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Cannabinoid System Contribution to Control Micturition

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ABSTRACT

Cannabinoid compounds, such as those that can be extracted from the Cannabis sativa plant (marijuana), produce a very wide array of central and peripheral effects, some of which may be of importance for the control of lower urinary tract function. Thus, stimulation of cannabinoid receptors, located both in the central nervous system and in different components of the lower urinary tract, has been shown to affect both normal micturition and various disturbances of bladder function. It is clear that systemically administered cannabinoids may be able to become clinically useful; however, a much greater understanding of the mechanisms of cannabinoid receptors in the control of the human lower urinary tract is necessary to facilitate development of novel cannabinoid drugs for the treatment of micturition disorders such as overactive bladder syndrome.

INTRODUCTION AND REVIEW

The Endocannabinoid System

Voiding dysfunction related to neurological lesions is particularly challenging to treat with our current pharmacological armamentarium due to the limited number of drugs that have an efficacy and adverse effect profile sufficient for approval and clinical use. Currently, the most commonly used drugs target the cholinergic (muscarinic acetylcholine receptors) and adrenergic systems (β3-adrenoceptors), or affect both autonomic and somatic nerves (botulinum toxin). As the different pathophysiological processes of lower urinary tract symptoms are under investigation, the understanding of the contribution of other endogenous systems to the control of micturition will expand our therapeutic options.

The endocannabinoid system plays a prominent role in several normal and pathological conditions, and has generated significant interest as a novel target in the academic and pharmaceutical fields. Phytocannabinoids can be extracted from the cannabis plant (marijuana). The main psychoactive compounds are Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol, and cannabinol. The chemical and pharmacological investigation of these compounds led to the discovery of 2 G-protein coupled cannabinoid (CB) receptors type I (CB_1) and type II (CB_2). A third receptor has recently been established to be sensitive to CB, called the G-protein coupled receptor 55 (GPR55; for review see [1]). The endocannabinoid system is composed of at least 2 major arachidonate-derived ligands, N-arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG), which mediate their effects by binding to CB_1 and CB_2 receptors (Figure 1). Both ligands are synthesized postsynaptically on demand and delivered in a retrograde fashion to bind to presynaptically localized CB1 receptors in the central nervous system (CNS) [2]. Activation of presynaptic CB_1 receptors in the brain or on primary afferents prevents neurotransmitter release by diminishing calcium conductance and by increasing potassium conductance [3]. They can modulate GABAergic and glutamatergic synapses and postsynaptic transmission of norepinephrine and dopamine. Activation of both receptors inhibits adenylyl cyclase by coupling to the α–subunit of the G protein of the Gi/o family.

In the nervous system, anandamide and 2-arachidonoylglycerol are primarily metabolized by the serine hydrolase enzymes

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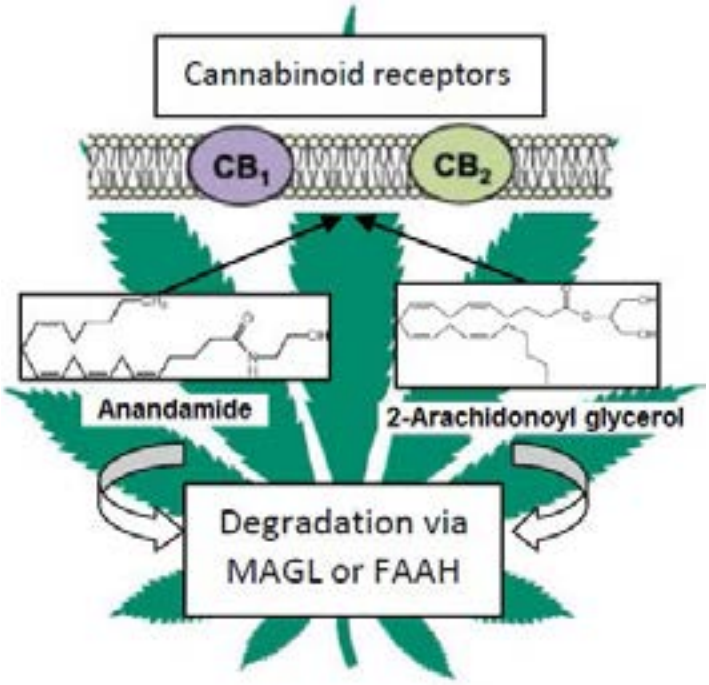
Figure 1. The endocannabinoid system and its metabolism. Anandamide and 2-Arachidonoyl glycerol are synthesized, and act at both cannabinoid receptor type 1 (CB_1) and type 2 (CB_2). They are then degraded by their respective enzymes FAAH = fatty acid amide hydrolase and MAGL = monoacylglycerollipase.



fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively [4]. Preventing their degradation with inhibitors of these enzymes can enhance their endogenous actions and avoid the deleterious side effects of direct agonists of CB receptors. Anandamide and other exogenous cannabinoids are known to react with other receptors such as the vanilloid TRPV1 channel [5]. The vanilloid TRPV1 channel is a nonselective cation channel activated by naturally occurring vanilloids, capsaicin, and resiniferatoxin. CB1 receptors are located in a much higher density within than outside the CNS [6]. CB2 receptors are present in peripheral cells such as lymphocytes and macrophages, and in organs such as the spleen and thymus. In the nervous system, they are found on infiltrating immune cells and resident microglia/macrophages. CB2 receptors are located on peripheral nerve terminals [7] but are also present on post-synaptic neurons in several regions of the brain and on non-neuronal cells of the CNS, such as infiltrating immune cells and resident microglia/macrophages [8, 9].

Cannabinoid Receptors in the Lower Urinary Tract

Both CB_1 and CB_2 receptors have been localized in the rat bladder, particularly on the urothelium [10]. In whole human bladders obtained from male organ donors, both CB_1 and CB_2 receptors were found to be expressed twice as much in the urothelium than in the detrusor, and were localized to the cell membranes. Overall, CB_1 receptor expression was higher than that of CB_2 receptors [11]. Bakali et al. also demonstrated that both humans and rats expressed CB_1 receptors, TRPV1 channels, and FAAH in their bladder [12]. CB_2 receptors was found to be expressed in higher densities in rat, monkey, and human bladder mucosa (urothelium and suburothelium) than in the detrusor, and was also co-localized with TRPV1 and calcitonin gene-related protein (CGRP) [13]. In the detrusor wall and CB_2 receptor immunoreactive fibers were identified on VAChT-positive nerve fibers [14]. CB_2 receptors, but not CB_1 receptors, were up-regulated in the bladder after acute and chronic inflammation induced by intravesical acrolein in rats [15]. CB_1 receptor immunoreactive fiber density was significantly increased in the suburothelium of the bladder specimen from patients with painful bladder syndrome and idiopathic detrusor overactivity, and correlated with their symptom scores, as compared to control [16]. Bladder CB_2 receptors possibly mediated the effects of oral cannabinoid agonists in a placebo-controlled study on multiple sclerosis (MS) patients. CB_2 mRNA expression was higher in the bladder of MS patients, and decreased after active treatment [17]. CB_1 and CB_2 receptors were identified in the spinal cord and dorsal root ganglia of rats, but bladder inflammation did not affect their expression [15]. Spinal cord and dorsal root ganglia CB_2 receptor expression was significantly up-regulated in inflammatory and neuropathic pain conditions in rats, and may help mediate analgesic effects [18].

Most studies identify CB_1 and CB_2 receptors in the bladder urothelium and detrusor along with other related proteins such as FAAH or TRPV1 channels, with variable density across species. The spinal cord also expresses cannabinoid receptors. Pathological processes related with inflammation or pain conditions can cause an up-regulation of these receptors, particularly CB_2.

Cannabinoid in Pain

Sativex (Δ9-THC with cannabidiol) is now licensed in Canada and in the UK for symptomatic relief of cancer pain and/or the management of neuropathic pain and spasticity in adults with multiple sclerosis. The antinocipeptive action of CB receptors is likely related to their peripheral spinal and supraspinal anatomical location relevant to pain in the brain, spinal dorsal horn, dorsal root ganglia, and peripheral afferent neurons [19]. CB receptor agonists have been extensively investigated in animal studies and in clinical trials, but their therapeutic effect has been limited by their psychoactive components. This has prompted interest in investigating compounds that inhibit

the metabolism of endocannabinoids, or compounds that are peripherally restricted.

Cannabinoids in Clinical Trials

The first clinical study of the potential effect of cannabinoids on bladder function was published in 1997. It was a questionnaire-based study where patients with MS using cannabis reported an improvement in urinary symptoms (urinary urgency in 64%, urinary hesitancy in 58.5%, and urinary incontinence in 54.7%) [20]. Whole plant cannabis extract was studied in an open-label trial in patients with advanced MS, and there was a decrease in severe lower urinary tract symptoms, urinary urgency, the number and volume of incontinence episodes, frequency, and nocturia [21]. These findings were followed by a randomized multicenter placebo-controlled clinical trial where oral administration of cannabis extract, Δ9-THC, or placebo was given to patients with MS. Both active compounds significantly decreased urgency incontinence episodes compared to placebo [22]. There are now 3 available medications that activate the CB1/CB2 receptors in the clinic: Cesamet (nabilone), Marinol (dronabinol; Δ9-THC), and Sativex (Δ9-THC with cannabidiol).

Cannabinoid in Micturition

The presence and activity of CB_1 receptors in the bladder was first suggested by the finding of an inhibition of electrically evoked contractions of the mouse urinary bladder in the presence of a CB_1 receptor agonist. In the same study, the selective CB_1 receptor antagonist, SR141716, caused parallel rightward shifts in the log concentration-response curves of CP 55,244, WIN 55,212-2 (nonsubtype selective CB receptor agonists), and anandamide (selective for CB_1 receptors) for inhibition of electrically evoked bladder contractions [23]. Martin et al. demonstrated some species differences for the effect of CB_1 receptor agonists on neuronally evoked bladder contractions, with a higher inhibitory effect in mice than in rats. SR141716 potentiated electrically evoked contractions through an undetermined mechanism [24]. Anandamide application produced slowly developing contractions in muscle strips isolated from the rat urinary bladder. These responses were attenuated by previous capsaicin sensitization [25]. The presence of either anandamide or CP55,940 did not affect carbachol-induced contractions in neither rat, monkey, nor human bladder preparations. However, anandamide increased electrical field stimulation- (EFS) induced contractions, while CP55,940 decreased them at all frequencies [13]. ACEA, a selective CB_1 receptor agonist, attenuated the EFS and carbachol-induced contractions of the rat bladder. GP1A, a CB_2 receptor agonist, only decreased carbachol-induced contractions in the rat bladder [12]. The application of ajulemic acid, a mixed CB_1/CB_2 receptor agonist, to rat bladder preparations significantly decreased the CGRP release compared to control, presumably from sensory afferent fibers [10]. Cannabidiol decreased the carbachol-induced contractions in both rat and human bladder preparations, but this effect was only attenuated by the TRPV1 channel antagonists ruthenium red and capsazepine in the rat [26].

CB receptor activation reduced afferent activity in an electrophysiological ex vivo preparation under normal conditions [27]. A nonselective CB receptor agonist was found to decrease afferent activity from inflamed bladders at certain intravesical pressures, an effect that was blocked by a selective CB_1 receptor antagonist [28]. These studies consistently show the lack of direct effect of cannabinoid agonists on bladder contractility. However, there are significant conflicting findings between the different CB receptor agonists and their action on carbachol or electrically induced bladder contractions. Cannabinoid receptor activation decreases contractility in vitro, as seen in several studies. The effect of cannabinoid agonists on carbachol-induced contractions has been less convincing, and may be mediated through other receptors, such as the TRPV1 channel.

The effect N-acylethanolamides, anandamide (via CB1 receptors) and palmitoylethanolamide (putative endogenous CB_2 receptor agonist), caused analgesia in models of viscero-visceral hyper-reflexia induced by inflammation of the urinary bladder [29,30]. These agents were found to decrease the expression of spinal cord c-fos at L6 following intravesical nerve growth factor (NGF) instillation [31]. Cyclophosphamide injection increased the anandamide content in the rat bladder, while its intravesical instillation increased c-fos expression in the spinal cord and increased the bladder reflex activity, which was blocked by TRPV1 channel antagonists, capsazepine and resiniferatoxin. The authors concluded that anandamide, via TRPV1 channel stimulation, is partly responsible for the bladder hyperactivity and hyperalgesia observed in cystitis [32]. Intraperitoneal administration of GP1a, a highly selective CB_2 receptor agonist, decreased the mechanical sensitivity in a mouse model of acrolein-induced cystitis, possibly by preventing phosphorylation of ERK1/2 via MAPK activation [33]. Treatment with a selective CB_2 receptor agonist (O-1966) following spinal cord injury improved bladder recovery in rats by modifying the inflammatory response [34]. CB_2 receptor agonism appears to decrease viscero-visceral pain caused by bladder inflammation, possibly by modulating afferent signaling in the spinal cord and promoting an anti-inflammatory effect. CB_2 receptor activation has an immunomodulatory function that can limit

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the endothelial inflammatory response, chemotaxis, and inflammatory cell adhesion and activation in atherosclerosis and reperfusion injury [35].

Administration of CP55,940 and methanandamide during cystometry in cats decreased micturition volume threshold at all doses but did not change the frequency of spontaneous detrusor contractions [36]. Intravesical anandamide increased threshold pressures and decreased micturition intervals in rats, while CP55,940 increased both threshold pressure and micturition interval [13]. Intra-arterial WIN55,212-2 in rat cystometry significantly increased micturition threshold at all doses, and was particularly enhanced following turpentine-induced bladder inflammation or bilateral hypogastric neurectomy [37]. Cannabinor, a highly selective CB_2 receptor agonist, increased micturition intervals and threshold pressures during conscious cystometry [14]. The chronic administration of this compound during 2 weeks following partial urethral obstruction in rats decreased post-void residual and a number of nonvoiding contractions, and increased bladder compliance compared to controls [38]. Stritmatter et al. demonstrated that FAAH is expressed in the bladder of rats, mice, and humans. They also demonstrated that systemic or intravesical administration of a FAAH inhibitor, Oleoyl ethyl amide (OeTA), during awake cystometry significantly increased intercontraction intervals, micturition volume, bladder capacity, and threshold pressure in rats. These effects were abolished with the concomitant use of SR144528, a CB_2 receptor antagonist, showing that FAAH inhibition mediated its effect on micturition via CB_2 receptors [39]. Selective CB agonists and antagonists have provided valuable information to understand their action in the control of micturition. However, their selectivity and potency are relative and cannot completely obviate their action at other sites. Knockout mouse technology can provide very powerful means of determining gene function in vivo. We assessed the voiding function in CB_2 knockout mice by quantitatively measuring urodynamic parameters at baseline and after administering different CB compounds. CB_2 knockout mice were found to have lower maximal pressure and basal pressure, and a higher intercontraction interval, bladder capacity, and compliance than control mice. However, no differences were observed in the in vitro responses to carbachol and EFS in bladder strips [40].

Overall, cannabinoid agonists have an inhibitory effect on micturition by increasing threshold pressures and decreasing frequency, possibly through afferent signaling. Anandamide has a more controversial mechanism of action, as it seems to influence micturition differently, demonstrated by in vitro and in vivo studies. The endocannabinoid anandamide is known to also activate TRPV1 channels, potentially via the release of CGRP [41]. Studies have found that a higher concentration of anandamide is required to evoke a TRPV1 channel-mediated release of this neuropeptide compared to that mediated via the CB_1 receptor [42].

Although there is a significant body of data demonstrating that cannabinoids affect micturition, there is very little known about the site of action that is primarily responsible for their action. As most cannabinoid agents easily cross the blood-brain barrier because of their lipophilicity, systemic administration cannot determine how much of their voiding effects are due to peripheral or central activation.

Intrathecal administration of compounds provides several applications. It allows the investigation of localized drug delivery of minimal concentration to distinguish their action at the spinal level. Also, restricting the distribution of active concentrations of these compounds to the spinal cord, we are avoiding deleterious psychoactive side effects from brain CB receptor activation. As the micturition reflex involves the spinal cord and ganglia, this approach may allow the development of new management strategies for the treatment of intractable detrusor over activity.

Füllhase et al. studied the effects of OeTA administered intrathecally on normal rats and rats with bladder over activity induced by partial urethral obstruction or intravesical prostaglandin E2. Intrathecal OeTA decreased micturition frequency in normal rats, and also decreased overall bladder pressures in rats with bladder over activity in a dose-dependent fashion, without affecting behavior. The same doses did not affect the cystometric parameters when given systemically. FAAH and CB_1 and CB_2 receptors were expressed in the rat sacral spinal cord, while CB_1 and CB_2 receptors were only increased in obstructed rats [43].

SUMMARY AND CONCLUSION

The role of the endocannabinoid system in the physiology and pharmacology of the lower urinary tract is an expanding field of study. The endocannabinoid system may be involved in the regulation of bladder function, possibly at several levels of the micturition pathway. Cannabinoid receptor agonists have an effect on micturition through a yet unknown mechanism, as demonstrated by clinical trials and in vivo and in vitro animal studies. There are likely interactions with other receptors or channels to ultimately inhibit micturition. Exogenous selective CB receptor agonists and antagonists have provided valuable information, increasing our understanding of the effects of

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cannabinoids in micturition control. However, further studies on both the central nervous and peripheral effects are warranted to increase our knowledge on how both therapeutic and unwanted effects of these agents can be balanced. To avoid CNS-related side effects of cannabinoids, drug approaches with peripheral CB receptor selective compounds, or drugs that target FAAH, may be preferable to harness the potential therapeutic effects of cannabinoids on lower urinary tract disorders.

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