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BRAIN RESEARCH REVIEWS

Review

Metabotropic receptors for glutamate and GABA in pain

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ABSTRACT

Glutamate and γ-amino butyric acid (GABA) are respectively two major excitatory and inhibitory neurotransmitters of the adult mammalian central nervous system. These neurotransmitters exert their action through two types of receptors: ionotropic and metabotropic receptors. While ionotropic receptors are ligand gated ion channels involved in fast synaptic transmission, metabotropic receptors belong to the superfamily of G-protein coupled receptors (GPCRs) and are responsible for the neuromodulatory effect of glutamate and GABA. Metabotropic glutamate receptors (mGluRs) and metabotropic GABA receptors (GABA-B) are present at different levels of the pain neuraxis where they regulate nociceptive transmission and pain. The present review will focus on the role of these receptors in the modulation of pain perception.

Contents

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Abbreviations: mGluR, metabotropic glutamate receptor; GABA, γ-aminobutiric acid; GABA-B, metabotropic GABA receptor; GPCR, G-protein coupled receptors; NAM, negative allosteric modulator; PAM, positive allosteric modulator; DRG, dorsal root ganglia; PNS, peripheral nervous system; PAG, midbrain periaqueductal grey region; CeA, central nucleus of the amygdala; NAAG, N-acetylaspartylglutamate

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1. Introduction: Class C G-protein coupled receptors

G-protein coupled receptors constitute a large family of membrane proteins responsible for transduction of various external signals into intracellular responses through heterotrimeric G-proteins. As a result, GPCRs are involved in the regulation of many physiological or pathological processes and are the target of about a quarter of drugs available on the market (Overington et al., 2006).

Based on sequence comparison, five main classes of GPCRs sharing no sequence similarity have been identified. However, all these receptors have in common a central core domain constituted of seven transmembrane helices which is responsible for G-protein coupling (Bockaert and Pin, 1999). mGluRs and GABA-B belong to the same class. They are members of class-C GPCRs (formerly known as family 3 GPCRs), which also includes the calcium-sensing receptor, the receptors for sweet and umami taste plus several pheromone and orphan receptors (Brauner-Osborne et al., 2007).

Class C GPCRs possess two remarkable features that are important for their regulations and function. The first structural particularity of most class-C receptors (except pheromone receptors) is the presence of a large bilobate extracellular domain where natural ligands bind. This domain is juxtaposed to the core transmembrane domain common to all GPCRs and responsible of G-protein coupling (Fig. 1). The second specific feature of class-C GPCRs is their constitutive dimeric nature (Fig. 1) (Pin et al., 2004b).

The transmembrane domain is important for the pharmacology of class C GPCRs (Pin et al., 2004b). In the late nineties, a new class of class C GPCRs ligands was identified, the allosteric

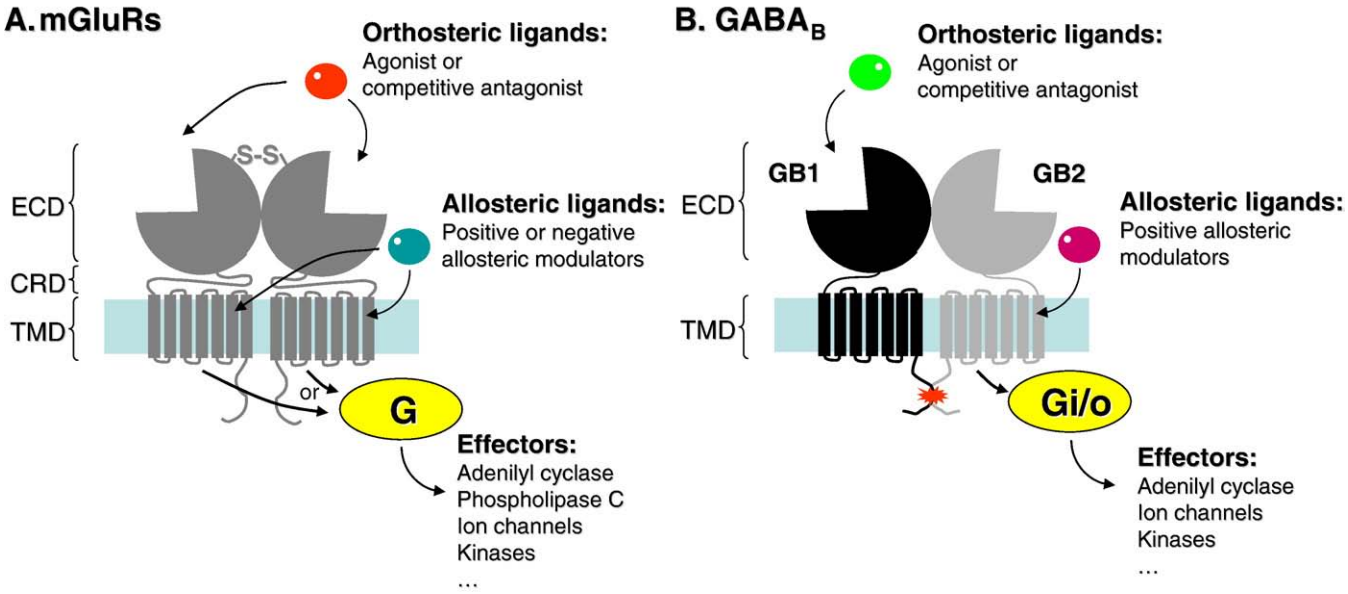

Fig. 1 – Structure of mGluRs and GABA-B. (A) mGluRs are constituted of 3 main domains: 1) a large bilobate extracellular domain (ECD) in which the natural ligand glutamate and other orthosteric ligands (agonists or competitive antagonists) bind, 2) a cysteine rich domain (CRD) constituted of about seventy amino acids which contains 9 cysteines and 3) a transmembrane domain (TMD) constituted of seven α helixes spanning the lipid membrane which is common to all GPCRs and is involved in G protein binding and activation. Allosteric ligands able to positively or negatively modulate receptor activation are binding within the TMD. mGluRs are obligatory homodimers crosslinked by a disulfide bridge across the lobe 2 of their ECD. (B) GABA-B is an obligatory heterodimer, constituted of two subunits GABA-B1 (GB1) and GABA-B2 (GB2). Each subunit is composed of an extracellular domain (ECD) and a transmembrane domain (TMD). Of note, two isoforms of GABA-B1 exist that differ mainly by the presence in GABA-B1a of two extracellular sushi domains. GABA-B1 is responsible of GABA and other orthosteric ligands recognition but is unable to bind and activate G-proteins and is unable to reach the cell surface by itself due to the presence of a retention site KRR in its C-terminus tail. GABA-B2 is unable to bind GABA but allows the expression of the heterodimer at the cell surface by masking the retention signal of GABA-B1 and is responsible of G-protein coupling of the dimer. Positive allosteric modulators binding within GABA-B2 TMD and able to enhance the receptor activity have been identified.