

Review Article

Int Neurorol J 2020;24(Suppl 2):S67-71
<https://doi.org/10.5213/inj.2040426.213>
pISSN 2093-4777 · eISSN 2093-6931



The Role of Apoptosis in Detrusor Contractility

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Apoptosis has been found in bladder affected by various types of voiding dysfunction. In animal studies, higher levels of apoptosis were observed in conditions of both detrusor overactivity and underactivity than in normal bladders. However, it has been difficult to establish the exact underlying mechanism of apoptosis in these conditions and to find new therapeutic targets because the causes of voiding dysfunction are diverse and the coexistence of various types of voiding problems is common. Furthermore, the lack of studies of the human detrusor contributes to our incomplete understanding of these issues. Therefore, this review discusses the role of apoptosis in detrusor contractility based on previous studies.

Keywords: Apoptosis; Bladder; Voiding dysfunction; Detrusor contractility

- **Fund/Grant Support:** This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2018R1D1A3B07048492).
- **Conflict of Interest:** SJK, an associate editor of *International Neurourology Journal*, is the author of this article. However, she played no role whatsoever in the editorial evaluation of this article or the decision to publish it. Except for that, no potential conflict of interest relevant to this article was reported.

INTRODUCTION


Voiding dysfunction is common health problems in the general population. The daily life of people with voiding dysfunction is often limited by lower urinary tract symptoms (LUTS) induced by overactive bladder (OAB), benign prostatic hyperplasia (BPH), and neurogenic bladder. Moreover, the socioeconomic burden associated with voiding dysfunction has increased concomitantly with population aging [1-5]. The management of voiding dysfunction involves both medical and surgical treatment. Depending on the disorder causing LUTS, alpha-blockers, anticholinergics, or beta-3 agonists can be used for medical treatment. Surgical treatment is considered for improving LUTS associated with BPH or stress urinary incontinence (SUI) [6-9].

The currently available treatment strategies were developed

based on our understanding of the underlying mechanism of each voiding disorder. However, these mechanisms have not been fully elucidated on the molecular level, and unknown areas still exist. Some patients also do not respond to conventional treatment; therefore, many studies have been performed to identify new biomarkers and target molecules. Apoptosis is associated with various diseases, and previous studies have observed apoptosis in bladders affected by voiding disorders. Therefore, the role of apoptosis in the bladder is reviewed below.

APOPTOSIS AND INCREASED DETRUSOR CONTRACTILITY

OAB is a representative disorder associated with increased detrusor activity. However, the cause of increased detrusor activity

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Submitted: October 9, 2020 / **Accepted after revision:** November 5, 2020



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in OAB has not been precisely established. The International Continence Society defined OAB as a symptom complex of urinary urgency with or without urgency urinary incontinence, urinary frequency, and nocturia. In general, OAB is diagnosed based on symptoms, after excluding other pathologic conditions such as urinary tract infections, urinary stones, and neurologic diseases inducing OAB-like symptoms [10-13]. Furthermore, other voiding problems such as BPH and SUI can coexist with OAB. In men with BPH, OAB occurs due to bladder outlet obstruction (BOO). The obstruction induced by an enlarged prostate results in changes of bladder function [14]. Therefore, several studies have analyzed morphological and molecular changes of the bladder in men with BPH.

Analysis of detrusor samples obtained during transurethral resection of the prostate (TURP) or cystoscopy showed increased amounts of smooth muscle cells and hypertrophy of smooth muscle [15-19]. The increased intravesical pressure due to BOO might induce detrusor hypertrophy. Several *in vitro* studies of human bladder tissue have identified molecular mechanisms of detrusor hypertrophy in BPH men with BPH in whom OAB is caused by BOO. These studies investigated the molecular changes of cultured human detrusor tissue after exposure to hydrostatic pressure, and noted increased expression of type 2 and 3 muscarinic receptors, activation of mitogen-activated protein kinase 1/2 and extracellular regulated protein kinase 1/2, and increased expression of platelet-derived growth factor receptor, and hypoxia inducible factor (HIF)-1 α [20-24]. However, these previous findings in men with OAB induced by BOO are not sufficient for understanding the underlying mechanism of OAB, because OAB can be also occur in men without BPH and BOO [25,26].

Surgical treatment of BPH reduces OAB symptoms induced by BOO. However, some patients show persistent OAB symptoms after surgical therapy. Mitterberger et al. [27] suggested that increased resistance of the bladder's blood vessels may contribute to persistent detrusor overactivity (DO) after TURP. They concluded that persistent DO occurs due to chronic ischemia of the bladder after the relief of BOO. Voiding dysfunction is prevalent in the elderly population, similar to metabolic syndrome [28]. Pelvic atherosclerosis associated with metabolic syndrome induces pelvic ischemia; therefore, hypoxic changes in the bladder due to pelvic ischemia may be one of the possible mechanisms of the OAB. An animal model of pelvic ischemia induced by bilateral partial ligation of the common iliac artery showed the cystometric change of a shortened intercontraction

interval in the pelvic ischemia group. Furthermore, higher levels of oxidative stress and apoptosis were observed in the pelvic ischemia group, which showed detrusor hyperactivity [29]. Tsai et al. [30] also showed increased levels of oxidative stress, pro-inflammatory PKC/ERK/NF- κ B/ICAM-1/IL-33 signaling, and apoptosis in OAB rats induced by substance P.

APOPTOSIS AND DECREASED DETRUSOR CONTRACTILITY

Other clinical and morphological changes of the bladder have also been noted in men with BPH associated with BOO. Several studies of human bladder samples obtained during surgery for BPH reported increased quantities of collagen and decreased amounts of smooth muscle of the detrusor. These morphological changes were often noted in patients with severe symptoms, a history of urinary retention, and a large postvoid residual urine volume [31-35]. Moreover, increased expression of HIF-1 α , transforming growth factor-beta (TGF- β), and fibronectin were noted [36,37]. BOO-induced functional changes of the bladder can vary according to the patient's age and comorbidities affecting the bladder such as diabetes mellitus (DM) and metabolic syndrome. As mentioned previously, metabolic syndrome is a risk factor for pelvic ischemia, and a relatively long period of pelvic ischemia may induce collagen deposition and fibrosis of the detrusor [38].

Gu et al. [39] showed increased collagen levels, oxidative stress, and apoptosis of the bladder at 4 weeks after BOO induction in rats. These results suggest that prolonged BOO decreased detrusor activity by reducing the proliferation of the smooth muscle and increasing bladder fibrosis. DM is a common disease that results in decreased detrusor contractility, as explored in a previous study using an animal model with DM. Morphological changes such as detrusor hypertrophy and fibrosis of the bladder were noted. In addition, the DM group showed increased collagen I and decreased elastin expression. Increased expression of TGF- β 1 and Bcl-2-associated X protein (Bax) was indicative of fibrosis and apoptosis. Kim et al. [40] evaluated functional and molecular changes in an animal model with detrusor underactivity (DU) associated with pelvic ischemia, which was induced by extensive vascular endothelial damage of the iliac artery. In this study, DO or DU was observed by cystometry according to the degree of vascular endothelial damage. Mild endothelial damage induced DO and severe damage induced DU. Increased amounts of collagen and de-

creased amounts of smooth muscle in the detrusor were observed regardless of the degree of damage. However, the group with severe damage showed significantly increased amounts of collagen and decreased amounts of smooth muscle compared with group with mild damage. Abnormal inflammation and apoptosis were also noted in the bladder of all animals. Significantly increased higher apoptosis of the detrusor was noted in the group with mild endothelial damage than in the sham group. However, apoptosis of the detrusor in the group with mild endothelial damage was significantly lower than in the group with severe endothelial damage.

APOPTOSIS AND DETRUSOR REMODELING

Studies on the role of apoptosis in the detrusor in various voiding disorders are limited. Therefore, it is difficult to reach definitive conclusions regarding the association between apoptosis and function of the detrusor. However, apoptosis has been noted in both hyperactive and underactive detrusors based in animal studies. Thus, apoptosis may occur when any type of voiding problem starts. DU, which involves decreased detrusor contractility, may be associated with a greater increase in apoptosis than DO, which involves increased detrusor contractility. Compared with the normal bladder, the detrusor is remodeled under conditions of DO and DU. Remodeling of the bladder can occur in both positive and negative ways, affected by various factors. A previous study suggested that vascular smooth muscle cell (VSMC) apoptosis promoted recovery in vessels that underwent unfavorable remodeling due to disease or surgery. A possible explanation may be that VSMC apoptosis stimulates adjacent cell proliferation and migration, thereby making it possible to repair the artery following injury through positive remodeling [41]. In general, apoptosis is considered to be a negative factor contributing to impaired voiding function. However, at present, further conclusions cannot be drawn due to the lack of studies from investigating this issue from the perspective of detrusor remodeling and associated conditions.

CONCLUSIONS

Apoptosis is found in both DO and DU, and different characteristics of apoptosis according detrusor contractility have also been observed in previous studies. The causes of voiding dysfunction are very diverse and the disease course can be influenced by complex factors. Additionally, voiding disorders com-

monly coexist, both with other voiding disorders and with other comorbidities. Therefore, further research on the role of apoptosis in various types of voiding disorders is necessary to achieve a better understanding of this relationship.

AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: *SJK*
- Data curation: *SJK*
- Formal analysis: *SJK*
- Funding acquisition: *SJK*
- Methodology: *SJK*
- Project administration: *SJK*
- Visualization: *SJK*
- Writing-original draft: *SJK*
- Writing-review & editing: *SJK*

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