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The Roles of β-Adrenergic Receptor Blockers in Interstitial Cystitis

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Authors' contributions

This work was carried out in collaboration between both authors. Author KL designed the study and wrote the protocol. Author LN managed the literature searches. All authors read and approved the final manuscript

Review Article

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ABSTRACT

Interstitial cystitis (IC) is a debilitating disease characterized by chronic inflammation of the urinary bladder. β-Adrenergic receptor blockers appear to have a beneficial clinical effect in IC. In this paper, we review the evidence of an association between β-adrenergic receptor blockade and IC. The information was obtained from MEDLINE. Genetic studies have provided the opportunity to determine which proteins link β-adrenergic receptor blockade to IC pathology. In particular, this link involves the major histocompatibility complex class II molecules, the renin-angiotensin system, the transcription factor nuclear factor-κB, the nerve growth factor, and the vascular endothelial growth factor. B-Adrenergic receptor blockers also exert anti-IC effects through non-genomic factors, including stress, mitogen-activated protein kinase pathways, prostaglandins, cyclooxygenase-2, oxidative stress, and nitric oxide synthase. In conclusion, β-adrenergic receptor blockade may play a beneficial role in IC treatment. Additional investigations that examine β-adrenergic receptor blockers as IC therapeutics are required to further elucidate this role.

Keywords: β-adrenergic receptor blocker; interstitial cystitis; neurogenic cystitis; β-adrenergic receptor antagonism.

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1. INTRODUCTION

Interstitial cystitis (IC) is a poorly understood chronic bladder disorder that is generally characterized by bladder discomfort and increased urinary urgency and frequency. A relationship between β-adrenergic receptor antagonism and IC has been suggested in the literature. The bladder expresses mRNA for all β-adrenergic receptors subtypes 1-3]. The presence of α- and β-adrenoceptors was reported in the detrusor muscle and bladder base of the pig and β-adrenoceptors in the detrusor muscle of man [4]. There is a functional and molecular biological evidence for a β_3-adrenoceptor in the human detrusor muscle [5]. Species differences in the distribution of β-adrenoceptor subtypes were demonstrated in bladder smooth muscle [6]. Additionally, sympathetic nervous system activity is increased in cats with feline IC. The norepinephrine (NE) concentration of the bladder tissue of cats with feline IC is significantly greater than the content in normal cats, and NE-mediated inhibition of contraction occur when propranolol is administered to these animals [7]. Buffington et al. [7] suggest that the presence of a postsynaptic β_3, an atypical β-adrenergic receptor, an inhibitory presynaptic β-adrenergic receptor, or some combination thereof is responsible for IC. Evidence suggests that β-adrenergic receptor signaling is increased in the inflamed urothelium. Functional β-adrenergic receptors expressed on human urothelial cell membranes increase the generation of cyclic adenosine monophosphate (cAMP) and the production of protein products that are associated with inflammation when activated by isoproterenol. However, these effects are inhibited by pretreatment with propranolol [8]. Inhaled salbutamol and salmeterol, which act as β_2-agonists, cause hemorrhagic cystitis 9]. ZD7114, [(S)-4-[2-(2-hydroxy-3 phenoxypropylamine)ethoxy]-N-(2-methoxyethyl) phenoxyacetamide] and ZD2079, [(R)-N-(2-[4- (carboxymethyl)phenoxy]ethyl)-N-(beta-hydroxyphenethyl)ammonium chloride] are β_3-adrenoceptor stimulants and cause ureteric inflammation, cystitis, and accumulation of crystalline inclusions throughout the urinary tract [10]. On the other hand, type 4 phosphodiesterase inhibitor (PDE4) suppressed experimental bladder inflammation [11] and induced elevation of cAMP[12]. Distention of the bladder results in the release of adenosine triphosphate (ATP) from urothelial cells, which activates purigenic P2X3 receptors. Neural up-regulation was suggested in IC. Activation by ATP of P2X3-expressing afferent was a fundamental signaling factor in bladder sensation and appeared to play a role in bladder reflexes [13]. An excess of distention-induced APT release from urothelium was found in IC [14-15]. Matsumoto-Miyai et al. [16] demonstrated that the adenylyl cyclase pathway enhanced distention-induced ATP release in mouse bladder. In the absence of bladder distention, adenyl cyclase activation by forkolin or cAMP increased by rolipram did not induce significant ATP release. These findings suggest that β-adrenergic receptor blockade may have different effects in IC rather than it depend on cAMP pathway. During chronic inflammation, the urinary bladder has a predominantly monocyte/macrophage infiltrate and a concomitant increase in the expression of the *β_2-adrenergic receptor* gene [17]. The *Tryp 64 Arg* polymorphism of the *β_3-adrenoceptor* gene is associated with idiopathic overactive bladder syndrome in the Brazilian population [18]. The *Arg16Gly* polymorphism of the *β_2-adrenergic receptor* gene shows a significant difference in prevalence between IC patients and controls [19]. The frequencies of the *Arg/Arg* genotype of the *β_2-adrenergic receptor* gene and the *TT* genotype of the *IL-4* gene are significantly higher in patients with IC than in controls [20]. These findings suggest that variants of the *β_2-adrenergic receptor* and *IL-4* genes may be related to a predisposition toward IC. Moreover, bladder contractions can be evoked by stimulation of the penis dorsal nerve only above a bladder volume threshold equal to 73 ± 12% of the distension-evoked reflex contraction volume threshold. However, administration of propranolol decreased the stimulation-evoked and distension-evoked volume thresholds by −25% to −39% [21]. Infusion of 0.7% acetic acid into the urethra elicits decreased micturition intervals that are

accompanied by continual bladder contractions. This bladder irritation can be reversed by intravenous infusion of propranolol and butoxamine, a selective β_2 antagonist [22]. Propranolol attenuates the electrical field stimulation-evoked contractile responses, particularly at low frequencies both in cyclophosphamide (CP)-induced bladder inflammation and controls [23]. These findings suggest that β-adrenergic receptor blockade may play a role in IC treatment. Based on the evidence described above, we discuss the role of β-adrenergic blockade in IC.

2. GENETIC FACTORS THAT RELATE TO β-ADRENERGIC RECEPTOR INHIBITION AND INTERSTITIAL CYSTITIS

2.1 Human Leukocyte Antigen (HLA) Genes

Studies have suggested that several genes in the major histocompatibility complex (MHC) region promote IC susceptibility. HLA genes are located in the MHC region and have also been implicated in IC susceptibility. In normal control bladders, the urothelium is negative for HLA class II molecule expression; in contrast, HLA-DR expression has been identified in urothelial cells from IC patients [24]. IC is associated with *HLA-DR6* [25]. Biopsied urothelial cells from IC patients also exhibit increased HLA-DR expression [26]. HLA-DR staining patterns correlate with symptoms, including bloating, constant urge to void, and absence of burning in patients with IC [27]. The differential effects on MHC class II molecules, including *HLA-DQB1, HLA-DRB1, HLA-DPA1, HLA-DOA, HLA-DMA*, and *HLA-DRA* are associated with Hunner's ulcer type IC [28]. Moreover, β_2-adrenoceptor agonists inhibited the allergen-induced mononuclear cell proliferation and down-regulated granulocyte macrophage colony-stimulating factor release and HLA-DR expression by monocytes [29]. A β-adrenergic agonist also modulated DR α gene transcription via enhanced cAMP levels in a glioblastoma multiforme line [30]. Furthermore, propranolol abrogates interferon-gamma-increased HLA class II expression and interleukin-1beta (IL-1β) secretion in human monocytic cells [31]. These findings suggest that β-adrenergic receptor blockers affect on IC by suppressing the expression of MHC class II antigens.

2.2 The Primary Function of the Renin-Angiotensin System (RAS)

RAS is to maintain fluid homeostasis and regulate blood pressure. Angiotensin-converting enzyme (ACE) is a key enzyme in the RAS that converts angiotensin (AT) I to the potent vasoconstrictor AT II [32]. The local RAS may influence tissue angiogenesis, cellular proliferation, apoptosis, and inflammation of the bladder [33]. RAS-related cells exist throughout the genito-urinary system, including the ureters and bladder [34-35]. AT II receptors are present in the rat urinary bladder smooth muscle. Activation of these receptors mediates contractions of bladder muscle strips *in vitro* [36]. The administration of captopril, an ACE inhibitor, causes a decrease in the amount of serosal hyperplasia and trans-mural collagen deposition in the bladder after partial outlet obstruction in neonatal rabbits compared to untreated animals [37]. Moreover, AT_1 receptor blockade ameliorates the inflammatory infiltration, submucosal edema, urothelial detachment, and lymphocytic infiltration observed in a murine auto-immune model of IC [38]. Additionally, catecholamines can alter the release of AT II. Ming et al. [39] demonstrated that isoproterenol enhances the stimulatory effect of dexamethasone on the expression of the *AT* gene via β_2-adrenergic receptors in mouse hepatoma cells. Isoproterenol increases the release of AT II from isolated perfused mesenteric arteries, and this release can be blocked by propranolol [40]. In other studies, isoproterenol also increased the secretion of AT II in neuronal cultures,

cultured bovine aortic endothelial cells, and the brachial arteries of hypertensive subjects [41-43]. Propranolol treatment also reduces plasma renin activity (PRA), AT I, AT II, and AT-(1-7) expression in the portal vein and the periphery of cirrhotic patients compared with non-treated patients [44]. Compared with untreated cells, carvediol inhibits both basal and stimulated ACE production in human endothelial cells [45] and exhibits beneficial effects on ACE activity and PRA levels in CHF patients [46]. Taken together, RAS can be activated in IC patients and β-adrenergic receptor blockers may play a role in these patients by modulating this RAS cascade.

2.3 The Transcription Factor Nuclear Factor Kappa B (NF-Kb)

NF-κB is a hetero-dimeric, sequence-specific transcription factor that is found in many cell types. NF-κB has been implicated in chronic inflammatory diseases and is a key regulator of genes involved in responses to infection, inflammation, and stress. NF-κB is predominantly activated in bladder urothelial cells and the cells of the submucosal layer in biopsies from patients with IC compared with controls [47]. The NF-κB-induced expression of pro-inflammatory cytokines correlates with increased protein levels of NF-κB-regulated pro-inflammatory factors in the urine of IC patients compared with controls [48]. These findings suggest a pivotal role for NF-κB in IC pathophysiology. Sodium pentosanpolysulfate (SPP) has been identified as an urothelial cytoprotective agent for treating IC. NF-κB activation by lipopolysaccharide (LPS) and double-stranded RNA is suppressed when samples of IC urothelium are incubated with SPP [49]. Moreover, cardiac collagen deposition and the amount of apoptotic cells were elevated in ketamine-treated rats compared with control animals; these effects can be prevented by the co-administration of metoprolol. Other studies have shown that the expression of NF-κB-light-chain-enhancer of activated B cells was increased after ketamine treatment and sharply reduced after metoprolol administration [50]. Carvedilol also blocks *in vitro* human peripheral blood T-cell activation by down regulating NF-κB activity [51]. Additionally, propranolol suppresses gastric cancer cell growth through downstream NF-κB activation [52-53]. Finally, β_2-adrenergic antagonists suppress the activation of NF-Kb [54] and potentiate the anti-proliferative effects of gemcitabine by inducing apoptosis in pancreatic cancer cells [55]. Taken together, these studies indicate that β-adrenergic receptor antagonists may suppress NF-κB activation in IC.

2.4 Nerve Growth Factor (NGF)

Urinary tract NGF is produced by the urothelium and smooth muscle [56]. Clinical and experimental data indicate a direct link between increased levels of NGF in the bladder tissue and urine in painful inflammatory conditions in the lower urinary tract. Urinary NGF levels are significantly higher in patients with IC than in controls [57-62]. NGF participates in the development of thermal and mechanical hyperalgesia [63-65]. Intra-vesicular instillation of NGF induces bladder hyperactivity in rats [66]. Blockade of NGF, using either an endogenous antibody or an antibody against the NGF receptor, prevents neural plasticity and bladder over-activity in experimental models of these conditions [58]. Urinary NGF levels are increased in patients with IC compared with healthy controls and decreased in those patients who respond to IC treatment [57,59] suggesting that urinary NGF levels can be a useful biomarker for detecting the severity of the IC. Clenbuterol, a long-acting β_2-adrenergic agonist, caused significant increases in both NGF mRNA and protein expression levels in Swiss mouse 3T3 cells [67]. Exposure of the nerve cells to isoproterenol, a β-adrenergic agonist, increase NGF mRNA, and this effect can be blocked by propranolol [68-69]. Interestingly, NGF acts with the β_2-adrenoceptor to induce spontaneous nociceptive

behavior during temporo-mandibular joint (TMJ) inflammatory hyperalgesia. However, co-administration of carrageenan with the β_2-adrenoceptor antagonist ICI 118.55 significantly reduces NGF-induced nociception [70]. One possible mechanism by which β-adrenergic receptors antagonists may be involved with nociceptive pain is related to its reported neuro-protective effects during cerebral ischemia [71-73]. Brain injury is reduced and neurological outcome are improved after middle cerebral artery occlusion in mice lacking the β_2-adrenergic receptor or in wild type mice that have been pretreated with a β_2-adrenergic receptor antagonist [74]. Taken together, β-adrenergic receptor antagonist may have a role in IC by modulating the secretion of NGF.

2.5 Vascular Endothelial Growth Factor (VEGF)

Finally, angiogenesis is a complex process involving the coordinated steps of endothelial cell activation, proliferation, migration, tube formation, and capillary sprouting, and it requires the participation of many intracellular signaling pathways. VEGF is a key mediator of angiogenesis. The vascular changes associated with angiogenesis usually occur in cancer, but they have also been reported in inflammatory diseases. VEGF signaling can occur in the bladder urothelium because the urothelium expresses the VEGF receptors and co-receptors neuropilins [75]. VEGF over-expression was reported in bladder biopsies from IC patients [76]. Specifically, IC bladder tissue expresses VEGF receptors and co-receptors throughout the urothelium, whereas these receptors and co-receptors are predominantly co-localized to apical cells in control bladders [77]. VEGF expression in the lamina propria was significantly higher in IC tissue compared with control samples. Among IC patients, VEGF expression is significantly higher in those patients with severe pain as opposed to those patients with mild pain [78]. Moreover, NE treatment increases VEGF levels in cultured nasopharyngeal carcinoma (NPC) tumor cells, and this increase can be inhibited by propranolol. NE also induces the invasiveness of all NPC cell lines in a dose-dependent manner, and this induction can be blocked by propranolol [79]. Propranolol significantly decreases VEGF activity in a phorbol myristate acetate (PMA)-activated human leukemic cell line [80]. This drug also represses gastric cancer cell growth through its downstream effects on VEGF [52-53]. Alternatively, NE increases the expression of VEGF, and these effects can be inhibited by propranolol in pancreatic cancer cells [81,54]. In addition, epenephrine enhances the expression of VEGF in colon adenocarcinoma cells. The stimulatory action of epinephrine on colon cancer growth can be blocked by atenolol and ICI 118,551, which are β_1- and β_2-selective receptor antagonists, respectively [82]. β_2-Adrenergic receptor blockade regulate VEGF production in a mouse model of oxygen-induced retinopathy [83]. Hypoxia-inducible factor-1α and VEGF mRNA and protein expression are up-regulated in a rat model of volume-overload heart failure; these abnormalities were reversed with carvedilol treatment [84]. These findings suggest that β-adrenergic receptor antagonists modulate VEGF expression in IC.

3. THE ROLE OF β-ADRENERGIC RECEPTOR BLOCKERS IN INTERSTITIAL CYSTITIS:

3.1 Stress

Patients with IC frequently report symptom exacerbation due to stress [85]. Robbins et al. [86] demonstrated enhanced nociceptive processing related to the urinary bladder following exposure to a chronic psychological stressor in a high-anxiety strain of rats. A significant relationship between stress and urgency was observed in patients with IC. In a life stress

model, higher levels of stress were related to greater pain and urgency in patients with IC but not in controls. In addition, the relationship between stress and IC symptoms is stronger among patients with more severe disease [87]. In a laboratory stress model, an acute stressor evokes increased symptoms of pain and urgency in patients with interstitial cystitis but not in controls [88]. Female patients with IC had an increased heart rate at baseline and throughout a laboratory mental stress challenge compared with healthy age- and sex-matched controls [89]. The effects of stress on immune and inflammatory processes are well documented [90-91]. Stress-related mechanisms are associated with bladder inflammatory processes such as mast cell activation in IC [92]. Increased peripheral sympathetic nerve density and activity in the bladder of patients with IC have also been reported [93]. There is a positive correlation between the number of sympathetic fibers supplying the bladder and the severity of IC symptoms [94]. These findings are consistent with sympathetic effects on inflammatory processes in interstitial cystitis. Moreover, acute premedication with the β-adrenergic receptor antagonist celiprolol can prevent a sudden drop in cardiac function after acute stress [95]. Stress-induced activation of the locus ceruleus-NE system produces significant cognitive and behavioral effects, including enhanced arousal and attention, and this effect is reversed by β-adrenergic receptor antagonism [96]. Social defeat stress induces hyperthermia by activating thermoregulatory sympathetic premotor neurons in the medullary raphe region, and the systemic blockade of β_3-adrenoreceptors, which are abundantly expressed in BAT, attenuates this stress-induced hyperthermia [97]. Rotational stress impairs cutaneous wound healing due to increased epinephrine levels, and propranolol administration reverses the deleterious effects of stress on wound contraction and re-epithelialization [98-99]. Psychosocial stress is associated with altered immune function and development of psychological disorders including anxiety and depression. Repeated social defeat also significantly increased the number of $CD11b^{+}/CD45^{high}/Ly6C^{high}$ macrophages and leads to increases in several inflammatory markers on the surface of microglia (e.g., CD14, CD86, and toll-like receptor-4) and macrophages (CD14 and CD86). These stress-dependent changes in the microglia and macrophages are prevented by propranolol [100]. In addition, propranolol also decreases post-traumatic stress symptoms [101]. These findings suggest that IC-associated stress, which is induced by the activation of β-adrenergic receptor agonists, could be modulated by β-adrenergic receptor antogonists.

3.2 The Mitogen-Activated Protein Kinase (MAPK) Pathways

The MAPK pathways provide a key link between the membrane-bound receptors and changes gene expression patterns, including the ERK cascade, the stress-activated protein kinases/c-jun N-terminal kinase (SAPK/JNK) cascade, and the p38MAPK/RK/HOG cascade [102]. MAPK signaling pathways are involved in experimental interstitial cystitis [103]. Epidermal growth factor receptor (EGFR)/ErbB1/HER1 peptide ligands, heparin-binding EGF-like growth factor (HB-EGF), EGF, and anti-proliferative factor (APF) have been identified in urine from IC patients [104-105]. HB-EGF and APF functionally antagonizes interstitial cystitis APF via MAPK pathway activation [106]. Enhanced p38MAPK expression levels in the urothelium are also evident in patients with Chernobyl cystitis, a urological disease caused by chronic exposure to low dose Cs radiation [107], suggesting that alterations in the p38MAPK cascade are early molecular events in the pathogenesis of bladder epithelial cells. In addition, JNK/SAPK expression may also be important for controlling uro-epithelial cell proliferation because JNK1 levels are decreased in both IC and APF-treated normal bladder epithelial cells compared with untreated cells [105]. These data suggest that the balance between urinary APF- and HB-EGF-induced effects on bladder epithelial cells may influence the rate of cell turnover in the bladder mucosa of patients with IC. Moreover, stimulating the β-adrenoceptors activates cAMP/protein kinase A (PKA) and

MAPK pathways in pancreatic cancer cells. β_2-Adrenergic antagonists suppress invasion and proliferation by inhibiting both cAMP/PKA and Ras, which regulate activation of the MAPK pathway [54]. NE stimulates pancreatic cancer cell proliferation, migration and invasion via β-adrenergic receptor-dependent activation of the p38/MAPK pathway. These stimulatory effects are completely abolished by propranolol or p38/MAPK inhibitor SB203580 [108]. Interestingly, propranolol exerts its suppressive effects on hemangiomas through the hypoxia-inducible factor (HIF)-1α-VEGF-A angiogenesis axis, with effects mediated by the PI3/Akt and the p38/MAPK pathways [109]. Taken together, β-adrenergic receptor antagonists may have a role in IC by suppressing the MAPK pathway.

3.3 Prostaglandins (PGs)

PGs play a role in inflammatory processes. Cyclooxygenase (COX) participates in the conversion of arachidonic acid into PGs. Human urinary bladder tissue can synthesize several types of PGE [110]. The rat bladder also produces prostacyclin and other PGs [111]. Chronic urothelial injury leads to increased urinary frequency and decreased voided volume, and is associated with increased PGE_2 levels in the bladder [112]. Urinary PGE_2 excretion is increased in IC patients [113]. Intra-vesicular administration of PGE_2 in rats causes detrusor over-activity and stimulates reflex micturition [114]. PGE_2 plays a critical role in the generation and maintenance of the hyperalgesia that develops at sites of inflammation [115]. PGE_2 also induced bladder pressure increases and has a direct contractile effect on the detrusor smooth muscle [114]. Furthermore, water avoidance stress increases voiding frequency through COX-2 expression at both the RNA and protein levels in a rat model; however, voiding frequency and high COX-2 expression are reduced by pretreatment with the COX-2 inhibitor etodolac [116]. COX-2 is up-regulated in epithelial cells isolated from IC bladder biopsies compared with control tissues [117]. Miki et al. [118] demonstrated that PGE_2 and its receptor participated in processing cystitis-related bladder pain in mice. ONO-8130, a selective PGE_2 receptor antagonist, relieves bladder pain in mice with CP-induced cystitis [118]. Moreover, immortalized human urothelial cells β-adrenergic receptor activation significantly increases the amount of COX-2 produced through a PKA-independent mechanism [8]. Epinephrine increases PGE_2 release in human colon adenocarcinoma HT-29 cells, and this increase can be blocked by a COX-2 inhibitor, β_1-selective adrenergic antagonist atenolol, and the β_1- and β_2-selective adrenergic antagonist ICI 118,551 [82]. The β_2-adrenergic antagonists suppressed COX-2 expression in pancreatic cancer cells [54]. Propranolol inhibits cell proliferation and represses gastric cancer cell growth through the downstream COX-2 pathway [52-53]. In addition, administering propranolol and a COX-2 inhibitor, which can be applied peri-operatively in most cancer patients with minimal risk and low cost, counteracts several immunologic and endocrinologic perturbations and improves recurrence-free survival rates in mice undergoing primary tumor excision [119-120]. These findings suggest that β-adrenergic receptor antagonists play a role in modulating the inflammatory process in IC.

3.4 Reactive Oxygen Species (ROS)

ROS play a role in IC [121]. CP causes hemorrhagic cystitis mainly via oxidative stress induction. In CP-treated animals, oxidative stress parameters are altered; protein carbonyl content, protein thiol, malondialdehyde (MDA), conjugated dienes, and lipid peroxidation are elevated. However, thioredoxin reductase and glutathione peroxidase activities were decreased [122-124]. Still, aminoguanidine and Satureja khuzestanica protect rats from CP-induced hemorrhagic cystitis by reducing free radical-induced toxic stress and bladder

damage [122-123]. Moreover, analysis of myocardial tissue sections revealed increased ROS after traumatic brain injuries. Treatment with propranolol decreases ROS levels [125]. Carvedilol can modulate ROS-induced signaling. Carvedilol significantly decreases ischemia-reperfusion-induced free radical production and NAD^+ catabolism, and decreases lipid peroxidation and red blood cell membrane damage as determined by free MDA production during heart perfusion and in a rheological model [126]. Nebivolol improves diastolic dysfunction and myocardial remodeling through reducing oxidative stress in the transgenic (mRen2) rat [127]. These findings suggest that β-adrenergic receptor antagonists modulate oxidative stress in IC.

3.5 Nitric Oxide (NO)

NO is involved in host defense reactions and plays a key role in vascular disorder pathophysiology. NO levels are altered in human with IC and in chemically-induced animal models of cystitis [128-129]. NO is involved in host defense reactions and plays a key role in vascular disorder pathophysiology. The urinary NO concentration is markedly elevated in patients with IC compared with control subjects [130,129]. Hosseini et al. [131] reported a statistically significant correlation between changes in symptom/problem score and changes in luminal bladder NO inpatients with IC. Inducible nitric oxide synthase (iNOS) expression and NO production are increased in incubated primary cell cultures with plasma from CP-treated rats [132]. Patients with IC have higher iNOS mRNA expression levels and NO production than control patients [133]. NO is a smooth muscle relaxant and vasodilator; however, NO can also be toxic when produced in excess for a prolonged time, leading to increased free radical formation and subsequent cellular damage [134]. Increased iNOS over-production may cause barrier dysfunction in several tissues [135]. These findings suggest that iNOS-dependent NO production may have a role in epithelial barrier dysfunction in IC. Moreover, activation of an immortalized human urothelial cell β-adrenergic receptor significantly increases the amount of iNOS produced through a PKA-independent mechanism [8]. Metipranolol blunted NO-induced lipid peroxidation in rat eye and retinas [136]. Nebivolol prevents vascular NOS III uncoupling in experimental hyperlipidemia [137]. Propranolol suppresses hemangioma growth by inhibiting the expression of eNOS protein and the subsequent production of nitric oxide [138]. Celiprolol activates eNOS through the PI3K-Akt pathway via NF-κB, which is induced by oxidative stress [139]. These findings suggest that β-adrenergic receptor antagonists may have a role in IC by inhibiting the expression of NOS.

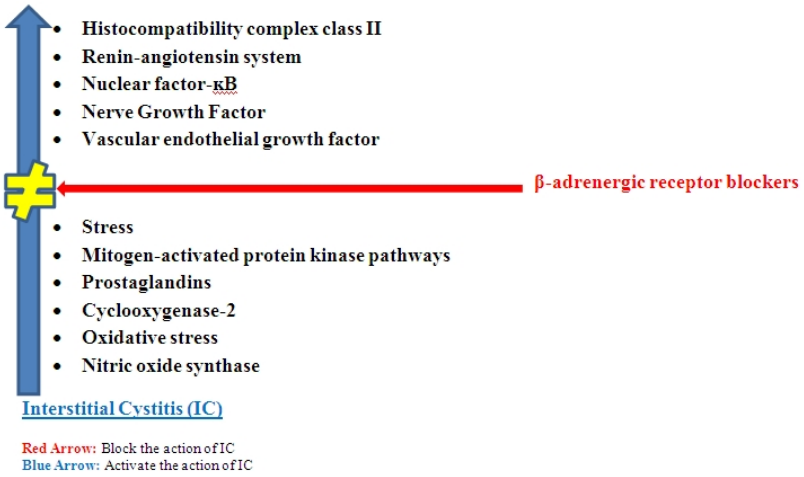

Fig. 1. Showed the role of β-adrenergic receptor and its inhibitors in interstitial cystitis

4. CONCLUSION

β-Adrenergic receptor blockade may play a role in the treatment of IC. Genetic studies have provided the opportunity to determine the proteins that link β-adrenergic receptor antagonism to IC pathology. β-Adrenergic receptor inhibition also exerts its effect on IC via non-genomic mechanisms. Further investigation of the relationship between β-adrenergic receptor antagonists and IC is required.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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