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Review

Receptome: Interactions between three pain-related receptors or the "Triumvirate" of cannabinoid, opioid and TRPV1 receptors

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ABSTRACT

A growing amount of data demonstrates the interactions between cannabinoid, opioid and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptors. These interactions can be bidirectional, inhibitory or excitatory, acute or chronic in their nature, and arise both at the molecular level (structurally and functionally) and in physiological processes, such as pain modulation or perception. The interactions of these three pain-related receptors may also reserve important and new therapeutic applications for the treatment of chronic pain or inflammation. In this review, we summarize the main findings on the interactions between the cannabinoid, opioid and the TRPV1 receptor regarding to pain modulation.

Contents

1. Introduction

After the successful cloning of the opioid, cannabinoid and transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptors [1–6], a large interest arose about their interactions: how they influence each other, owing to their related functions for example in pain inhibition and pain promotion. Because these receptors are often localized on the same cell, it is possible that they might form a receptome [7] (patterned after genome, proteome, lipidome etc.), through their mutual excitatory or inhibitory interactions. This triangle linkage is represented in Fig. 1.

In this review, we will summarize the pairwise interactions between the cannabinoid-opioid, the type 1 cannabinoid receptor-TRPV1 and the opioid-TRPV1 receptors. The communication between them can be direct or indirect, the latter mainly through protein kinases (Fig. 1). Direct activation occurs for exam-

Abbreviations: 2-AG, 2-arachidonoylglycerol; 2-AGE, 2-arachidonyl glyceryl ether; AEA, anandamide; AM251, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-piperidin-1-ylpyrazole-3-carboxamide; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; CNS, central nervous system; CP55,940, 2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl)cyclohexyl]-5-(2-methyloctan- 2-yl)phenol; DOR, delta opioid receptor; DRG, dorsal root ganglion; FAAH, fatty acid amide hydrolase; KOR, kappa opioid receptor; MAPK, mitogen-activated protein kinase; MOR, mu opioid receptor; NADA, *N* -arachidonoyl dopamine; PKA, protein kinase A; PKC, protein kinase C; RTX, resiniferatoxin; SR141716, rimonabant,5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-piperidin-1-ylpyrazole-3-carboxamide; SR144528, 5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-N-[(1R,3S,4S)-2,2,4-trimethyl-3-bicyclo[2.2.1]heptanyl]pyrazole-3-carboxamide; THC, Δ^9tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid type 1.

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ple between cannabinoid receptor type 1 (CB_1) ligands and opioid receptor or the TRPV1 receptor [8–11], and indirect activation between mu opioid receptor (MOR) and TRPV1 receptor [12–15] (Fig. 1).

A great number of reviews discuss the interaction between these receptors separately, especially between the cannabinoid and opioid receptors. The cannabinoid-opioid receptor cross-talks have been extensively reviewed regarding the interaction among the molecular and cellular mechanisms [16,17], as well as their function in eating behavior [18], alcohol intake [19]. Other behavioral conditions and processes have also been summarized such as withdrawal, dependence, tolerance [20,21], reward and reinforcement [21,22], learning, memory and emotional-like responses [21]. Very recently, a new study reviewed the possible mechanisms in MOR-TRPV1 cross-talk in nociception, tolerance and dependence [23]. Some data also showed interaction between the endocannabinoid system and TRPV1 in psychiatric disorders [24,25]. At the same time, pain is the only stimulus that all three receptors can affect and pain modulation is the only process in which all of three receptor pairs exert mutual effects. Thus this review will mainly focus on those changes which are involved in the interactions between these three receptors, which are, or might be, related to nociception. This study will also discuss those possible therapeutic strategies in pain management which utilize the interaction and cross-talk between them and provide a general introduction to opioid and cannabinoid receptors and the TRPV1 channel.

2. Opioid, cannabinoid receptors and the TRPV1 channel in general

There are three major types of opioid receptors according to the classical division, mu, kappa and delta, (MOR, KOR, DOR, respectively) and two types of cannabinoid receptors, type 1 (CB_1) and type 2 (CB_2). Opioid and cannabinoid receptors belong to the G-protein coupled receptor (GPCR) superfamily and they predominantly couple to $G_{\alpha i/o}$ type inhibitory G-proteins [26,27]. Opioid and cannabinoid receptor activation leads to diminished release of several neurotransmitters, such as GABA, dopamine, acetylcholine, noradrenaline, serotonin, or glutamate, allowing these receptors to take part in several important physiological functions [27–30]. Both opioid and cannabinoid receptors are widely distributed in the central nervous system as well as in the periphery [31–37] binding endogenous opioids and cannabinoids (endocannabinoids), respectively. Endogenous opioids are peptides, the most typical ones are enkephalins [38], endorphins [39], dynorphins [40], and endomorphins [41]. Opioid receptors also interact with exogenous opioid ligands of natural (plant derived) or synthetic origin. One of the most significant plant derived opioid is

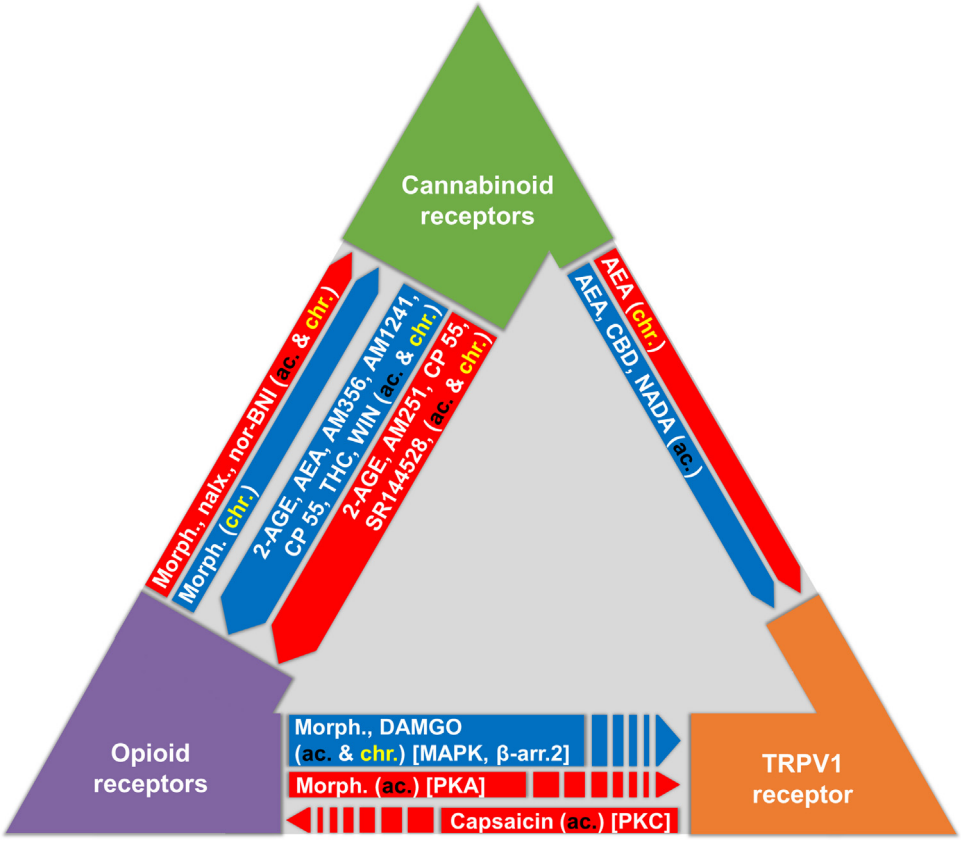

Fig. 1. The "Triumvirate" triangle of cannabinoid, TRPV1 and opioid receptors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The figure shows the interactions between the three receptor types according to Tables 1–3. Red arrows indicate inhibitory, while blue arrows indicate excitatory effects. The ligands which are mediating the inhibitory or excitatory effects are presented within the arrows. The dashed arrows denote the indirect effect between the two receptors through the indicated intermediers in square brackets. The acute (ac.) and chronic (chr.) administration of the ligands are also indicated in brackets in black and yellow color, respectively. *Legends and abbreviations*: *2-AGE*: 2-arachidonyl glyceryl ether (endocannabinoid); *ac.*: acute treatment; *AEA*: anandamide (endocannabinoid); *AM251*: CB_1 receptor inverse agonist/antagonist; *AM356*: methanandamide (CB_1 agonist); *AM1241*: CB_2 agonist; β-arr.2: β-arrestin-2; *CBD*: cannabidiol (CB_1 antagonist and CB_2 inverse agonist); *chr.*:chronic treatment; *CP* 55:CP 55,940 (cannabinoid receptor agonist); *DAMGO*: [D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin (MOR agonist); *MAPK*: mitogen-activated protein kinase; *morph.*: morphine (MOR agonist); NADA:N-arachidonoyl-dopamine (endocannabinoid); nalx.: naloxone (non-selective opioid antagonist); *nor-BNI*: norbinaltorphimine (KOR antagonist); *PKA*: protein kinase A; *PKC*: protein kinase C; *SR144528*: CB_2 receptor inverse agonist/antagonist; *THC*: tetrahydrocannabinol(cannabinoid receptor agonist); *WIN*: WIN55,212 (cannabinoid receptor agonist).