THE ROLE OF PROSTANOIDS IN THE URINARY BLADDER FUNCTION AND A POTENTIAL USE OF PROSTANOID-TARGETING PHARMACOLOGICAL AGENTS IN BLADDER OVERACTIVITY TREATMENT

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Abstract: Overactive bladder (OAB) is a syndrome involving urinary urgency with accompanying increased daytime urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of an urinary tract infection or other obvious pathology. The detailed OAB pathophysiology remains unclear. There is evidence that OAB pathogenesis also includes abnormal bladder paracrine activity, associated with release of local prostanoids. Those agents contribute to disturbances of peripheral neuronal bladder control resulting in detrusor instability. Thus, pharmacological agents abolishing prostanoid-induced bladder overactivity seem to be a potential, future OAB therapeutic option. This paper shortly describes the rationale for nonsteroidal anti-inflammatory drugs (NSAIDs) and EP-1 receptor antagonists administration in future OAB pharmacotherapy.

Keywords: overactive bladder, prostanoids, cyclooxygenase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), prostaglandin receptor antagonists


General introduction

Overactive bladder (OAB) is a complex syndrome defined by the International Continence Society (ICS) as the urinary urgency with accompanying increased daytime urinary frequency and nocturia, with (“wet” OAB) or without (“dry” OAB) urgency urinary incontinence, in the absence of an urinary tract infection or other obvious pathology (1–3). According to that report, urinary urgency is “a complaint of a sudden, compelling desire to pass urine which is difficult to defer”, increased daytime urinary frequency means “complaint that micturition occurs more frequently during waking hours than previously deemed normal”, nocturia is “complaint of interruption of sleep one or more times because of the need to micturate (each void is preceded and followed by sleep), urgency (urinary) incontinence is defined as “complaint of involuntary loss of urine associated with urgency (3).

The key OAB symptom is a sudden and strong desire to void that cannot be postponed – “urgency” and the term replaced “urge” as the “accepted” terminology for the abnormal rather than the normal phenomenon (3). The urgency and increased daily urination observed in OAB patients result from a reduced functional bladder capacity and the frequency is, at least partly, caused by adaptation of the patients to avoid urine leakage by maintaining a relatively low urinary volume inside the bladder (4).

OAB symptoms may also occur in neurological lesions involving central nervous system (stroke, Alzheimer disease, Parkinson one or multiple sclerosis) and the condition is referred to as neurogenic OAB, with a different etiology comparing to idiopathic OAB mentioned in the ICS definition above (4).

In overall estimation, OAB is reported to affect about 16.6% of European population, with the incidence increasing with age – thus being an increasing
problem in aging societies (5). Despite the clinical importance of OAB, the detailed pathogenesis of this syndrome still remains unclear. In general, an unifying OAB development theory has been proposed, involving two main pathophysiological concepts: the neurogenic and the myogenic one. They have been described in many reviews in this field (6–11), also of our authorship (12). To sum up, disturbances of both central mechanisms and peripheral afferent/efferent bladder innervation contribute to neurogenic background of OAB while bladder smooth muscle and interstitial cells abnormal electrical activity are key factors of myogenic OAB pathophysiological theory. Considering the problem discussed in this paper, paracrine modulation of the peripheral, autonomic bladder neural control through many locally synthetized and released mediators is regarded to be critical.

According to the anatomical description, the urinary bladder is divided into the bladder dome and the base, composed of the trigone, ureterovesical junction, lateral wall of the detrusor along with the anterior bladder wall (4, 13). Cross-sections of that organ reveal three essential separate layers: the urothelium, the suburothelial layer and the detrusor muscle. Moreover, the urothelium surface is covered by a glycosaminoglycan (GAG) external layer, which is most probably responsible for maintenance of an osmotic barrier and constitutes an antibacterial coating (4, 13).

At present, some greater attention is being drawn to the urothelium (uro-epithelium), which is perceived no longer as a mere barrier separating the bladder lumen from its underlying tissues, but also as the sensor with a particular endocrine/paracrine activity. The urothelium consists of three layers: basal cells attached to a basement membrane, intermediate cells and superficial, apical cells referred to as “umbrella cells”, covered by GAG. The suburothelium is richly supplied by blood vessels, nerves and interstitial cells (IC) that are suggested to modulate the activity of the suburothelial afferents. The bladder muscle layer also contains IC cells; however, they are similar to intestinal interstitial cells of Cajal, mediating contractions. Therefore, the bladder IC detrusor cells are thought to play a pacing role (4, 13, 14). The term “lamina propria” has been also implemented to distinguish the bladder wall from the detrusor and all remaining tissues. The bladder lamina propria (urothelium and suburothelium) has been shown to release several substances, acting via appropriated receptors in response to various stimuli: bradykinin, purines, adenosine triphosphate (ATP), nitric oxide (NO), neuropeptides (e.g., substance P), cytokines and some others. Among them, there are also the – so-called – eicosanoids (involving prostaglandins, prostacyclins, thromboxanes and leukotrienes) that are treated as lipids mediators, being derivatives of 20-carbon unsaturated fatty acids (mostly the arachidonic one) (4, 13).

Prostanoids – a brief general outline

Eicosanoids (also known as isosanoids) are oxygenated derivatives of three different 20-carbon fatty acids. The origin of that term is associated with the Greek name “eikosi” meaning “twenty” (15). They are synthetized from either ω-3 (eicosapentanoic; EPA – with 5 double bonds) or ω-6 (arachidonic; AA – with 4 double bonds or dihomo-γ-linolenic; DGLA – with 3 double bonds), 20-carbon, unsaturated fatty acids (16).

Current usage limits the term “eicosanoids” to leukotrienes (LT) and three types of prostanoids – prostaglandins (PG), prostacyclins (PGI) and thromboxanes (TX) (15). The further part of this paper will be limited to the description of the role of prostanoids (especially prostaglandins) in bladder physiology and pathophysiology. Prostaglandins contain a 5-membered cyclopentane ring and two side ω and ω chains linked to the ring. The thromboxanes have a 6-membered ring (an oxane one), instead of the cyclopentane structure (16). As it has already been mentioned above, prostanoids may be synthesized from DGLA acid (8,11,14-eicosatrienoic acid), AA acid (5,8,11,14-eicosatetraenoic acid) and EPA acid (5,8,11,14,17-eicosapentanoic acid). However, the second one is the most abundant in mammalian cells, therefore it is the main substrate for eicosanoid synthesis. The arachidonic acid (AA) is released from cell membrane phospholipids in response to various physiological and pathological stimuli by the action of phospholipases and converted into eicosanoids by subsequent synthases. Phospholipase A2 is a membrane-bound enzyme that cleaves AA from membrane phospholipids. The other enzyme that is also able to liberate the AA is phospholipase C. The released arachidonic acid is a substrate for prostanoid synthesis – along the cyclooxygenation pathway; or for leukotriene production – along the lipoxygenation pathway. The lipoxygenase pathway and leukotrienes will be not discussed in this paper. PG production is associated with the activity of PGH₃ synthase and PG endoperoxide synthase. Those enzymes are usually denoted to be cyclooxygenases (COXs; COX-1 and COX-2) and they were shown to occur in two isoforms, initially termed PGH₁ and PGH₂ synthases. The first “cyclooxygation” reaction is based on the addition of
an oxygen molecule to the AA structure to form an intermediate compound named PGG2. In the second step, PGG2 is converted into PGH2. The process uses the peroxidase activity of COX. Finally, the transformation of PGH1 occurs, depending on the several, cell-specific enzymes, including synthases, isomerases and reductases. With regard to a specific cell, prostaglandins (PGE2, PGI2, PGD2, PGE3), thromboxanes (TXA2) or prostacyclin (PGI2) are synthesized. Cyclooxygenases are encoded by genes located on the chromosome 9 (COX-1) and 1 (COX-2). COX-1 is expressed in most cells (mostly in vascular endothelial cells, stomach, kidney, vascular smooth muscles, blood cells but except red blood cells) and it is a source of – so called – housekeeping prostanooids, involved in numerous physiological functions, preserving homeostasis of most systems. COX-2 level is low in normal tissues but it becomes induced by inflammatory stimuli as well as hormones or growth factors and is responsible for prostanooids formation in inflammatory or cancer conditions (15, 17, 18).

Prostanoids exert their effect via the receptor mechanism. They are ligands for prostanoid receptors that belong to the rhodopsin-like 7-transmembrane-spanning G protein-coupled receptors family. The family is divided into 8 classes: E-prostaglandin receptor (EP); with further subclassification into 1–4 subtypes (EP1–EP4), PGD receptor – for prostaglandin D (DP1); PGF receptor – for prostaglandin F (FP), PGI receptor (IP) and thromboxane (TP). Moreover, there is also another receptor that responds to PGG2, called the chemoattractant receptor – homologous molecule expressed on T-helper 2 cells (CRTH2 or DP2) that belongs to the chemokine receptor family (N-formyl-methionyl-leucyl-phenylalanine chemoattractant receptor superfamilly). Two additional isoforms of the TP receptor (TPα, TPβ) as well as of the FP receptor (FPA, FPB) may be also distinguished (17, 19).

The intracellular signalling pathway of prostanoid receptors differs between subtypes. EP2, EP4, IP and DP receptors act through adenyl cyclase activation via Gs protein resulting in intracellular cAMP elevation. EP1 and FP are linked to the Gq and phosphatidylinositol with its derivatives (IP3, DAG), finally leading to intracellular calcium mobilization. Moreover, FP receptors also act through a small G-protein Rho via a Gq-independent mechanism. TP receptors are associated with both Gq and G13 proteins and phospholipase C but they can be also coupled via Gh to phospholipase C as well as via Gi/Gs to adenylylate cyclase (17).

Prostanoids exert variety of actions. Usually, they affect smooth muscles causing either their relaxation or contraction, acting via appropriate receptors and opening or closing calcium channels. Prostanoids are also demonstrated to modulate neuronal activity by several ways: inhibiting or stimulating neurotransmitter release, sensitizing sensory fibres, inducing some general actions (such as fever). One of the most important regulatory role of prostanoids is their modulatory influence on both secretion and motility of the gastrointestinal tract as well as on renal blood flow and transport of ions and water in kidneys. Prostanoids also regulate the activity of both platelets and endothelial cells and are involved in vascular homeostasis and hemostasis (15).

Moreover, prostanoids belong to crucial mediators involved in various inflammatory mechanisms, resulting in development of pain, fever, redness and local edema. Those acute inflammatory symptoms result from both vascular (redness, local swelling) and central / peripheral neuronal (pain, fever) actions of prostanoids. Moreover, prostanoids exert other pro-inflammatory actions by their amplification in secretion of many cytokines, inflammatory cells activation and the role in the neuroinflammatory process (17). There are also reports confirming the role of prostanoids in transition and maintenance of chronic inflammation by development of a positive feedback loop and by induction of chemokines and recruitment of inflammatory cells to alternate active cell populations at affected sites or contribution in tissue remodelling as seen in angiogenesis and fibrosis (20). As it has already been mentioned above and according to the commonly accepted consensus, COX-1 is constitutively expressed under basic conditions in most cells, contributing to maintenance of local homeostasis, whereas COX-2 level is high in inflammatory states (15). Both COX isoforms are targets of non-steroidal anti-inflammatory drugs (NSAID), and that observation have become a background for general NSAID classification into non-selective, classical NSAID (inhibiting both COX isoforms) and selective COX-2 blocking agents. However, further studies resulted in more precise division of the NSAID group and according to recent arrangements, it is possible to distinguish selective COX-1 inhibitors, nonselective COX-1/2 ones, relatively selective – preferential COX-2 inhibitors and highly selective COX-2 ones. There are a lot of reviews (e.g., 21–24) offering detailed information on that subject.

Moreover, besides COX-1 and COX-2 isoforms, there is also a central COX-3 isoform currently distinguished, responsible for fever and co-responsible for central pain nociception, that is a...
target for paracetamol (25). Nevertheless, the existence of that COX-3 as well as the central paracetamol action associated with its influence on that isoform are controversial and require further studies. That issue is also a subject of many reviews (e.g., 26, 27) in this field. The detailed discussion of numerous pharmacological aspects of NSAID is beyond the framework of this paper and can be found in many available reviews.

Prostanoids and their role in bladder function

The early interest in the prostanoids role in the bladder function is dated back to early 1970s when it was demonstrated for the first time that those agents were released inside the bladder in response to distention and mechanical or inflammatory injury of the mucosa (28, 29).

The primary prostanoids: PGE$_2$, PGF$_{2\alpha}$, PGI$_2$, PGD$_2$ and TXA$_2$ are synthesized by cyclooxygenases in the bladder under both physiological and pathological conditions (29). There are some species-specific differences regarding the bladder prostanoid synthesis: in rabbits the main prostanoid is PGE$_2$, whereas PGI$_2$ is the principle prostanoid in rats (30, 31). In humans, the major prostanoid is PGI$_2$, followed by PGE$_2$, PGF$_{2\alpha}$ and TXA$_2$ (31). Those compounds are produced by both COX-1 and COX-2 in various tissues of the bladder. There is a general belief that, similarly to other organs, bladder COX-1 is a constitutive enzyme responsible for prostanoids required for maintenance of local bladder homeostasis, while bladder COX-2 expression is induced by various pathophysiological factors (29).

The expression of COX-1 is demonstrated in the urothelium, especially in its basal and intermediate layers. It suggests that prostanoids belong to a complex signaling system connecting urothelium, suburothelial cells of the lamina propria and the muscular layer. Bladder muscular layer shows expression of both COX-1 and COX-2 (29, 32).

All the prostanoid receptors, except those for PGD$_2$, and PGF$_{2\alpha}$, are expressed in the bladder (29). Moreover, the detailed distribution of bladder receptors for PGI$_2$ remains unknown. However, PGI$_2$ is produced inside the bladder in response to a distention, injury and inflammation (33). Additionally, no data have been published regarding bladder receptors for TXA$_2$, although it has been shown that thromboxane A$_2$ induced contractions of isolated smooth muscle of the bladder, while thromboxane A$_2$ receptor antagonist inhibited rhythmic rabbit bladder contractions (34, 35). A majority of reports referring to bladder prostanoids are associated with PGE$_2$, that mediates their effects by EP receptors found in the urothelium and suburothelial layer. In general, EP$_1$ and EP$_3$ receptors are believed to cause bladder contractions, whereas EP$_2$ and EP$_4$ induce bladder relaxation (36). Moreover, it was shown that the EP$_{3}$ receptor is involved in the initiation of the micturition in both humans and animals (37).

It is well documented that prostaglandins alter bladder motility and influence the micturition reflex in both humans and animals. Those agents decrease functional bladder capacity and micturition volume and increase voiding contraction amplitudes in urodynamic recordings (29). Thus, prostaglandins seem to be one of the agents involved in bladder overactivity. Among prostaglandins contributing to bladder overactivity, PGE$_2$ is thought to be the most likely compound (29). That finding is also consistent with reports confirming that overactivation of the EP$_1$ receptors is responsible for bladder overactivity in animal model of bladder outlet obstruction (37). It seems, that prostaglandins, locally produced mostly in the urothelium, are likely to influence bladder contractility via at least three mechanisms: a direct, receptor-manner effect on smooth muscle cells of the bladder, effects mediated by the interstitial cells activation, and a neuromodulatory influence on sensory fibers (29).

Apart from experimental studies, the arachidonate cascade products abnormalities have also been demonstrated in clinical trials, although results seem to be conflicting so far. Urinary levels of PGE$_2$ and PGF$_{2\alpha}$ were found to be higher in patients with OAB symptoms compared to the control (38). However, another study did not confirm those findings, showing no differences in urinary PGE$_2$ level in patients with interstitial cystitis and healthy controls (39). The discrepancy requires some further studies to explicitly investigate the role of prostanoids and disturbances in OAB patients as well as in healthy individuals.

Prostanoids as a possible target for therapeutic OAB agents

Currently used OAB pharmacological agents diminish the increased bladder contractility and that way alleviate symptoms of bladder overactivity. Because of the fact, that final activity of the detrusor is initiated by excitation of cholinergic, muscarinic receptors (mostly M$_3$, M$_4$), drugs targeting that mechanism are considered to be the principal pharmacotherapy. Thus, antimuscarinics – antagonists of M$_3$/M$_4$ receptors – are the fist-line treatment (4). The detailed description designed for current pharmacological OAB guidelines may be found in many
reviews, also of our authorship (40). There are also some new agents, studied as a potential novel OAB pharmacological options. They include drugs targeting the glutamate, glycnergic, GABA, enkephaline or purinergic systems, dopaminergic D₃, or adenergic β2 receptor agonists, vanilloids affecting TRPV₁ receptors, calcium L-channels antagonists and some other. The rationale of both use of antimuscarinics and studies of new agents mentioned above is associated with OAB pathophysiological implications that may also be found in many reviews (e.g. 6–10), also written by us (12, 40). Therefore, it will not be discussed in this paper. Among new potential OAB drugs, the agents based on the prostanoids system are also being considered. As it has already been mentioned above, prostaglandins were demonstrated to be involved in bladder overactivity, thus inhibition of their synthesis or the use of prostaglandin receptor antagonists seem to be a rational way to treat OAB patients. That hypothesis was confirmed repeatedly in some animal studies. One of the first research in this field was the work by Bultitude et al. (41), who in 1976 reported that COX inhibitors affected detrusor muscle activity in both in vivo and in vitro experiments. Further studies clarified the effects of selected NSAIDs in amelioration of OAB symptoms in various animal models. Lecci et al. (42) studied the influence of both non-selective COX inhibitor – dextropropofen and NS-398, a non-commercially available selective COX-2 inhibitor, in experimental cystitis in rats. They revealed that selective COX-2 inhibitors improved recorded urodynamic features resulting from inflammation-triggered bladder overactivity. Then, Angelico et al. (43) revealed that both non-selective and selective COX inhibitors were effective in suppression of the micturition reflex and in increasing of the bladder volume capacity in rats with overactive bladder, early following the bladder irritation evoked by intravesical instillation of diluted (0.2%) acetic acid. In the subsequent study, Kibar et al. (44) observed the tendency for reduced bladder contractile response to cholinergic stimulation following the intravesical aspirin administration in rabbit model of partially obstructed bladders. An interesting research also performed Takagi-Matsumoto et al. (45), who examined the effect of selected NSAIDs (aspirin, indomethacin, or ketoprofen) on urodynamic parameters in normal and cystitis rats and compared their ulcerogenic activity in the gastrointestinal mucosa. They revealed that NSAIDs (in the following rank order of potency: ketoprofen > indomethacin > aspirin) increased bladder capacity without any effect on micturition pressure in normal rats, while in cystitis rats, bladder capacity was increased and micturition frequency was decreased. Moreover, the bladder levels of prostaglandin were significantly decreased in cystitis rats pretreated with NSAIDs. Those researchers demonstrated also that both ketoprofen and indomethacin administered intraduodenally induced lesions in the gastrointestinal mucosa, but aspirin had no significant effect. They concluded that since aspirin, in contrast to ketoprofen or indomethacin, did not cause any gastrointestinal lesions, aspirin might be the NSAIDs treatment of choice for overactive bladder (45). In one of the latest study, Jang et al. (46) examined the effects of intravesical cyclooxygenase-2 (COX-2) inhibitors on the expression of inducible nitric oxide synthase (iNOS) and nerve growth factor (NGF) in cyclophosphamide (CYP)-induced overactive bladder (OAB). They showed that COX-2 inhibitor-treated rats displayed significant elongation of the contraction and intercontraction intervals compared to OAB non-treated rats and the contraction time was significantly shorter. On immunohistochemical staining, there was no iNOS activity and NGF activity was minimally localized in the mucosa and submucosa in healthy animals. In OAB rats, NGF activity in the mucosa and submucosa were increased, and there was greater expression of iNOS in all layers and of NGF in detrusor while in the COX-2 inhibitor-treated rats, their expression was less pronounced in all layers. They concluded that intravesical instillation with COX-2 inhibitors may reduce CYP-induced bladder hyperactivity and expression of iNOS and NGF (46).

Despite the increasing number of encouraging results originating from experimental studies, the clinical trials of NSAIDs as a potential therapeutic OAB option are rather scant. Cardozo et al. tested non-selective COX inhibitors: flurbiprofen (47) and indomethacin (48). They demonstrated that both examined NSAIDs were effective in alleviation of OAB symptoms. Flurbiprofen, administrated in 30 female OAB patients in a dose of 50 mg three times a day caused a significant reduction in frequency, urgency and urge incontinence. However, significant side effects (mostly indigestion, nausea, vomiting, dizziness, headache) occurred in 13 patients receiving flurbiprofen compared to 5 healthy individuals (47). Indomethacin, administrated for 1 month in a group of 32 OAB patients, also displayed the improvement in both nocturnal and diurnal voiding frequency (48). A reliable clinical estimation was performed by Sprem et al. (49), who evaluated the therapeutic efficacy of intravesically administered ketoprofen in 30 patients with urodynamically verified detrusor instability in double-
blind randomized placebo-controlled cross-over study. They found that ketoprofen was a feasible and effective treatment for detrusor instability as the maximum cystometric capacity and the urinary bladder volume at which the patients felt urgency to void were larger after ketoprofen administration than before it. Moreover, ketoprofen administrated intravesically produced no significant adverse effects (49). There are also reports concerning beneficial effects of EP$_1$ receptor antagonists in OAB. Wilbraham et al. (50) published a paper focusing on the assessment of the safety, tolerability and pharmacokinetic properties of ONO-8539, an EP$_1$ receptor antagonist, administrated in OAB patients and healthy subjects in phase I of the clinical study. This agent has been followed into the next stage of the clinical trial.

CONCLUSIONS

It should be expected that NSAIDs will be further evaluated, both in experimental and clinical studies, as a potential, novel OAB pharmacological option. Despite the common agreement that prostanoids play an important role in the bladder physiology as well as in OAB pathogenesis, and despite the rationale for potential application of agents targeting prostanoids synthesis or blocking prostanoids receptors, the clinical approaches have not yet brought satisfactory results. None of the NSAIDs or EP receptor antagonists studied in animal models of OAB have entered the standard therapeutic arsenal for OAB treatment so far. This failure is at least due to the relatively small number of studied subjects in the clinical trials, observed numerous adverse drug reactions or clinically unpractical and patients’ unfriendly route of administration (e.g., intravesically). However, those setbacks will not cease the efforts to find effective and safe prostanoids-based strategies to treat bladder overactivity and, therefore, it seems that NSAIDs (as well as EP receptor antagonists) will be able to be indicated also in that clinical entity in the future.

REFERENCES


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