Vasoactive intestinal peptide in vaginal epithelium of patients with pelvic organ prolapse and stress urinary incontinence

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A B S T R A C T

Objective: To determine the distribution of vasoactive intestinal peptide (VIP) in vaginal epithelium among women with stress urinary incontinence (SUI), pelvic organ prolapse (POP), and control groups to clarify its role in the etiology of SUI and POP. Methods: A total of 40 biopsy specimens from anterior and posterior vaginal epithelium were obtained from 3 groups of patients: SUI, POP, and symptomatic controls. Routine hematoxylin and eosin staining and semiquantitative immunohistochemical staining for VIP were performed. Results: VIP was found in 27.5% of the specimens. In the control group, VIP expression was significantly higher in anterior than in posterior epithelium (P = 0.046). There were no significant differences in the expression of VIP in the anterior and posterior epithelium in a comparison among the 3 groups. In the POP group, the expression of VIP was negatively correlated with age and menopause status. Conclusions: There is evidence that VIP is a neurotransmitter in the vaginal epithelium. The anterior vaginal wall has a more important role than the posterior vaginal wall. Change of VIP is related to age in POP patients.

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1. Introduction

Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are common medical problems, especially among older women. These two diseases have an etiologically close relationship [1]. The effects of pelvic support weakness may contribute to the development of POP and SUI [2,3]. Previous histochemical and electrophysiological investigations of the pelvic muscle have suggested that SUI is associated with partial denervation of the pelvic floor [4]; however, the underlying neuropathophysiology of SUI and POP is unclear. The aim of the present study was to explore the relationship between the neurotransmitter, vasoactive intestinal peptide (VIP), in the vaginal epithelium and the occurrence of SUI and POP. The study investigated the distribution of VIP in the vaginal epithelium of control, SUI, and POP patients. A quantitative analysis of VIP immunocytochemical staining was also performed.

2. Materials and methods

Forty biopsy specimens of the anterior and posterior vaginal walls near the fornix were obtained from 40 patients undergoing total vaginal hysterectomy (TVH), laparoscopic-assisted hysterectomy (LAVH), and tension-free vaginal tape (TVT) procedures in control (n = 13), SUI (n = 13), and POP (n = 14) groups. Routine hematoxylin and eosin (HE) staining and immunohistochemical staining for VIP were performed for all specimens.

None of the patients took hormonal drugs during the 3 months prior to surgery. Patients in the control group had no estrogen-related diseases (endometriosis, myoma, and functional ovary tumors). The indications for LAVH in the control group were cervical intraepithelial neoplasia (CIN) grade 3/cervical carcinoma in situ and postmenopausal ovarian cyst. SUI was defined objectively by gynecologic examination and urodynamic examination. Valsalva leak point pressure (VLPP) and postvoid residual (PVR) volume and other data were recorded. SUI was subdivided according to 1-hour pad test results with 2–10 g defined as moderate SUI and more than 10 g defined as severe SUI. Among the 13 women with SUI, 9 had moderate SUI, and 4 had severe SUI. Every patient with SUI also had POP. Patients in the POP group had varying degrees of cystocele without urinary incontinence. The degree of POP was defined by vaginal examination according to Pelvic Organ Prolapse Quantification (POP-Q) classification system. Among the 14 patients with POP, 2 had first-degree uterine prolapse with mild or moderate cystocele, 7 had second-degree uterine prolapse cases with moderate or severe cystocele, and 5 had third-degree uterine prolapse cases with severe cystocele.

Consent to participate in the study was obtained from the patients prior to surgery. The specimens were stored in liquid nitrogen. Sections of 10 µm were thawed onto gelatin-coated slides. Routine HE staining...
3. Results

There were no significant differences among the groups in age, body mass index (calculated as weight in kilograms divided by height in meters squared), parity, and time since menopause among the 3 groups (Table 1). VIP was positive in 27.5% of the vaginal epithelium samples. VIP immunoreactive nerves were mainly localized around blood vessels. VIP-containing nerves were seen beneath the vaginal epithelium. The VIP profiles of the vaginal epithelium in the control, SUI, and POP groups are shown in Table 2. In the control group, the expression of VIP in the anterior vaginal epithelium was significantly higher than in the posterior epithelium (6 vs 3; P = 0.046). There were no significant differences in the expression of VIP in the anterior and posterior vaginal epithelium walls in a comparison among the 3 groups using Mann–Whitney U analysis (Table 3).

Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SUI (n = 13)</th>
<th>POP (n = 14)</th>
<th>Control (n = 13)</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.85 ± 3.1</td>
<td>56.57 ± 5.02</td>
<td>56.38 ± 3.76</td>
<td>0.032</td>
<td>0.968</td>
</tr>
<tr>
<td>BMI</td>
<td>24.76 ± 1.23</td>
<td>23.89 ± 1.34</td>
<td>25.81 ± 1.96</td>
<td>1.51</td>
<td>0.234</td>
</tr>
<tr>
<td>Parity</td>
<td>2.38 ± 0.66</td>
<td>2.0 ± 0.41</td>
<td>2.15 ± 0.82</td>
<td>0.34</td>
<td>0.714</td>
</tr>
<tr>
<td>Time since menopause, y</td>
<td>4.92 ± 2.18</td>
<td>6.71 ± 2.65</td>
<td>5.46 ± 3.67</td>
<td>0.398</td>
<td>0.674</td>
</tr>
</tbody>
</table>

Abbreviations: SUI, stress urinary incontinence; POP, pelvic organ prolapse. BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

4. Discussion

Pelvic floor dysfunction is a disease mainly comprising POP and SUI. Epidemiologic data show that birth trauma is one of the important risk factors for this disease [5]. Another study has suggested that damage to the innervation of the pelvic floor may be an important factor in the etiology of SUI and POP [6]. Neuropeptides, which are considered a marker of nerve damage, are used in the study of pelvic floor dysfunction. A neuropeptide is a peptide released by different tissues, which acts as a neural messenger. Neuropeptides are widely distributed in the central and peripheral nervous system and in many areas of the human body, including the gut, pancreas, heart, lung, and genital tract. Neuropeptides act as neurotransmitters, neuromodulators, or neural modulators. Peptide signals play a role in information processing, which differs from conventional neurotransmitters. Among other activities, they can affect gene expression, local blood flow, synaptogenesis, and glial cell morphology. Peptides tend to have prolonged actions, and some have striking effects on behavior. In 1980, Alm et al. [7] reported the existence of VIP-containing nerves in the vaginal wall. VIP-containing nerves have been described throughout the human female genital tract, being most abundant in the vagina, cervix, and clitoris [8].

The VIP gene is on human chromosome 6, spanning 8837 base pairs, and contains 7 exons and 6 introns, each encoding a distinct functional domain of the VIP precursor. The amino acid sequence of the precursor, preproVIP, is deduced from the messenger RNA sequence. Its functional domain of the VIP precursor. The amino acid sequence of the precursor, preproVIP, is deduced from the messenger RNA sequence. Its functional domain of the VIP precursor.
seems to induce smooth muscle relaxation, and dilate peripheral blood vessels, as well as functioning in vaginal lubrication [9]. Other studies have shown that VIP enhances its own expression after neuron injury [10], and accumulation of VIP has been found at the site of neural injury [11].

In the present study, 27.5% of the vaginal epithelium samples were positive for VIP, suggesting that VIP is a neurotransmitter in the vaginal epithelium. In the control group, the expression of VIP in the anterior vaginal epithelium was significantly higher than in the posterior epithelium. The anterior vaginal wall plays a more important role than the posterior vaginal wall in the etiology of SUI.

In women with SUI, with or without POP, there is an increase in the number of muscular fibers showing pathological damage. The possibility, therefore, exists that damage to the innervation of the urogenital tract may also be a factor in the etiology of SUI and POP. The possibility, therefore, exists that damage to the innervation of the urogenital tract may also be a factor in the etiology of SUI and POP.

Previous studies have shown that VIP levels were significantly decreased in the anterior vaginal wall in premenopausal and postmenopausal SUI or POP patients. VIP levels were reversely correlated with age and menopausal status in SUI or POP patients [14]. In the correlation analysis in the present study, VIP expression had no correlation with age or menopausal status in the SUI group, but was negatively correlated with age and menopausal status in the POP group. The distribution of VIP-immunoreactive nerves is closely associated with changes in the pelvic vessels, implying that VIP is involved in the regulation of blood flow in the female genital tract. The reduction of these messengers causes reduced vascularity of the pelvic floor, consequently causing altered tissue trophism and aggravation of POP.

In SUI patients, pelvic support tissue becomes weakened with age, and has more correlation with VIP-containing nerves. Thus, the causes of SUI and POP share a common weakness of the pelvic support tissue; however, the underlying neuropathophysiology of SUI and POP is still unclear and there are likely significant differences in their causes.

References


Table 4

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Correlation analysis between vasoactive intestinal peptide profiles and clinical data in patients with stress urinary incontinence and pelvic organ prolapse and control patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SU (n = 13)</td>
</tr>
<tr>
<td></td>
<td>AW</td>
</tr>
<tr>
<td>Age, y</td>
<td>−0.029 (0.926)</td>
</tr>
<tr>
<td>Parity</td>
<td>−0.297 (0.324)</td>
</tr>
<tr>
<td>Time since menopause, y</td>
<td>−0.402 (0.174)</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.057 (0.853)</td>
</tr>
</tbody>
</table>

Abbreviations: SUI, stress urinary incontinence; POP, pelvic organ prolapse; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

a Values in parenthesis are P values.

b P<0.05.