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Analysis of natural product regulation of opioid receptors in the treatment of human disease

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ABSTRACT

Opioid receptors (ORs), μOR, δOR, κOR and ORL1 mediate numerous signalling cascades, most importantly, through the modulation of ion channels. Research demonstrates the role of OR mediated signal transduction in treating pain, cancer, neurodegenerative disorders and cardiac insults. Yet, the primary application of drugs that modulate ORs is analgesia. Current opioids like morphine that are mainly μOR orthosteric agonists attract many undesirable side-effects (constipation, urinary retention, respiratory depression and hypotension) and the existing modus operandi against these is the inclusion of a μOR antagonist (for example, naloxone) which itself produces side-effects. As such, there is a current thrust to delineate the anti-nociceptive pathways mediated by ORs from the pathways involved in their induction of debilitating side-effects, in order to develop enhanced lead molecules. This review discusses the effects of natural products on the OR-induced signalling cascades and compares these to current synthetic leads and drugs. Important to these discussions is the complexity of OR signalling which involves OR trafficking, de- and re-sensitization, homo- and hetero-dimerization, the type of ligand binding (agonist, antagonist, reverse antagonist, orthosteric and allosteric agonist and antagonist in the context of biased agonism) and reasons for dysregulation that primarily occur because of inter-individual variations. Our current understanding of the different forms of ORs has expanded, thus introducing the concept of allosterism, which is also discussed. The authors present possible combination therapies to be explored towards developing the 'Holy Grail' of analgesics, for example, ignavine, the natural μOR positive allosteric modulator (PAM) with codeine and the natural fascaplysin, a balanced agonist with fentanyl. There remain many gaps in natural products research on ORs, more so on ORL1 and δ- and κ receptors. Furthermore, additional exploration of ORs' modulation is needed for ameliorating other associated disease conditions of global concern.

1. Introduction

ORs are a group of G protein-coupled receptors (GPCRs) whose endogenous ligands are peptides that possess congruent functionality to naturally derived exogenous ligands termed opiates. The term opioids is now used when describing both natural and synthetically derived OR ligands. Interestingly, the most recently derived OR, opioid receptor 1 like (ORL1) shares little to affinity for opioid peptides or opioids. Structural activity relationship studies on a group of synthetic opioids carried out by Beckett and Casy in 1954 (Beckett & Casy, 1954) led to the proposition of these A4 γ rhodopsin type GPCRs that are widely distributed in the nervous system (Abbadie, Pan, & Pasternak, 2004; Bunzow et al., 1994; Fukuda et al., 1994; Mansour, Fox, Akil, & Watson, 1995; Peng, Sarkar, & Chang, 2012; Vogt, Wiley, & Jensen, 1995; Wittert, Hope, & Pyle, 1996; Xia & Haddad, 1991), peripheral tissues; gastrointestinal and reproductive tracts, lungs, liver, heart (Fickel, Bagnol, Watson, & Akil, 1997; Peng et al., 2012; Villemagne, Dannals, Ravert, & Frost, 2002; Wittert et al., 1996) and immune cells (Sharp,

Abbreviations: 4HNE, 4-Hydroxy-2-nonenal; AC, Adenylyl cyclase; AD, Alzheimer's disease; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; cAMP, Cyclic adenosine 3′,5′-monophosphate; CB, Cannabinoid receptor; CHO, Chinese hamster ovary; DAL, Dehydro-α-lapachone; DALDE, ([D-Ala^2, D-Leu^5]-enkephalin); DAMGO, [D-Ala^2,*N*-Me-Phe^4,Gly-ol^5]enkephalin; FQ, Nociceptin/orphanin; GAPs, GTPases activating proteins; GDP, Guanosine diphosphate; GIRK, G protein coupled inwardly rectifying potassium; GPCR, G protein-coupled receptor; GTP, Guanosine triphosphate; GTPases, Guanosine triphosphatases; iNOS, Inducible nitric oxide synthase; MAPK, Mitogen-activated protein kinase; MRCKα, Myotonic dystrophy kinase-related Cdc42-binding kinase α; OPRM1, Mu opioid receptor gene; ORL1, Opioid receptor like-1; ORs, Opioid receptors; PAM, Positive allosteric modulator; PI 3-K/Akt, Phosphatidylinositol 3-kinase/Akt; RafA/Mapk3/Mapk1, Rapidly accelerated fibrosarcoma/mitogen-activated protein kinase3/mitogen-activated protein kinase1; RGS, Regulator of G protein signalling; RGS4, Regulator of G protein signalling 4; RhoA, Ras homolog gene family, member A; Rock, Rho associated protein kinase; VEGFR2, Vascular endothelial growth factor receptor 2

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Roy, & Bidlack, 1998). Their expression and distribution varies significantly among different organs and species. Subsequently, in 1965, Portoghese and colleagues suggested that there might be more than one OR, or multiple binding pockets for each (Portoghese, 1965). These inquests led to the identification of four main opioid systems, the first three are named either after the prototypic drugs or pharmacological analysis used in their investigations; μ (mu for morphine), δ (delta for deferens) and κ (kappa for ketocyclazocine) (Lord, Waterfield, Hughes, & Kosterlitz, 1977) and the most recently derived ORL1 also termed nociceptive receptor (NOR) (Dhawan et al., 1996).

Opioid systems which comprise of ORs and their effectors play functional roles in modulating pain behavior and anti-nociception, hence their usage as pain relievers for thousands of years. In the United States in 2010, the total financial cost of pain, ranged from 560 to 635 billion dollars, higher than the annual cost of heart disease (309 billion dollars), cancer (243 billion dollars), and diabetes (188 billion dollars) (Gaskin & Richard, 2011). Notwithstanding, current opioids attract numerous side-effects; constipation, urinary retention, respiratory depression and hypotension to name a few (Al-Hasani & Bruchas, 2011). Therefore, OR ligands and modulators of the other targets within the OR induced signal transduction pathway are believed to hold a myriad of potential efficacies. As well as neurotransmitters, opioids can function as growth factors, as demonstrated for the endogenous compound [Met5]-enkephalin, which is involved in the homeostasis of proliferating cells (McLaughlin & Zagon, 2012) which maybe applicable to cancer treatment. ORs are also associated with neurodegenerative disorders, Alzheimer's disease (Sarajarvi et al., 2015) and Parkinson's disease (Piccini, Weeks, & Brooks, 1997). Ischemic preconditioning using male Wistar rats was found to be attenuated by using OR antagonists (Schultz, Rose, Yao, & Gross, 1995) and mirrored by using OR agonist morphine (Schultz, Hsu, & Gross, 1996). Taken together, ligands that modulate ORs present opportunities for not only treating pain but as anticancer agents, the treatment of neurodegenerative disorders including depression and reducing myocardial injury.

The need for safer treatments with optimal efficacy continues to drive the search for lead molecules. Natural products remain ideal screening agents in the paradigm of drug discovery particularly since more than 50% of traditional drugs are of natural origin or are templates from natural sources (Newman & Cragg, 2012). Indeed, the first opiate discovered, morphine (Macht, 1915; Serturner, 1805), is a natural drug whose benzylisoquinoline scaffold, possessed by natural alkaloids observed in Fig. 1 are important when binding to the μOR. This proves invaluable as a guide to identifying other naturally derived lead molecules or steering the synthesis of comparable compounds with enhanced efficacy (de Sa Alves, Barreiro, & Fraga, 2009). Many believe that natural products are associated with fewer side-effects, however, research demonstrates that this belief is more anecdotal than evidence-based (Meier & Lappas, 2015). Paracelsus, the father of toxicology, a Roman physician believed that all things are poisonous, with the distinction between safety and toxicity residing in the dose (Borzelleca, 2000). Safer effects or not, natural products' chemistry have and continue to provide cues for elucidating numerous biological pathways as they did with OR signalling and the development of lead molecules towards the treatment of debilitating diseases.

This review presents an overview of the signalling cascades mediated by ORs and their effectors, reasons for their dysregulation, the use of natural and synthetic products for OR related diseases and future considerations. Prominence will be placed on natural products' modulation of the ORs and their effectors and whether based on a gestalt outlook of the OR mediating signal transduction pathway, they are improved alternatives.

2. The physiology of OR mediated signalling

2.1. OR signalling

Challenges with the nomenclature of ORs have been reviewed extensively by Cox and co-workers (Cox, Christie, Devi, Toll, & Traynor, 2015). The four identified ORs share about 60% identity at the amino acid level within the transmembrane (TM) domains but vary at the amino and carboxyl termini (Mollereau et al., 1994). Receptors which bind to opioid compounds with high affinity are referred to as classical ORs and include: μOR, δOR and κOR. Pharmacologically, these classical ORs have been subdivided into three putative subtypes of μORs, two putative subtypes of δORs and at least three putative subtypes of κORs based on different ligand binding affinities (Dietis, Rowbotham, & Lambert, 2011; Holzer, 2014). A fourth receptor, the ORL1 has also been described which shares high sequence identity with the classical ORs but possesses very low affinity for opioid compounds (Bunzow et al., 1994; Chen, Mestek, Liu, Hurley, & Yu, 1993; Mollereau et al., 1994).

ORs were cloned in the 1990s (Abbadie et al., 2004; Chen et al.,

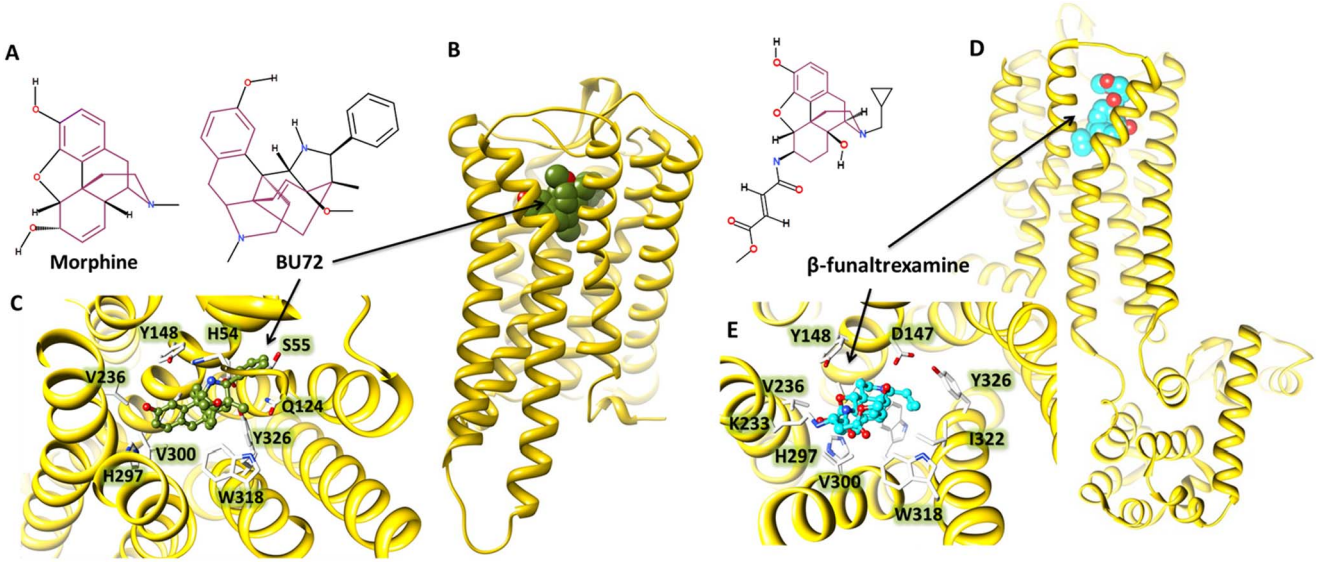

Fig. 1. Structure of μOR (PDB: 5C1M; rendered in yellow) in complex with a morphinan derivative BU72 (green). The morphine pharmacophore is highlighted in magenta (A). Binding site residues within a 4 Å zone of bound ligand are highlighted in C. Structure of μORs (PDB: 4DKL; rendered in yellow) in complex with β-funaltrexamine (D, cyan). Binding site residues within a 4 Å zone of bound ligand are highlighted in E. The graphics were created in UCSF Chimera.