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Review

Emerging therapeutic targets in cancer induced bone disease: A focus on the peripheral type 2 cannabinoid receptor

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ABSTRACT

Skeletal complications are a common cause of morbidity in patients with primary bone cancer and bone metastases. The type 2 cannabinoid (Cnr2) receptor is implicated in cancer, bone metabolism and pain perception. Emerging data have uncovered the role of Cnr2 in the regulation of tumour–bone cell interactions and suggest that agents that target Cnr2 in the skeleton have potential efficacy in the reduction of skeletal complications associated with cancer. This review aims to provide an overview of findings relating to the role of Cnr2 receptor in the regulation of skeletal tumour growth, osteolysis and bone pain, and highlights the many unanswered questions and unmet needs. This review argues that development and testing of peripherally-acting, tumour-, Cnr2-selective ligands in preclinical models of metastatic cancer will pave the way for future research that will advance our knowledge about the basic mechanism(s) by which the endocannabinoid system regulate cancer metastasis, stimulate the development of a safer cannabis-based therapy for the treatment of cancer and provide policy makers with powerful tools to assess the science and therapeutic potential of cannabinoid-based therapy. Thus, offering the prospect of identifying selective Cnr2 ligands, as novel, alternative to cannabis herbal extracts for the treatment of advanced cancer patients.

Contents

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Preparations of *Cannabis sativa* L. plants have been used for medicinal and recreational purposes for thousands of years and its constituents are known to modulate a diverse set of physiological responses through interaction with the endogenous cannabinoid (endocannabinoid) system [1,2]. The endocannabinoid system consists of a family of receptors, endogenous ligands and the molecular machinery for their synthesis, transport and metabolism (reviewed in [3]). The majority of biological effects associated with cannabinoid receptors are mediated by endocannabinoid ligands, plant-derived (phytocannabinoids), and various synthetic compounds through their interactions with the classic cannabinoid type 1 (Cnr1) and type 2 (Cnr2) receptors albeit with different degrees of selectivity [4,5]. Physiological processes associated with the activation of the endocannabinoid system include neurotransmission, pain perception, memory and learning, emotions, appetite, motor and endocrine functions, cardiovascular homeostasis and immune response (reviewed in [6–10]). There is increasing evidence that most members of the endocannabinoid system of ligands, receptors and enzymes exert significant effects on tumour cell growth, motility, invasion, spread and colonization of distant organs [6,11,12]. Of relevance to this review is the Cnr2 receptor has been detected in bone and cancer cells, and its pharmacological and genetic modulation have been shown to influence bone cell activity and bone remodelling in health and in disease. Thus, this article focuses on the role of Cnr2 in skeletal tumour growth, osteolytic bone damage and bone pain and argues in favour of the notion that therapeutic targeting of the peripheral Cnr2 may be of value for the reduction of skeletal complications associated with various metastatic cancers.

1. The peripheral Cnr2 receptor

The CNR2 gene, which encodes the Cnr2 receptor, is located on chromosome 1p36 in human [13]. Structurally, Cnr2 shares 44% and 68% amino acid and transmembrane region homology with Cnr1 receptor, but these two classic cannabinoid receptors are functionally not identical as demonstrated by the different binding specificity of cannabinoid agonists and antagonists to either receptor [14]. Cnr2 is differentially expressed in highly localized regions of the central nervous system and peripheral tissues (Fig. 1) and its activation is associated with various physiological effects in a discrete and tissue specific manner [15].

1.1. Cnr2 expression and function

The Cnr2 receptor is widely expressed in a number of peripheral tissues including liver, colon, pancreas, kidney, myocardium, testis, ovarium, uterus and endothelial cells of various origin (Fig. 1) where it is implicated in a diverse range of physiological and pathological processes (reviewed in [16]). In the immune system, the Cnr2 receptor is highly expressed in T and B lymphocytes, monocyte/macrophages, dendritic cells, natural killer cells and neutrophils and a number of studies have demonstrated that Cnr2 in these cells is responsible for cannabinoid-mediated anti-inflammatory and immune-modulating effects [17–20]. Expression of functional Cnr2 in peripheral and sensory neurons, particularly nociceptive neurons, confirms the role this receptor in the regulation of inflammatory, neuropathic and cancer-related pain [21–23]. In the skeleton, Cnr2 is detected in various cells that found within the bone marrow cavity including monocytes and macrophages (pre-osteoclasts), in cells that reside on the bone matrix such as human and murine osteoclasts (bone resorbing cells), osteoblasts (bone forming cells) and their precursors, and in osteocytes embedded within bone matrix [24–29]. The expression levels of Cnr2 in osteoblasts, osteoclasts, and osteocytes are significantly higher than the reported for Cnr1 [24,27–29]. Furthermore, unlike the Cnr1 receptor, Cnr2 has not been detected in the neuronal fibres intervening the skeleton [28,30–32].

1.2. Cnr2 ligands

A plethora of endocannabinoids, phytocannabinoids and synthetic ligands bind to Cnr2 receptor (Table 1) [33,34]. The endocannabinoid ligand 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine (anandamide, AEA) are polyunsaturated fatty acids derived from hydrolysis of membrane phospholipids on demand (reviewed in [35,36]). Both endocannabinoids serve as a precursor to free fatty acids including arachidonic acid and act as lipid signalling molecules in a site- and in a time-specific manner (reviewed in [37–39]). The action of 2-AG is terminated by enzymatic hydrolysis mediated primarily by the monoacylglycerol lipase (MAGL), whereas AEA is mainly metabolized by serine hydrolases fatty acid amide hydrolase (FAAH) [6,11,38,40,41]. Both endocannabinoids bind with high and similar affinity to Cnr1 receptor. 2AG act as a full agonist with higher efficacy for Cnr2 receptor whereas anandamide has been classified as a partial agonist (Table 1) [42–45]. Cnr2 is also a target to a number of the phytocannabinoids including psychotropic Δ9-tetrahydrocannabinol (Δ9-THC) and non-psychoactive cannabidiol (CBD) (Table 1). The pharmacology of these ligands is complex, incompletely understood; a number of studies have reported that most phytocannabinoids bind Cnr2 as partial agonist or antagonist depending on the ligand and receptor expression levels in the tissue (reviewed in [33,46,47]). Several synthetic cannabinoids, mostly structurally similar to phytocannabinoids, such as JWH133, JWH015, HU308 [48] and AM1241 act as Cnr2 agonist and/or inverse agonist depending on the tissue and species [49] (Table 1). Conversely, Cnr2 selective agents such as AM630 and SR144528 act as either silent antagonists or as inverse agonists by activating downstream pathways in an opposite fashion from Cnr2 agonists [47]. Other synthetic cannabinoid receptor ligands including WIN55-212-2 have been reported to equally activate both Cnr2 and Cnr1 [43]

1.3. Cnr2 structure and signalling

The Cnr2 receptor is a single peptide seven-transmembrane domain receptor that belongs to the family of G protein-coupled receptors (GPR). Cnr2 contains an extracellular glycosilated N-terminus and an internal C-terminus domain that is coupled to a Gi/o protein (Fig. 2) [17,50,51]. Cnr2 activation negatively regulates adenylyl cyclase activity [52], causing a reduction of intracellular level of cyclic adenosine monophosphate [53,54], that in turn leads to the modulation of an array of signalling pathways (Fig. 2). Numerous studies have shown that Cnr2 selective ligands regulate cell proliferation, differentiation, transformation and death by triggering the activation of three major components of the mitogen-activated protein kinase (MAPK), namely extracellular signal-regulated kinases1/2 (ERK1/2), p38 and c-Jun N-terminal kinases (JNK). Cnr2 was also found to exert apoptosis, necrosis and autophagy through the modulations of the Akt-phosphoinositide 3′-kinase (PI3K), AMP-activated kinase (AMPK) and ceramide synthesis. Furthermore, Cnr2 influences cell motility in particular migration and invasion by regulating the levels of intracellular calcium, and the expression and activity of adhesion molecules like ICAM or VCAM, matrix metalloproteinases, focal adhesion kinase (FAK) and small GTP binding proteins RhoA (Fig. 2). Cnr2 activation is also associated with inhibition of nuclear factor of kappa B (NFκB) and cyclooxygenase-2 (COX-2) that often leads to significant reductions of levels of various pro-inflammatory mediators (reviewed in [53,55–59]).