This Month in Investigative Urology

Bladder Physiology.  E. J. McGuire .......................... 1242
Norepinephrine Involvement in Penile Detumescence.  W. Diedericks, C. G. Stief, T. F. Lue and E. A. Tanagho .......................... 1264
Epidermal Growth Factor Receptor mRNA Levels in Human Prostatic Tumors and Cell Lines.  G. L. Morris and J. G. Dodd .......................... 1272
Acute Physiological Changes in Canine Kidneys Following Exposure to Extracorporeal Shock Waves.  S. J. Karlsen, B. Smevik, J. Stenström and K. J. Berg .......................... 1280
Investigative Grammar .......................... 1284
NOREPINEPHRINE INVOLVEMENT IN PENILE DETUMESCENCE

W. DIEDERICH,* C. G. STIEF, T. F. LUE AND E. A. TANAGHO

From the Department of Urology, University of California School of Medicine, San Francisco, California

ABSTRACT

Adrenergic neurotransmission was studied in dogs. Blood samples for catecholamine assay were collected from the flaccid penis, the erect penis after cavernous nerve stimulation and during detumescence induced by sympathetic trunk stimulation. Epinephrine concentration was not significantly different in these three stages. However, norepinephrine concentration increased significantly (p < 0.005) during induced detumescence from 505 ± 311 [pg./ml.] to 747 ± 489 [pg./ml.].

Intracavernous application of norepinephrine abolished cavernous nerve induced erection in a dose dependent manner. Sympathetic trunk stimulation reduced or abolished erection induced by acetylcholine or by vasoactive intestinal polypeptide. We conclude that norepinephrine is an important neurotransmitter in the control of penile detumescence. (J. Urol, 143: 1264–1266, 1990)

VARIOUS PROTOCOLS OF NEUROSTIMULATION and intracavernous (i.e.) injection of various neurotransmitters can elicit erection and detumescence. For example, acetylcholine (Ach), norepinephrine and vasoactive intestinal polypeptide (VIP) have been extensively used in studies on erection. In dogs, erection can be induced by i.e. application of Ach, VIP, and also by pelvic or cavernous nerve stimulation. Penile detumescence has been induced by sympathetic trunk stimulation and/or i.e. norepinephrine injection. These results suggest that neurostimulation is effective on penile tissue probably via the release of one of the neurotransmitters mentioned above.

The present study was designed to clarify, in vivo, adrenergic effects on erection. We measured epinephrine (E) and norepinephrine (NE) levels in penile blood during erection and detumescence phases induced by neurostimulation. We also compared effects of neurostimulation to the action of (i.e.) injected neurotransmitters.

MATERIALS AND METHOD

Experiments were performed on sixteen adult male mongrel dogs (19.2 to 43.3 kg.). The animals were premedicated with acepromazine (0.1 mg./kg.) and ketamine (five mg./kg.) subcutaneously and anesthetized with pentobarbital (i.e., 130 mg. as a bolus; additional doses as required). Fluid was maintained by infusion of saline at 100 ml./hr. The dogs were placed in the supine position on a water heated pad at 39°C, and the lower abdomen was exposed by a midline incision. The lumbar sympathetic trunks were separated from the aorta and fitted with bipolar cuff electrodes (Avery Laboratories). The right and left cavernous nerves were identified close to the prostate, and cuff electrodes were placed around them. The right internal pudendal artery was fitted with an ultrasonic flow probe (Transonics Systems, Inc., Ithaca, NY). The midshaft of the penis was dissected free from the skin and the subcutaneous layers.

Each corpus cavernosum was punctured with two 19 gauge scalp vein needles. One needle was used to collect blood samples from the penis and the other for recording the pressure. Systemic blood pressure was recorded through a 16 gauge angiocath needle placed in the right femoral artery. One scalp vein needle was used to collect blood samples for catecholamine assay. Blood samples were withdrawn into syringes containing EGTA and glutathion, stored in ice, centrifuged (4°C, 1000 g for 20 minutes), and the plasma separated and stored at 12°C.

The assay can detect one pg. (20 pg./ml. of plasma) of NE or E. The following neurotransmitters were used for (i.e.) injection after dilution with saline to 0.3 to 0.5 ml.: Acetylcholine: Cooper Vision, Pharmaceutical, Inc. (Dose: 10–50 μg.)

Norepinephrine: Wintrop-Breon Lab, (Dose: 10–50 μg.)

VIP (porcine synthetic): Sigma (Dose: 10–20 μg.)

The assay was used with an external antenna (Avery Laboratories) was used for neurostimulation (parameters: 20 Hz; 200 micro-

Accepted for publication January 22, 1990.

* Requests for reprints: Urologische Klinik, Marienhospital Herne, Universitätsklinik, Ruhr Universität Bochum, Widumerstr. 9, 4690 Herne, West Germany.
TABLE 1. Epinephrine (E) and norepinephrine (NE) values

<table>
<thead>
<tr>
<th>Sample</th>
<th>E Mean [pg./ml.]</th>
<th>E SD</th>
<th>NE Mean [pg./ml.]</th>
<th>NE SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>224*</td>
<td>49</td>
<td>298†</td>
<td>158</td>
</tr>
<tr>
<td>2</td>
<td>685*</td>
<td>337</td>
<td>803†</td>
<td>416</td>
</tr>
<tr>
<td>3</td>
<td>982</td>
<td>574</td>
<td>804</td>
<td>487</td>
</tr>
<tr>
<td>4</td>
<td>426</td>
<td>251</td>
<td>396</td>
<td>264</td>
</tr>
<tr>
<td>5</td>
<td>513</td>
<td>270</td>
<td>506§</td>
<td>311</td>
</tr>
<tr>
<td>6</td>
<td>556</td>
<td>304</td>
<td>747§</td>
<td>489</td>
</tr>
</tbody>
</table>

§,† Pairs indicated by these symbols consist of two significantly different means (p < 0.05).

Sample 1: from cephalic vein
Sample 2: from femoral artery
Sample 3: from femoral artery
Sample 4: from cavernous body (no stimulation)
Sample 5: from cavernous body after CNS
Sample 6: from cavernous body after STS

discussion

Catecholamine serum levels in conscious and anesthetized dogs were studied by Bridle et al., and the concentrations of epinephrine and norepinephrine that we found in the periphery are about 40% higher than their findings. Our elevated E and NE levels are from blood samples taken when the abdominal
cavity was open, and the nerves and penis were exposed. This surgical stress might be the source of the relatively elevated levels we observed. However, a side dependence from our E and NE levels can not be excluded because the first samples were collected from the cephalic vein and the second samples from the femoral artery.

Ultrastructural examination of the erectile tissue showed that smaller granular vesicles, which are believed to contain norepinephrine, lay close to the smooth muscle cells of the penis. After the release of NE, its effects are attenuated by reuptake into the pre-synaptic nerve terminals, metabolic transformation, and dilution by diffusion out of the junctional cleft. The transmitter level assayed in the cavernous blood reflects all these release and elimination phenomena. We do not know whether the cavernous blood levels of transmitters correlate with the amount of synaptic release of transmitters. However, we do believe that the elevated plasma levels of norepinephrine during STS is a reflection of the norepinephrine released by the neural vesicles.

Blood samples from the penis were collected before and during various neurostimulations. Catecholamine levels in blood from a flaccid penis were much lower than from the femoral artery. This might be due to low arterial inflow into the cavernous spaces during the flaccid state and a lower rate of synaptic release. When tumescence was induced by CNS there was a large inflow of blood containing catecholamines at higher concentrations than in flaccid penile blood. Nevertheless, we found an increase only of NE and not of E during the tumescence phase. NE levels continued to increase during detumescence, when arterial inflow decreases.

We collected blood samples while hemodynamic changes were occurring in the penis (owing to neurostimulation) in order to correlate catecholamine levels to the different phases of erection. Using a lower voltage for neurostimulation, one might expect to observe an increase of the norepinephrine level but not a reduction in the intracavernous pressure, the latter of which is related to a tension of the smooth muscles. A previous study suggested that the cavernous nerve is composed of parasympathetic and sympathetic fibers. This composition might explain elevated norepinephrine levels during cavernous nerve stimulation. These norepinephrine levels seem too low to abolish erection. Furthermore, our results show that the sympathetic inhibition of erection occurs at smooth muscle level. Previously Langley and Anderson observed a strong contraction of the muscles by sympathetic trunk stimulation when they cut open the penile bodies of cats and rabbits. In addition they described a contraction of penile arteries and a contraction in the cavernous bodies. In a muscle bath, it was generally believed that several transmitters are involved in the autonomic transmission and NE is probably not the only transmitter in the smooth muscle contraction process.

The relaxation effect of acetylcholine on penile smooth muscles is controversial especially in vitro. Hedlund and Andersson mentioned that pelvic nerve activity leading to a release of Ach may contribute to relaxation of tissue by counteracting the postjunctional effects of NE. This effect might also be important on the reduction of VIP induced erection by STS. The intracavernous pressure increase during VIP was only of about 65% compared to the maximum pressure by Ach or CNS.

We conclude that the inhibition of penile erection during STS is due to a release of norepinephrine in the penis tissue. STS also inhibits tumescence induced by intracavernous injection of VIP or acetylcholine through the same mechanism. Whether acetylcholine or VIP are involved in the detumescence process is still under investigation, but our results seem to indicate that norepinephrine is definitely involved in the detumescence process.

REFERENCES