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Therapeutic targets for urinary incontinence

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CONTENTS

Abstract

Urinary incontinence is a common condition associated with the involuntary loss of urine which can be a social and/or hygienic handicap. Urination involves a complex and balanced action of nerves, muscles of the urinary bladder, the spinal cord and the brain. Disturbances in this balanced action of nerves, muscles and brain can lead to urinary incontinence. The condition increases progressively with age and the potential causes are numerous and tend to vary between different age groups. Several subtypes of urinary incontinence have been reported, involving urgency, frequency, incontinence and nocturia. Many types of urinary incontinence can be effectively treated by relaxing bladder detrusor muscles or by tightening muscles in the urethral sphincter, thereby preventing leakage. In the interest of facilitating access to information on the principal targets for therapeutic intervention in urinary incontinence, this article presents those targets that are currently under active investigation.

Introduction

Urinary incontinence is a condition in which the involuntary loss of urine represents a social and/or hygienic problem. It can and does occur at any age, although the incidence increases progressively with age and the causes tend to vary between different age groups. Urination, or voiding, is a complex activity involving the coordination and correct function of nerves, muscles of the urinary bladder, the spinal cord and the brain. The bladder is comprised of two types of muscles: the detrusor, a muscular sac that stores urine and squeezes to empty, and the sphincter, a circular group of muscles at the neck of the bladder that automatically remain contracted to hold urine in and automatically relax when the detrusor contracts to let urine into the urethra. When the bladder is full, nerves in the bladder signal the brain, which supplies the urge to void. Under socially acceptable conditions for voiding, the brain sends a message to the detrusor to contract, squeezing urine out of the bladder. At the same time, the brain signals the sphincter and pelvic floor muscles to relax, allowing urine to pass through. At the end of urination, the sphincters again contract and the bladder muscle relaxes (1, 2). Disturbances in this balanced action of nerves, muscles and brain can lead to urinary incontinence.

Urinary incontinence is a common problem affecting more than 200 million people worldwide and its potential causes are numerous. The most frequently reported subtype of urinary incontinence is urge urinary incontinence, which is characterized by abnormal spontaneous bladder smooth muscle contractions that may be unrelated to bladder urinary volume, leading to leakage of large amounts of urine. Stress incontinence, another subtype, often results from physical changes occurring in women during pregnancy, childbirth and menopause, and is characterized by the leakage of urine while coughing, laughing, sneezing or making other movements that put pressure on the bladder (3). Overactive bladder is a highly prevalent and largely age-related condition characterized by the four typical symptoms of urinary urgency, frequency, incontinence and nocturia (4, 5). The prevalence of urinary incontinence is significantly greater in geriatric and psychogeriatric populations and the incidence is twice as high in women as in men.

Treatment for urinary incontinence depends on the type of incontinence, the severity of the problem and the underlying cause. Medications can effectively treat many types of incontinence by relaxing muscles so that the bladder empties more completely or by tightening muscles in the urethral sphincter, thereby preventing leakage. Pharmacotherapy of urinary incontinence can act either at the peripheral level, modulating contractions of bladder smooth muscle, or at the central level, affecting neurological control of the process of urination (6, 7).

The search for effective treatment strategies for urinary incontinence continues, with special attention focused on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

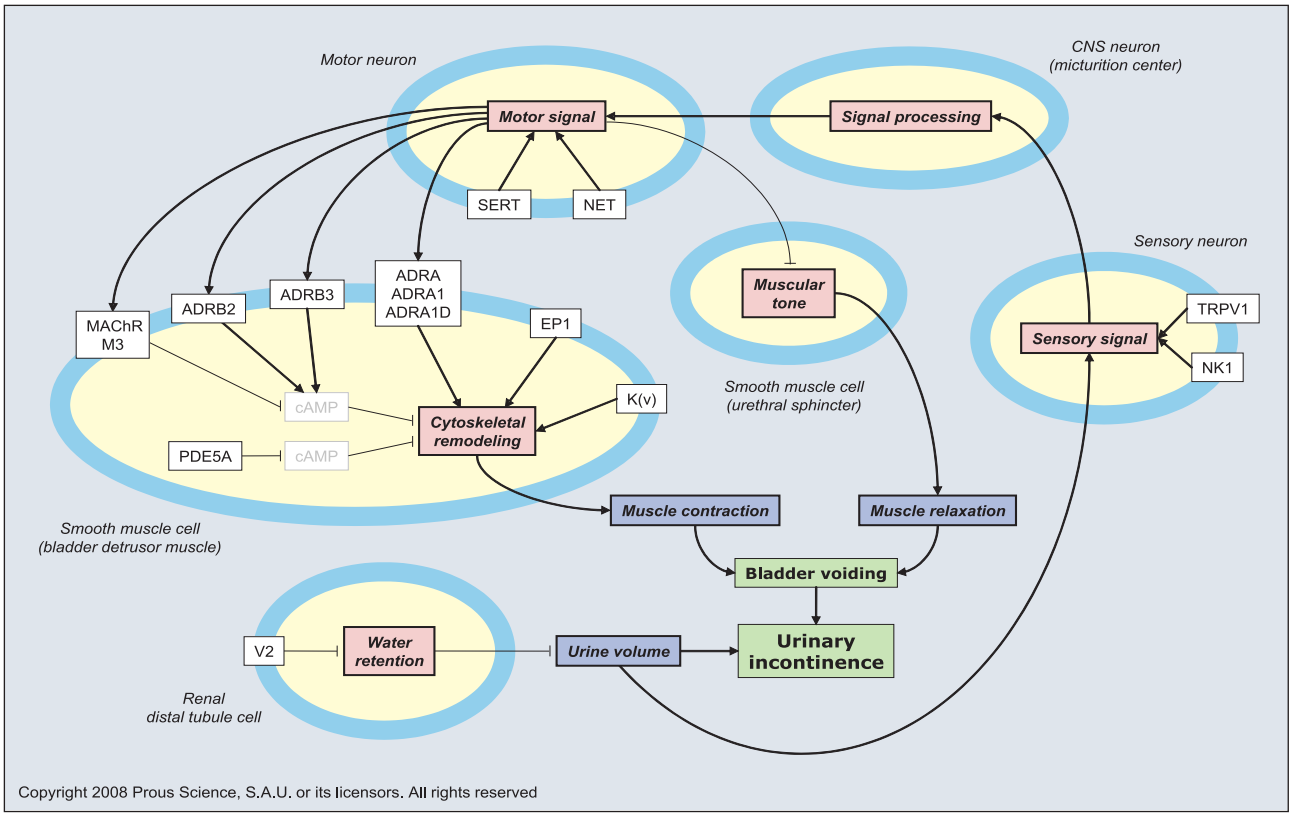

Fig. 1. Diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of urinary incontinence and their biological actions. Arrow: positive effect; dash: negative effect. Abbreviations: ADRA: α-adrenoceptor; ADRA1: α_1-adrenoceptor; ADRA1D: α_{1D}-adrenoceptor; ADRB2: β_2-adrenoceptor; ADRB3: β_3-adrenoceptor; MAChR: muscarinic acetylcholine receptor; M3: muscarinic M_3 receptor; NET: norepinephrine transporter; PDE5A: phosphodiesterase 5A; EP1: prostanoid EP_1 receptor; SERT: serotonin transporter; NK1: tachykinin NK_1 receptor; TRPV1: transient receptor potential TRPV1 cation channel; V2: vasopressin V_2 receptor; K(v): voltage-gated K_v channel.

Targets

α-Adrenoceptors

Adrenergic receptors, or adrenoceptors, are G-protein-coupled receptors present in effector tissues innervated by sympathetic adrenergic postganglionic fibers. They are activated by catecholamines (*i.e.*, epinephrine, norepinephrine), producing a change in tissue function (*e.g.*, smooth muscle contraction or relaxation). They can be subdivided into α_1, α_2, β_1, β_2 and β_3 subtypes based on their distribution in the body and on responses to activating or blocking agents. Activation of α-adrenoceptors is particularly important in the urinary system because it has a stimulatory effect on smooth muscle contraction. The α_1-adrenoceptor subtype transduces signals via G_q proteins when activated. It acts via activation of phospholipase C (PLC), which phosphorylates phosphatidylinositol to produce inositol trisphosphate (IP_3) and diacylglycerol, thus leading to the activation of Ca^{2+} channels of intracellular reservoirs and activation of protein kinase C (PKC). Increased cytosolic Ca^{2+} levels and activated PKC are key elements causing cell stimulation responses. Moreover, the α_{1D}-adrenoceptor subtype has been reported to play an important role in regulating bladder function. Since antagonists of these receptors can cause relaxation of the urinary bladder detrusor muscle, α-, α_1- and α_{1D}-adrenoceptors may be effective targets for the treatment of urinary incontinence (8-11).

β_2-Adrenoceptor

Like α-adrenoceptors, β-adrenoceptors are G-protein-coupled receptors that are present in effector tissues. β-Adrenoceptors are linked to G_s proteins. After catecholamine binding, G_s activates adenylate cyclase, causing an increase in intracellular cyclic adenosine monophosphate (cAMP). Moreover, this receptor is associated with the class C L-type Ca^{2+} channel $Ca_v1.2$, thus providing a mechanism that facilitates specific and rapid signaling by G_s protein-coupled receptors. Since high levels of intracellular cAMP oppose any cell stimulation response, activation of this receptor type generally causes sympathetic effects such as relaxation of smooth muscle cells. The β_2 subtype is widely distributed, including in urinary bladder detrusor muscle. Agonists of this receptor have been described to counteract bladder overactivity and may be effective in the treatment of urinary incontinence (12, 13).

Table I: Selected targets and products being actively investigated for urinary incontinence (from Prous Science Integrity®).

Target	Product	Source	Phase
α_1-Adrenoceptor (unspecified subtype)	Tamsulosin	Astellas Pharma	NDA filed
α_{1D}-Adrenoceptor	Naftopidil	Asahi Kasei	II
α-Adrenoceptor (unspecified subtype)	PSD-503	Plethora Solutions	II
β_2-Adrenoceptor	Clenbuterol	Teijin Pharma	Launched
β_3-Adrenoceptor	KRP-204 KUC-7483 Mirabegron Solabegron hydrochloride MN-246	Kyorin/Nisshin Pharma Kissei Astellas Pharma GlaxoSmithKline MediciNova	II II II II I
Muscarinic M_3 receptor	Tolterodine Darifenacin hydrobromide Solifenacin succinate Imidafenacin RO-3202904 SVT-40776	Pfizer Bayer Astellas Pharma Kyorin/Ono Plethora Solutions Salvat	L-1997 L-2004 L-2005 L-2007 II II
Muscarinic receptor (unspecified subtype)	Oxybutynin chloride Trospium HCl Propiverine Fesoterodine fumarate	Alza Madaus Schering-Plough Pfizer	L-1975 L-2000 L-2004 R-2007
Norepinephrine transporter (NET)	Duloxetine hydrochloride	Lilly	L-2004
Phosphodiesterase 5A (PDE5A)	Vardenafil hydrochloride hydrate	Bayer	II
Prostanoid EP_1 receptor	ONO-8539	Ono	I
Serotonin transporter (SERT)	Duloxetine hydrochloride	Lilly	L-2004
Tachykinin NK_1 receptor	AV-608 SSR-240600 TA-5538	Avera Pharmaceuticals sanofi-aventis Mitsubishi Tanabe Pharma	II II II
Transient receptor potential TRPV1 cation channel	GRC-6211	Glenmark Pharmaceuticals	I
Vasopressin V_2 receptor	FE-106483 SOU-003	Ferring Sosei	II I
Voltage-gated K_v channel	Besipirdine hydrochloride	Urogene	II

β_3-Adrenoceptor

Like β_2-adrenoceptors, the β_3-adrenoceptors are linked to G_s proteins, thus favoring the activation of adenylate cyclase and the subsequent increase in intracellular cAMP. Although β_3-adrenoceptors are located mainly in adipose tissue and are involved in the regulation of lipolysis and thermogenesis, functional studies have demonstrated that β_3-adrenoceptors also play an important role in the modulation of smooth muscle tone in human bladder. Moreover, recent studies demonstrate that selective activation of β_3-adrenoceptors induces bladder relaxation and facilitates urine storage mechanisms. Thus, β_3-adrenoceptor agonists may be effective therapies for the treatment of urinary frequency, urgency and urge incontinence (13-15).

Muscarinic receptors

Muscarinic receptors are G-protein-coupled seven-transmembrane-spanning acetylcholine receptor (AChR) proteins that have a high degree of sequence homology across species and receptor subtypes. Five subtypes of muscarinic receptor have been identified and found to be predominantly expressed within the parasympathetic nervous system and innervated tissues, and to exert inhibitory and excitatory control and play a role in physiological functions such as heart rate, arousal, cognition, sensory processing and motor control. However, only three subtypes (M_1, M_2 and M_3) have been pharmacologically well characterized. Activation of the stimulatory receptors M_1, M_3 and M_5 induces signal transduction through G_q proteins, which results in mobilization of intracellular Ca^{2+} and activation of PKC, while inhibitory M_2 and M_4 receptors transduce signals through G_i proteins, which negatively influence adenylate cyclase, thereby reducing cytoplasmic levels of cAMP. Low levels of cAMP upregulate cytosolic Ca^{2+} levels, which, together with activated PKC, are key elements causing cell stimulation responses. Muscarinic receptors are the main receptors regulating the detrusor muscle tone of the urinary bladder. Although M_3 is known to be primarily responsible for bladder con-

Table II: Selected patents for targets being pursued or explored for urinary incontinence (from Prous Science Integrity®).

Target	Patent	Source	Phase
5-HT_{1A} receptor	US 2007270436	Recordati	Biological testing
	WO 2006082872	Eisai	Biological testing
	WO 2006121106	Eisai	Biological testing
	WO 2006121104	Eisai	Biological testing
	JP 2005239578	Aska Pharmaceutical	Biological testing
	JP 2005225845	Aska Pharmaceutical	Biological testing
	WO 2005108389	Eisai	Biological testing
	WO 2003106444	Recordati	Biological testing
	WO 2003106443	Recordati	Biological testing
	WO 2003106421	Recordati	Biological testing
	WO 2003097060	Nippon Kayaku	Biological testing
	WO 2002044159	Lilly	Biological testing
	JP 2002114684	Eisai	Biological testing
	WO 1999006383	Recordati	Biological testing
	WO 1999006382	Recordati	Biological testing
	WO 1993017007	Recordati	Biological testing
5-HT_4 receptor	WO 2005013989	ACRAF	Biological testing
	WO 2004017960	Janssen	Biological testing
	WO 2001064671	sanofi-aventis	Biological testing
	FR 2769914	sanofi-aventis	Biological testing
	WO 1999025710	sanofi-aventis	Biological testing
	WO 1998004546	sanofi-aventis	Biological testing
	WO 1997017345	sanofi-aventis	Biological testing
	EP 0748807	sanofi-aventis	Biological testing
	WO 1993003725	ACRAF	Biological testing
Acetylcholinesterase	WO 1998043942	Pfizer	Biological testing
$P2X_3$ receptor	WO 2008000645	Roche	Biological testing
	WO 2007025899	Roche/Roche Palo Alto	Biological testing
	WO 2005095359	Roche	Preclinical/Biological testing
	US 6693136	Abbott	Biological testing
$mGlu_5$ receptor	WO 2007113276	Novartis	Biological testing
	WO 2007093542	Roche	Biological testing
	WO 2007072095	Gedeon Richter	Biological testing
	WO 2007072094	Gedeon Richter	Biological testing
	WO 2007072091	Gedeon Richter	Biological testing
	WO 2007072090	Gedeon Richter	Biological testing
	WO 2007072089	Gedeon Richter	Biological testing
	WO 2007071358	Novartis	Biological testing
$mGlu_1$ receptor	WO 2007072095	Gedeon Richter	Biological testing
	WO 2007072094	Gedeon Richter	Biological testing
	WO 2007072091	Gedeon Richter	Biological testing
	WO 2007072090	Gedeon Richter	Biological testing
	WO 2007038209	Schering Corp.	Biological testing
	WO 2007032854	Schering Corp.	Biological testing
	WO 2007024593	Schering Corp.	Biological testing
	WO 2006002051	Schering Corp.	Preclinical/Biological testing
$GABA_B$ receptor	WO 2005039569	Bayer	Biological testing
Vasopressin V_{1b} receptor	WO 2006072458	Abbott	Biological testing
Muscarinic M_4 receptor	JP 2005289890	Mitsubishi Tanabe Pharma	Biological testing
	JP 2004123649	Mitsubishi Tanabe Pharma	Biological testing
Prostanoid EP_3 receptor	WO 2006014024	Ono	Biological testing
	WO 2005000356	Ono	Biological testing
	WO 2003016254	Ono	Biological testing
Melanin-concentrating hormone MCH1 receptor	US 2005154022	Lundbeck	Biological testing
	US 2005154020	Lundbeck Research	Biological testing
	WO 2004004714	Lundbeck Research	Biological testing
	WO 2004005257	Lundbeck Research	Biological testing
Lysophosphatidic acid LPA_1 receptor	WO 2005058790	Ono	Biological testing
	WO 2005009469	Dainippon Sumitomo Pharma	Biological testing
	WO 2004031118	Ono	Biological testing
	WO 2003099765	Ono	Biological testing

Continuation

Table II (Cont.): Selected patents for targets being pursued or explored for urinary incontinence (from Prous Science Integrity®).

Target	Patent	Source	Phase
Fatty acid amide hydrolase	WO 2008023720	Astellas Pharma	Biological testing
	WO 2006088075	Astellas Pharma	Biological testing
	JP 2006306746	Astellas Pharma	Biological testing
α_{1B}-Adrenoceptor	WO 2005005397	Roche	Biological testing
	WO 2005005395	Roche	Preclinical/Biological testing
	WO 2002018348	Roche	Biological testing
	WO 2000078716	Toray	Biological testing
	WO 2000055143	Roche	Biological testing
5-HT_{2C} receptor	WO 2008007664	Takeda	Biological testing
	WO 2008007661	Takeda	Biological testing
	WO 2007132841	Takeda	Biological testing
	WO 2006103511	Pfizer	Biological testing

traction (see below), it has been shown that global activation of coexisting muscarinic receptor subtypes in detrusor muscle causes contraction. Thus, muscarinic receptor dysfunction may lead to micturition disorders such as urinary incontinence and overactive bladder, and antagonists for these receptors can be used as a therapeutic approach for micturition disorders (16-18).

Muscarinic M_3 receptor

A number of studies have demonstrated that M_3 receptors are widely expressed in bladder detrusor smooth muscle cells and play a major role in bladder contraction and micturition. This receptor subtype transduces signals through G_q proteins, which results in activation of PLC, upregulation of IP_3 and increases in intracellular Ca^{2+} and PKC activation, ultimately causing contraction of smooth muscle such as that observed in bladder detrusor muscle during micturition. Thus, M_3 antagonism may downregulate overactivity of these receptors and in consequence be effective in the management of urinary incontinence (16, 19).

Norepinephrine transporter (NET)

A monoamine transporter for the neurotransmitter norepinephrine (NE), the NET belongs to the solute carrier family 6 (SLC6), a family of Na^+/Cl^--coupled transporters. Like other neurotransmitter transporters, NET is a 12-membrane-spanning protein located in the cellular membrane of neurons that removes NE from the postsynaptic space back to synaptic vesicles, thus preventing its action. To do this, NET uses the Na^+/Cl^- electrochemical gradient that exists across the cell membrane. The function of NET and other neurotransmitter transporters is the maintenance of physiological balance and modulation of neurotransmission. Although NETs are ubiquitously distributed throughout the peripheral and central nervous system, the pudendal somatic motor nucleus of the spinal cord is densely innervated by serotonin (5-HT) and NE terminals, indicating a key role in the neural control of external urethral sphincter closure. It is believed that pudendal nerve activity causes the sphincter to contract, making it able to resist sudden increases in abdominal pressure, thereby preventing leakage of urine. Inhibitors of NET may therefore be suitable agents for the treatment of stress urinary incontinence because they may enhance the effects of NE on the pudendal nerve by increasing the time this neurotransmitter remains in the synaptic cleft, thus enhancing its beneficial action (20-23).

Phosphodiesterase 5A (PDE5A)

PDE5A is a PDE isozyme (EC class 3.1.4) that has relatively high affinity for cyclic guanosine monophosphate (cGMP) and hydrolyzes cAMP poorly. Phosphodiesterases regulate the tissue concentrations of cGMP, which in turn triggers smooth muscle relaxation. The enzyme soluble guanylate cyclase converts guanosine triphosphate (GTP) to cGMP, which in turn activates protein kinase G (PKG). Activated PKG initiates a phosphorylation cascade that results in maintenance of the Ca^{2+} internally sequestered in intracellular reservoirs such as the endoplasmic reticulum. Low intracellular Ca^{2+} levels prevent myosin-actin cross-bridge formation, thus inducing smooth muscle relaxation. The enzyme PDE5A blocks this cascade of events and thus the smooth muscle relaxation process by rapidly converting cGMP to the inactive 5'-GMP. Inhibitors of PDE5 block this enzyme, thereby sustaining muscle relaxation. Since a number of studies have demonstrated that PDE5A is present and biologically active in the human bladder and regulates bladder smooth muscle tone, this enzyme may be an affective therapeutic target in the treatment of urinary incontinence (24-26).

Prostanoid EP_1 receptor

The prostanoid EP_1 receptor is a G-protein-coupled receptor that mediates the actions of prostaglandin E_2 (PGE_2) and is characterized by a long intracellular loop compared to other prostanoid receptors. EP_1 receptors are mainly responsible for PGE_2-induced elevation of the free Ca^{2+} concentration via a still unidentified G-protein, although studies performed in *Xenopus* oocytes suggest that EP_1 couples to TRP5, which is a candidate for the receptor-activated Ca^{2+} channel, and is likely to exert its

actions via G_q/G_{11}. Prostaglandins are suggested to be involved in the pathophysiology of different bladder disorders, and the EP_1 receptor appears to have a role in the development of detrusor overactivity caused by PGE_2. Thus, EP_1 receptor antagonists may have potential in the treatment of detrusor overactivity (27-29).

Serotonin transporter (SERT)

The serotonin (5-HT) transporter (SERT) is a 12-membrane-spanning monoamine transporter protein. SERT allows neurons and other cells to accumulate 5-HT and is thought to be primarily responsible for the cessation of action of 5-HT after it is released from the nerve terminal into the synaptic cleft. As detailed for the NET (see above), the pudendal somatic motor nucleus of the spinal cord is densely innervated by 5-HT and NE terminals, thus playing a key role in the control of external urethral sphincter closure and prevention of urine leakage. Similar to NET inhibitors, SERT inhibition can be an appropriate strategy for the treatment of urinary incontinence because it would increase the availability of 5-HT to its receptor, enhancing serotonergic neurotransmission. Moreover, because of the close functional relationship between NET and SERT in lower urinary tract neuronal modulation, dual NET/SERT inhibition may provide a maximal beneficial effect (20, 22, 23, 30).

Tachykinin NK_1 receptor

The NK_1 receptor is a member of the tachykinin family of receptors that is activated by substance P. All tachykinin receptors are members of the superfamily of q type G-protein-coupled, seven-transmembrane-spanning receptors. Activation of G_q proteins transduces signals via activation of PLC, which phosphorylates phosphatidylinositol to produce IP_3 and diacylglycerol, thus leading to activation of Ca^{2+} channels of intracellular reservoirs and activation of PKC. Increased cytosolic Ca^{2+} levels and activated PKC are key elements causing cell excitatory responses. The NK_1 receptor is localized in both the central and peripheral nervous systems and is involved in nociception. The NK_1 receptor is commonly found in the afferent fibers that innervate smooth muscle. In the urinary bladder the NK_1 receptor facilitates afferent signaling. Moreover, bladder hyperactivity has been observed to be associated with high NK_1 receptor density in bladder muscle. Thus, NK_1 antagonists may be effective in the treatment of urinary incontinence and overactive bladder (31, 32).

Transient receptor potential TRPV1 cation channel

The transient receptor potential TRPV1 cation channel, also known as the vanilloid/capsaicin receptor, or VR1, is a membrane-bound nonselective, ligand-gated cation channel expressed by primary sensory neurons, including those in the dorsal root ganglia, which is a transducer of noxious stimuli. The channel is activated by capsaicin and other vanilloids and also by protons (*i.e.*, acidic pH) and heat. It is thought to contribute to increases in nociceptor function in pain states, but the molecular mechanisms of TRPV1 action are not well known. TRPV1 modulators may be effective analgesic agents and in the treatment of refractory detrusor overactivity that leads to urgency associated with overactive bladder (33, 34).

Vasopressin V_2 receptor

The vasopressin V_2 receptor is a G-protein-coupled receptor for arginine vasopressin that is involved in the control of water homeostasis. Vasopressin is a peptide hormone, also known as antidiuretic hormone (ADH), that is synthesized in the hypothalamus and released from the posterior pituitary. There are two forms which differ only in the amino acid at position 8: arginine vasopressin (AVP), which is widespread, and lysine vasopressin, which is found only in pigs. The hormone has antidiuretic and vasopressor actions. Two vasopressin receptor types (V_1 and V_2) have been identified and antagonists of either may be effective in the treatment of hypertension, whereas V_2 agonists are under development for the treatment of urinary incontinence, nocturnal enuresis and diabetes insipidus. The V_2 receptor belongs to the s type of G-protein-coupled receptors which are linked to the adenylate cyclase signaling pathway, with intracellular cAMP acting as the second messenger. High intracellular levels of cAMP regulate renal free water excretion by shuttling aquaporin AQP2 water channels from intracellular vesicles into the apical plasma membrane of the renal collecting duct cells, thereby increasing water permeability of the membrane and producing an antidiuresis. Thus, selective vasopressin V_2 receptor agonism resulting in increased water reabsorption in the kidneys may be expected to reduce urine production and in consequence be a useful strategy for urinary incontinence (35, 36).

Voltage-gated K_v channels

Voltage-gated K^+ channels are a very diverse group of ion channels. They are heteromultimeric transmembrane ion pores formed by several subunits specific for K^+ and play a critical role in controlling the membrane potential. It is thought that the membrane potential is a key factor determining detrusor muscle contractility, although the basic mechanisms remain incompletely understood. Urinary bladder smooth muscle membrane potential regulates the entry of Ca^{2+} through voltage-dependent Ca^{2+} channels and thereby the contractile state of the cell. K^+ channels play a critical role in modulating the membrane potential, acting as the major hyperpolarizing influence. K^+ channels fall into several families: the six-transmembrane-helix voltage-gated (K_v) channels, the two-transmembrane-helix inward rectifier (K_{IR}) channels, the Ca^{2+}-activated channels (K_{Ca}) and the tandem-pore domain (K_{2P}) channels. The K_v family has more than 40 members and although such diversity contributes significantly to shaping a multitude of electrical activities, K_v channels

have been characterized in isolated smooth muscle myocytes of urinary bladder tissues, among other organs. The properties of K_V channels make them prime candidates as potential therapeutic targets for the modulation of detrusor function in the treatment of urinary incontinence (37, 38).

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