Medical Hypotheses 131 (2019) 109321

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Monoacylglycerol lipase inhibition as potential treatment for interstitial cystitis

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A B S T R A C T

Interstitial cystitis is a chronic inflammatory condition of the urinary bladder with an unclear etiology. Currently, there are no widely accepted long-term treatment options available for patients with IC, with the European Association of Urology (EAU, 2017 guidelines), American Urology Association (AUA, 2014 guidelines), and the Royal College of Obstetricians and Gynaecologists (RCOG, 2016 guidelines) all suggesting various different conservative, pharmacological, intravesical, and surgical interventions. The endocannabinoid system represents a potential target for IC treatment and management. Activation of cannabinoid receptor 2 (CBR2) with various agonists has previously been shown to reduce leukocyte differentiation and migration, in addition to inhibiting the release of pro-inflammatory cytokines at the site of inflammation. These receptors have been identified in the detrusor and sensory nerves of the urothelium in various mammalian species, including humans. We hypothesize that by inhibiting the enzymes responsible for the catabolism of endogenous cannabinoids locally, bladder concentrations of CBR2 agonists will increase, particularly 2-arachidonyl glycerol, resulting in a diminished inflammatory response.

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than six weeks, in the absence of infection or other identifiable causes" (AUA Guideline, 2015) [1]. Approximately 16% of patients will be found to have Hunner's lesions, or ulcers, within the bladder [2]. Population studies show that IC/BPS predominantly affects females above the age of 40 [3], estimated 2.7–6.5% of American women reporting symptoms consistent with this diagnosis [4,5]. The disorder often manifests symptoms similar to other pelvic illnesses such as urinary tract infection (UTI), overactive bladder (OAB), or endometriosis, which often leads to complications in the evaluation and treatment for IC [6]. IC/BPS is recognized as a serious medical condition associated with a profoundly negative impact on patients' quality of life. To date, the origin of this disorder remains unknown and therefore, no causative, longstanding treatments are available. The unmet need of effective therapy calls for novel approaches to treat this disorder.

The endocannabinoid system (ECS) plays a major role in several physiological functions, many of which are associated with homeostatic balance, including roles in appetite regulation, neuronal protection, sensory perception and modulation of the immune response [7,8]. The ECS consists of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and endocannabinoid metabolizing enzymes. The most well studied endocannabinoids are N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG). Recently, the ECS has been extensively studied for its therapeutic effects in inflammatory disorders [9,10]. The effects of cannabinoids and endocannabinoids are primarily mediated by the cannabinoid receptors 1 (CBR1) and 2 (CBR2). CBR1 are expressed throughout the central nervous system and in non-neural tissues, while CBR2 is highly expressed on cells of the immune system [11–13], and activation of this receptor has anti-inflammatory actions [14]. Both receptors have been detected on the detrusor and sensory nerves of the urothelium within the bladders of various species, including rats, mice, monkeys and humans [15,16], suggesting that the ECS may be a target for therapy for IC/BPS. Support for this includes evidence that cannabinoids when administered systemically and locally reduce pain following inflammation of the urinary bladder [17,18].

However, systemic administration of cannabinoids, particularly those that activate CBR1, have been reported to result in side-effects, including cardiovascular dysfunction, digestion failure, and psychoactivity [19,20]. Evidence suggests that alternative strategies that result in local tissue activation of cannabinoid receptors, specifically

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https://doi.org/10.1016/j.mehy.2019.109321
Received 7 February 2019; Accepted 19 July 2019
0306-9877/

CBR2, may be more promising for chronic treatment of inflammatory pain pathologies [21,22].

Activation of CBR2, unlike CBR1, is not associated with behavioural effects, and has been shown to have immunomodulatory and anti-inflammatory actions in a number of tissues, making it a good target for inflammatory pain [23,24]. In support of this, agonists of CBR2 have been reported to decrease the inflammatory response by reducing neutrophil differentiation and migration [25] and by inhibiting the production of pro-inflammatory cytokines [26].

With respect to the endocannabinoids, changes in the levels of endogenous AEA and 2-AG have been reported following injury or disease. Increase in endocannabinoid levels via inhibition of degradative metabolism has been associated with anti-inflammatory and anti-nociceptive actions [27–29]. 2-AG acts as a full agonist, whereas AEA is a partial agonist, at both CBR1 and CBR2 [30,31]. 2-AG has antinociception effects mediated by both CBR1 and CBR2 [32], whereas AEA-mediated antinociception is largely via CBR1 [33,34]. Furthermore, 2-AG levels in tissues are generally much higher than that of AEA. Activation of CBR2 by 2-AG also shows promise for reducing inflammation [35], suggesting that strategies that increase local endocannabinoid levels, specifically 2-AG levels, may be useful to activate the ECS to reduce inflammatory pain.

Hypotheses

We hypothesize that local inhibition of enzymes involved in the catabolism of endogenous cannabinoids that activate CBR2, in particular monoacylglycerol lipase that degrades 2-AG, may reduce inflammation of the urinary bladder and alleviate the symptoms associated with IC/BPS.

Discussion

The two cannabinoid receptors, CBR1 and CBR2, are family A G protein coupled receptors (GPCR) and when activated couple to Gi proteins to modify the activity of various signalling molecules including adenylate cyclases and ion channels to induce a biological response [15,36]. These responses include a variety of physiological processes from thermoregulation and immune function, to stress response and nociception. Several endogenous ligands (endocannabinoids) have been identified within the ECS, the most widely studied being AEA and 2-AG.

AEA is produced on demand by Ca^{2+} dependent enzyme activity in postsynaptic nerves following excitatory neurotransmission [37]. AEA levels were shown to be increased in CNS inflammation which is supposed to protect neurons from excitotoxicity and inflammatory damage [38]. CBR1 immuno-reactive nerves were identified in OAB, suggesting a role of CBR1 in the reduction of afferent neuronal activity and modulation of bladder contractility and hyperreflexia [39]. These findings indicate a possible role for cannabinoids in the management of neurogenic bladder dysfunction arising from spinal cord injury or multiple sclerosis. AEA is cleaved by the hydrolytic enzyme, fatty acid amide hydrolase (FAAH), to ethanolamine and arachidonate. Therefore, FAAH represents another drugable target to augment CBR1 activity. Since therapeutic FAAH inhibition would preferably affect regions with increased AEA levels, this approach might exhibit superior outcomes when compared to (systemic) CBR1 agonist administration with potential supraphysiologic activation and/or desensitization of the receptor [40].

2-AG belongs to the family of monoglycerols consisting of arachidonic acid on a glycerol backbone [41]. 2-AG breakdown is metabolized by three serine hydrolases - monoacylglycerol lipase (MAGL), ABHD6 and ABHD12 - as well as COX-2 generating prostaglandin glycerol esters and prostaglandins [42,43]. By inhibition of MAGL, 2-AG levels will be increased and enhance activation of CBR2. From preclinical studies, it is evident that CBR2 selective ligands inhibit nociception without producing behavioural side effects [44]. In a recent study on experimental cystitis in mice, treatment with the CBR2 agonist, GP1a, reduced the severity of the disorder and also attenuated heightened peripheral sensitivity to physical stimuli associated with cystitis [45]. Another study by Klegeris et al. demonstrated reduced levels of inflammatory cytokines in cystitis by CBR2 activation. These results suggest that suppression of cystitis-related hyperalgesia by CBR2 agonists is an outcome of the combined effects of diminished inflammation and decreased afferent nerve activity following CBR2 activation [46].

MAGL and FAAH are shown to be expressed in the detrusor muscle of the urinary bladder [47]. In a study by Wang et al. on IC attenuation in FAAH KO mice, increased concentrations of AEA were correlated with decreased hyperactivity, peripheral sensitivity, and mRNA expression of pro-inflammatory mediators [48]. However, when compared to FAAH, expression and control of MAGL has not been extensively explored yet for inflammation in the lower urinary tract. Therapeutic approaches directed towards inhibiting MAGL are also promising to treat the clinical symptoms associated with IC. With the emerging development of reversible MAGL inhibitors, such as CL6a, unwanted chronic MAGL inactivation can be avoided [49].

Several methods for the administration of eCB degradation enzyme inhibitors have been studied. In one study on IC in rats, the FAAH inhibitor, URB597, was administered intraperitoneally (IP) to control inflammation [50]. Similarly, another group administered the MAGL inhibitor JZL184, IP to study its therapeutic potential in FAAH knockout mice [51]. While IP administration of drugs is popular and effective in animal experiments, it is not feasible in humans. The principal pharmacological treatment for patients with IC is currently oral drug therapy. The only FDA approved oral drug is Pentosan Polysulfate (PPS). While PPS administration is simple, less than 10% of the orally ingested drug is absorbed and arrives in the bladder [52]. This drug can also be accompanied by significant systemic side effects such gastric discomfort and hair loss [53]. Intravesical instillation therapy has provided an alternative and more direct approach for IC therapy. The treatment involves instillation of therapeutic medication directly into the bladder via insertion of a Foley catheter [54]. With the deposition of high concentrations of the drug and minimized systemic effects, intravesical instillation therapy could be a potentially effective method of administration for MAGL inhibitors. The localized access to the organ ensures that the manipulation of 2-AG concentrations is limited to the bladder and the ECS is not affected systemically.

However, intravesical therapy with MAGL inhibitors does possess limitations. One potential obstacle lies in reported observation that increased systemic 2-AG leads to an enhanced response to painful stimuli, attributed to desensitization of CBR1 [55,56]. However, there is evidence of different expression levels of 2-AG among organs and CBR1 desensitization may not be induced due to tissue-specific regulation and low-dose administration of MAGL inhibitors [56,57]. Our approach also focuses on inhibition at a local level, thus potentially bypassing systemic effects altogether. Another limitation, which applies to every intravesical therapy, includes the discomfort accompanied with the insertion of the Foley catheter into the urethra and the potential risk of urinary tract infection [58]. Furthermore, chronic use of MAGL inhibitors may also exhibit certain drawbacks. A previous study by Schlosburg et al. found that prolonged exposure to the MAGL inhibitor, JZL184, resulted in a reduced analgesic efficacy by decreased CBR1 receptor expression in mice [56]. MAGL also contributes to the breakdown of triacylglycerol (TAG) in adipocytes which, in a state of glucose deprivation, supplies tissues with energy [59]. Manipulation of MAGL may induce lipid imbalances and hyperglycemia [60,61].

Conclusion

The ECS represents a pharmacological target for the treatment of IC/BPS. In contrast to systemic administration of cannabinoids, local (intravesical) treatment with inhibitors of enzymes involved in eCB

catabolism appears to be the better approach in order to avoid acute and chronic side effects. In particular, CBR2 activation by inhibition of MAGL-mediated 2-AG degradation holds promises as novel approach in IC/BPS treatment due to its anti-inflammatory and anti-nociceptive effects.

Declaration of Competing Interest

The authors declare no conflict of interest related to the work.

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