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Biased agonism at kappa opioid receptors: Implication in pain and mood disorders

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ABSTRACT

The kappa opioid receptor (k receptor) and its endogenous ligand dynorphin have received significant attention due to their involvement in pathophysiology of mood disorders, drug addiction, psychotic disorders and pain. Multiple lines of evidences suggest that the k receptor modulates overlapping neurocircuits connecting brainstem monoaminergic nuclei with forebrain limbic structures and thereby regulates neurobiological effects of stress and psychostimulants. The emerging concept of "biased agonism" (also known as functional selectivity) for G Protein Coupled Receptor (GPCR) ligands have provided new insights into overall response generated by a ligand, which could be exploited for drug discovery. According to this concept, every ligand possesses the unique ability (coded in its structure) that dictates distinct signalling pattern, and consequently beneficial or adverse response. Although still a long way to comprehend the clinical potential of biased GPCR ligands, such ligand could be vital pharmacological probes. This article highlights various lines of evidence, which indicates different ligands of k receptor as "biased", and their potential implications in mood and pain disorders.

1. Introduction

The G Protein Coupled Receptors (GPCRs) are the largest receptor class in the human genome (Allen and Roth, 2011), and known to modulate almost every human physiological function. Due to being involved in such diverse physiological processes, GPCRs are the most frequently targeted receptor class for therapeutic interventions (Ma and Zemmel, 2002). However, the development of GPCR selective drugs is challenging due to following reasons: 1—high degree of homology among many receptors which regulates diverse physiologic functions; 2—one GPCR may couple to more than one type of G proteins; 3—allosteric modulation of receptor signalling via biophysical interactions with small molecules and other proteins present in the microenvironment. Thus, the predominant signalling pattern of a GPCR may differ from cell to cell in various tissues and organs.

Classically, drug development programs targeting GPCRs have focused on the concepts of agonism and antagonism of one receptor target, in which a ligand (agonist or antagonist) upon binding the receptor, stabilizes it in one conformation and dictates the same nature of the downstream effector signalling, and thus ligand efficacy in most of the systems. However, over the last decade, the emerging concept of "biased agonism", also called as "functional selectivity" have revealed that the nature of GPCR signalling is not so rigid (Kenakin, 1995) and that ligand structure can direct (bias) signal output by stabilizing active receptor states in different proportions than the endogenous ligand. Thus, a biased or a functionally selective ligand is a novel chemical entity that holds the unique ability to qualitatively guide GPCR signalling, leading to distinct efficacy profile determined by ligand structure. Actually, the classical models of allosterism had already predicted the existence of multiple conformational states in the absence of ligand as a fundamental characteristic of allosteric proteins (Monod et al., 1965). The recently solved GPCRs structure support this previous theoretical notion that GPCRs exist in several microconformations and different ligands can stabilize different conformations favouring distinct signalling profiles (Deupi and Kobilka, 2010; Wacker et al., 2013). Furthermore, receptor interacting proteins, such as β-arrestins and G proteins, can allosterically modulate agonist binding affinity and therefore receptor conformations (Nygaard et al., 2013). Thus, bidirectional modulation of receptor conformation from both the ligand and interacting proteins regulate final outcome-physiological/pharmacological response. Finally, the promise of "biased agonism" lies in its ability to produce therapeutically beneficial signals while minimizing adverse effects. Due to the prevailing notion in the field that "biased agonists" might have superior therapeutic benefits, effort for many GPCR targets for drug discovery and developments have been revitalized.

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Opioids have been used since ancient times for the treatment of pain and other human ailments (Brownstein, 1993), and are still the most effective and widely used analgesics. Most of the opioid analgesics are agonists of the mu (μ), delta (δ) and kappa (κ) opioid receptors (also known as μ receptor, δ receptor, and k receptor, respectively). Opioid receptors are activated by a family of endogenous peptides to inhibit neuronal activity as they are coupled with inhibitory G proteins (Gαi/o) in physiological conditions. Although opioid receptors are the most widely known therapeutic targets for the treatment of acute as well as chronic pain conditions, their clinical use is constrained by adverse side effects, such as development of tolerance and addiction (Williams et al., 2013). Therefore, improving the side effect profile and reducing the development of analgesic tolerance have remained major goals in the opioid receptor field. The k receptor belongs to the opioid system, a neuromodulatory system that is widely expressed throughout the central and peripheral nervous systems. Among opioid peptides, dynorphins (encoded by the *Pdyn* gene) primarily activate the k receptor and have very low affinity for μ or δ receptor. On the other hand, the other opioid peptides—endorphin and enkephalins, exhibit very low affinity with k receptor. Therefore, the dynorphin/k receptor signalling pathway forms a distinct process within the opioid system (Chavkin et al., 1982; Goldstein et al., 1979). In contrast to μ receptor and δ receptor agonists, k receptor agonists have long been recognized to be analgesics with no addiction and tolerance liability. However, almost all k receptor agonists cause dysphoria, anhedonia, and hallucinations (Carlezon et al., 1998; Pfeiffer et al., 1986; Roth et al., 2002). The present review is mainly focused on various lines of evidence that indicate different ligands of k receptor as "biased", and their potential implications in mood and pain disorders.

2. Biased agonism at k receptor

The dynorphin/k receptor system is implicated in several psychiatric conditions such as depression, anxiety, drug addiction and schizophrenia (Bruchas et al., 2011; Schindler et al., 2012; Tejeda et al., 2013). High levels of k receptor expression were observed using the human genomic sequence analysis and RT-PCR technology in almost all regions of the human and rodent brain (ventral tegmental area, prefrontal cortex, claustrum, hippocampus, striatum, amygdala, locus coeruleus, dorsal raphe, and hypothalamus) involved in the modulation of reward, mood, cognition, and perception (Arvidsson et al., 1995; Leitl et al., 2014; Simonin et al., 1995). Dysfunction of the reward circuitry is a well known cause of many psychiatric disorders, including depression and addiction (Navratilova and Porreca, 2014). Moreover, emerging evidence from the investigation of pain processing and reward (pleasure) processing circuitry suggests extensive similarities in the anatomical substrates of painful and pleasant sensations (Leknes and Tracey, 2008). Interestingly but not surprising (given the well recognized effects of opioids), opioid receptors are highly enriched in neurons that modulate reward and pain. Several groups have demonstrated that in contrast to other opioid receptors' agonists, k receptor agonists, including the endogenous ligand dynorphin A(1–17), inhibit dopamine efflux in mesolimbic system, and also block the rewarding effects of drugs of abuse like heroin and cocaine (Di Chiara and Imperato, 1988; Narita et al., 2001; Spanagel et al., 1990). Further, k receptor agonists have also been shown to inhibit hyperalgesia induced by chronic μ receptor agonists (Meng et al., 2005). Therefore, identifying biased k receptor agonists with extreme signaling bias will help in characterizing a signaling pathway for therapeutic efficacy or adverse effects (Allen et al., 2011; White et al., 2015). Most of the k receptor agonists belong to five chemical classes: the endogenous peptides (dynorphins), benzodiazepines (Diazepam, tifluadom), benzazociness (Bremazocines, Pentazocine), arylacetamides (Enadoline, U50488), and diterpenes (salvinorin A). The benzazocines, such as bremazocine, are not very selective k receptor agonists but show strong analgesic effects. However, these molecules were dropped from clinical development due to psychotomimetic and dysphoric effects (Dortch-Carnes and Potter, 2005), even though they had low potential for drug tolerance and dependence. Earlier, it was generally believed that k receptor agonists show adverse effects due to off-targets, and therefore new class of selective k receptor agonists, the arylacetamide derivatives (Enadolines, U69593, U50488), were developed to evade psychotomimetic and dysphoric effects. However, this class of compounds were also shown to produce hallucinations and aversion (Land et al., 2009; Robles et al., 2014). Salvinorin A, a highly potent and selective k receptor agonist with no considerable affinity for any other known receptor, is widely known for its psychedelic effects (Roth et al., 2002). Despite of such diverse structure/chemical scaffold and decades of research on mechanism of k receptor signaling, all k receptor agonists have more or less some psychotomimetic effects and therefore failed clinical development. Not surprising though, given the wide expression of k receptor in multiple brain regions (cortex, striatum, VTA, hippocampus, amygdala) and cell types (serotonergic neurons in raphe, dopaminergic neurons in VTA and nor-adrenergic neurons in locus coeruleus), simultaneous inhibition of multiple neurotransmitter systems by k receptor agonist could result in complex multidimensional effects such as hallucination, dysphoria and analgesia.

The endogenous ligands of k receptor, dynorphins, are released during stress and produce behavioural correlates of dysphoria, depression and anxiety, effects that have been coupled to addiction and drug relapse (Bruchas et al., 2010). Moreover, agonist induced G protein receptor kinase 3 (GRK3) phosphorylation of k receptor (in C-terminal region) and consequent recruitment of β-arrestins, which are scaffolding proteins (moonlighting proteins would be a more appropriate term as arrestins are emerging as multifunctional proteins), leads to p38 MAPK phosphorylation (Bruchas et al., 2006; McLaughlin et al., 2003). The identification of G-protein independent activation of p38 MAPK in serotonergic neurons of dorsal raphe by k receptor agonist U50488, thereby inducing dysphoria (Bruchas et al., 2007a, 2006 2011), was a major step towards elucidation of underlying mechanisms of k receptor mediated adverse effects. Interference of this signaling pathway in mice via receptor mutation (KORS369A) or GRK3 deletion or conditional deletion of p38-MAPK blocks the aversive effects of k receptor agonists without reducing their analgesic effects (Pradhan et al., 2012). These studies have important therapeutic implications because a selective partial k receptor agonist that does not efficiently activate arrestin-dependent signaling might produce analgesia without significant dysphoria (Schattauer et al., 2012). Such system bias (although purported as "Biased Agonism", but no systematic analysis were made in these studies to support the notion of U50488 is a biased agonist), where one ligand preferentially activates one type of signaling pathway, has also been demonstrated for other receptor systems (Berg et al., 1998; Whistler et al., 1999), including μ receptor. μ receptor agonist fentanyl effectively causes receptor internalization, but morphine does not; even though both are potent analgesics (Keith et al., 1998). In addition, k receptor mediated activation of the p38 MAPK pathway in glia also appears to be important for the development of hyperalgesia following peripheral neuropathy (Xu et al., 2007). Clearly, these findings imply that the development of k receptor agonists that only activate G-protein-dependent signaling may produce analgesia without dysphoric effects. Although no such k receptor ligand existed until recently, where Roth and colleagues (White et al., 2015, 2014; Yan et al., 2009) performed elegant and

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