure 1 with the result of each injection with ACh 0.5 μg. and VIP 3 μg. alone.

When we repeated the same injection of the ACh and VIP combination, nearly identical results were obtained in four dogs examined. Following these studies, we found that in four dogs pretreatment of the same corpus cavernosum with atropine sulfate (20 or 50 μg.) completely inhibited the synergistic effect of the combination of ACh and VIP (figure 2).

After intracavernous injection with the combination of atropine and VIP-antibody, the erectile response to neurostimulation was performed every 15 minutes. The maximum suppression of ICP was observed 12 to 90 minutes after the injection. There was a significant difference in the peak level of ICP before the injection (148 $\pm$ 22 cm. H_2O, mean $\pm$ standard deviation) and after injection (106 $\pm$ 43 cm. H_2O) in the response of maximum suppression ($p = 0.046$). We also found a significant difference in the duration of ICP greater than 60% of the peak ICP before injection (65 $\pm$ 25 seconds) and after (31 $\pm$ 31 seconds) ($p = 0.012$). Interestingly, there was no significant change in arterial flow (28 $\pm$ 28 ml./minute before and 29 $\pm$ 30 ml./minute after injection) (table 2).

DISCUSSION

The minimum doses of ACh and VIP that increased ICP varied so much probably due to the interindividual difference, however, we observed a consistent, synergistic effect of simultaneous intracavernous injection of ACh and VIP on canine penile erection in all dogs studied. We found that the synergistic effect was atropine sensitive, suggesting an effect of VIP on the cholinergic mechanism.

ACh can induce smooth muscle relaxation but does not relax the smooth muscle directly.[11] When ACh is injected intracavernously, it probably diffuses gradually into the sinusoids and mediates endothelium-derived relaxing factor (EDRF). EDRF is now known to be nitric oxide released from the endothelium of various vascular beds.[12] The receptor on endothelial cells for ACh may be muscarinic because pretreatment of the corpus cavernosum with atropine inhibits the effect of exogenous ACh in vivo[6, 13] and in vitro.[11]

On the other hand, it has been suggested that VIP plays a major role as one of the NANC transmitters in penile erection[14] and induces cavernous smooth muscle relaxation in both in vivo[15] as well as in vitro[16] studies. The combination of ACh and VIP injection probably plays a cooperative role through the muscarinic receptors on endothelial cells of the sinusoidal space in the corpus cavernosum, because the synergistic effect was completely abolished by atropine pretreatment.

The precise mechanism of the cooperative relationship between ACh and VIP in penile erection is still unknown. However, it has recently become clear that perivascular nerves

TABLE 2. *Penile response to stimulation before and after intracavernous injection with VIP-antibody and atropine*

Dosage of Inj.		Peak of ICP		Erection Time*		Change of BF		Time to Max. Effect**
VIP-ab	Atropine	Before	After	Before	After	Before	After	
(μg.)		($cm.H_2O$)		(Seconds)		(ml./min.)		(Minutes)
300	100	120	44	48	0	17	16	12
300	40	180	84	56	0	9	4	40
500	10	136	84	54	12	20	21	90
500	100	146	136	114	68	28	38	58
500	100	168	160	69	64	85	84	72
500	40	136	128	50	42	9	8	40
Mean		148†	106†	65‡	31‡	28	29	
±SD		±22	±43	±25	±31	±28	±30	

ICP = Intracavernous pressure, BF = Blood flow, VIP-ab = VIP-antibody.
* Length of time that ICP is greater than 60% of the peak ICP before the injection.
** The time from the point of injection to maximum effect.
† Significant difference between 148 and 106 ($p = 0.046$).
‡ Significant difference between 65 and 31 ($p = 0.012$).

contain a number of biologically active peptides, and amino acids in addition to the classical neurotransmitters, ACh and noradrenaline. In 1987, Burnstock proposed a mechanism of interaction between peptides and nonpeptides.[9] Some findings about the interaction of ACh and VIP in parasympathetic nerves have been reported as follows:

1) VIP increased the affinity of the muscarinic receptor for ACh by about 10^5-fold in cat submandibular glands.[10]
2) Intravenously infused VIP decreased the ACh turnover rate by about 50% in rodent salivary glands.[17]
3) VIP increased the ACh synthesis, possibly by enhancing the activity of choline acetyltransferase in rat hippocampal slices.[18]

It can be speculated that VIP increases the affinity of muscarinic receptors for ACh on the endothelial cells in the corpus cavernosum and also reduces the ACh turnover rate, and thus plays a synergistic role with ACh in canine penile erection.

The results in this study showed that the erectile response induced by cavernous nerve stimulation was suppressed by the intracavernous pretreatment with atropine and VIP-antibody. The suppression is supposed to be due to the combination of the two drugs but not due to each drug alone because atropine modified only the response induced by neurostimulation,[6] and VIP-antibody blocked only the continuation of the response;[15] neither of them reduced the peak level of ICP. Although the time from injection to maximum suppression and the degree of suppression was not consistent in six dogs, the difference in ICP before and after the injection was statistically significant ($p < 0.05$). Andersson et al. suggested that erection in the dog is due to arterial vasodilation caused by VIP release, followed by a filling of the cavernous bodies under the control of the cholinergic mechanism and that both of these events have to occur to induce a full erection.[11] We propose that the interaction of ACh and VIP may play an important physiologic role in canine penile erection.

In vivo experiments with intracavernous injections of VIP in monkeys and in humans have yielded contradictory results.[19, 20] Studies with simultaneous injections of ACh and VIP in monkeys and in men are planned.

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