Promising Therapeutic Agents: Delta Opioid Receptor Agonists

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ABSTRACT

Adequate characterization of the endogenous opioid system’s peptides and receptors; in addition to, the development of highly selective ligands, have improved research approaches and understanding the roles of this system. Delta-Opioid Receptor (DOR) was found to exhibit distinctive pharmacological profile and tissue distribution compared to other opioid receptors. Hence, DOR has been extensively investigated in the last decade as a potential target in the treatment of various disorders. Research findings indicate high potential of DOR agonists in the modulation of brain as well as cardiovascular system functions. DOR activation was found to display cytoprotective effects against ischemia/reperfusion injury in neurons and cardiomyocytes. DOR affects cellular functions on the level of gene expression, ion channels, enzymatic activity and membrane-receptors functions through multiple signaling pathways and second messenger systems. Moreover, DOR has been implicated in mood disorders; in vivo administration of DOR agonists and enkephalinase inhibitors had significant anxiolytic and antidepressant effects. More recent research findings have shown consistent and statistically significant results on DOR activation beneficial effects in cardiac conditioning, neural ischemia protection, anxiety and depression management. Further advances in research would potentially reveal the exact molecular mechanisms underlying DOR functions in relation to receptor subtypes and signaling pathways.

Keywords: Delta Opioid Receptor, Neuroprotective, Ischemia, Antidepressant, Anxiolytic

1. INTRODUCTION

Opioids are considered the most effective analgesics that are commonly used for the treatment of moderate to severe pain. Synthetic and endogenously occurring opioids work on three major receptor subtypes that belong to the G-protein superfamily: μ-Mu, κ-Kappa and δ-Delta opioid receptors; in addition to, other non-opioid targets. Besides from analgesia, opioids are believed to affect autonomic, endocrine, gastrointestinal functions and potential cognitive roles(1). Most clinically used agents target mu receptor, which is associated with severe side effects; however, recent advances in research have shown multiple physiological functions controlled by delta (DOR) receptors (δ1 and δ2 subtypes). DOR is highly distributed across the CNS and periphery, it has been found to be largely expressed in the brain as well as root ganglia, and to a lower extent in the pancreas, small intestine, heart, lungs, kidneys, skeletal muscles, thymus and adrenal glands(2). Similar to other opioid receptors, DOR is coupled to Gαi-protein, in addition to multiple other signalling pathways, the activation of which results in reduced cAMP levels, enhanced K+...
conductance and inhibited Ca+ signalling, which ultimately lead to reduced neuronal excitability and inhibited cellular functions(3). Most DOR selective ligands are enkephalin-related amphibian skin derived peptides; however, non-peptide agonists and antagonists have been developed. DADLE ([D-Ala², D-Leu⁵]-enkephalin) is considered the prototype selective agonist that has been used to evaluate DOR mediated effects. DOR activation was found to control inflammatory(4,5) as well as neuropathic pain(6,7), treat/prevent migraine attacks(8), enhance the analgesic potency of mu receptor agonists while reducing tolerance and dependence(9), attenuate hyperalgesia(10), modulate urinary bladder functions(11) and promote locomotion through differential signalling pathways(12). On the other hand, DOR antagonists have been found to reduce alcohol seeking and abuse(13). Moreover, DOR antagonists modulate gastrointestinal motility with mixed mu activation, which may serve as potential antidiarrheal agents in irritable bowel syndrome(14). The DOR agonists has been extensively investigated for the last few years as novel therapies for mixed anxiety depression disorder (MADD), together with potent cardio- and neuro-protective effects. This review will focus on and highlight the most recent research findings on DOR activation potentials in the prevention of ischemia/reperfusion injury and the management of anxiety/depression disorders.

2. DELTA OPIOID RECEPTOR & ISCHEMIA: CYTOPROTECTIVE ROLES

DOR neuroprotective effects
Brain ischemia, most commonly due to cardiovascular diseases, is one of the leading causes of acute neuronal death and neurological disorders. Hypoxic stress results in severe alteration of homeostasis with subsequent disruption of pH, ions and neurotransmitters (i.e. glutamate) balance; in addition to, the formation of reactive oxygen species, excitotoxicity and apoptosis induction. Various in vivo and in vitro studies have recently investigated the possible effects of DOR agonist pretreatment on the consequences of induced-hypoxia animal models. Using asphyxial cardiac arrest induced brain ischemia in rats and the selective DOR agonist BW373U86, a study was conducted to evaluate acute and chronic treatment effects on neuronal recovery and long-term sequelae. It was found that DOR activation significantly reduced neuronal loss and functional deficits compared to control, the application of naltrindole, a selective DOR antagonist, abolished the acute-phase protective effects but not the long-term ones concluding that BW373U86 neuronal protection was mediated by both DOR-dependent as well as independent mechanisms(15). In order to evaluate DOR protective effects on spinal cord neuronal ischemia-reperfusion injury, an experiment investigated the effects of DADLE aortic administration during a 30-minute ischemic period induced by occluding the aorta infrarenally in rabbits, neurofunctional assessment was done during a 48 hours post-reperfusion period and counting the grey matter functional motor-neurons, Tarlov scores were significantly higher in the DADLE pre-treated group compared to control; moreover, DOR activation significantly reduced neuronal loss and paraplegia incidence(16). Various DOR-mediated cellular effects have been shown experimentally to oppose the biochemical and homeostatic alterations in ischemic stroke that might be involved in the observed neuroprotective effects. The possible mechanisms are collectively found in a review article and include: the activation of mitochondrial K+ pumps, reduced Na+ and Ca+ cellular influx, reduced glutamate exocytosis and NMDAR-mediated excitatory post-synaptic potentials (EPSP) both of which are key determinants of excitotoxicity(17). Furthermore, a study was done using HEK293t cells that were exposed to low oxygen levels (0.5%) followed by adequate oxygenation providing a model of both ischemic and reperfusion stress to investigate the DOR agonist UFP-512 protective effects and possible roles mediated through Nrf2 gene activator. The Nrf2 was found to induce expression of various antioxidants, UFP-512 potentiated Nrf2 function and preserved cellular viability, the effects were eliminated by DOR blockade and transfection with siRNA of Nrf2(18). In addition, cerebral administration of DADLE at the onset of reperfusion following ischemia induction in rats significantly improved water maze performance, potentiated newly formed neurons differentiation, proliferation and reduced neuronal transformation into astrocytes; the protective effects were completely abolished by blocking DOR(19).

DOR Cardioprotective Effects
Since the early development of DOR selective ligands, experimental screening on mediated effects in vivo has shown a wide range of cardiovascular effects on the level of organ perfusion and cardiac contractility. Research on DOR roles in cardiac ischemia has been

gaining momentum to determine the extent of therapeutic potential in pre- and post-ischemia conditioning. In vitro evaluation of DOR activation effects on isolated porcine hearts upon reperfusion has shown that post-conditioning with the selective DOR agonist Deltorphin D resulted in significant diastolic relaxation improvement, enhanced tissue perfusion over a period of two hours and largely reduced ventricular arrhythmias incidence\(^{(20)}\). Of the pre-conditioning methods used to reduce acute ischemic episodes risk is the intermittent hypoxic exposure. As DOR roles in this setting are not completely understood; DOR blockade effects were evaluated through monitoring its interference with 20-days of hypoxic exposure protection on dogs before occluding coronary arteries. Naltrindole administration at every exposure session almost completely abolished the beneficial effects of hypoxia pre-conditioning through monitoring the severity of arrhythmias and infarct sizes, which indicates the key roles of endogenous DOR activity in cardiac protective conditioning\(^{(21)}\). In addition to the established DOR protective roles, mu receptors have also been investigated; sedatin, which is a synthetic mixed agonist of delta/mu receptors, was investigated on isolated pulmonary fibroblastic cells, sedatin significantly reduced oxidative stress effects on cellular morphology and DNA synthesis ability\(^{(22)}\). The results suggest a cellular non-specific protection of hypoxic stress; nevertheless, the presence of DOR across cardiac tissue makes it an interesting cardioprotective target. Furthermore, it was found in rats that prolonged hypoxia exposure over a period of 10 days resulted in a significant alteration in gene expression as evident through quantitative detection of various microRNAs. The administration of the DOR agonist UFP-512 mimicked hypoxic conditions effects on multiple miRNA molecules through potentiated expression while reduced others\(^{(23)}\). Observed results indicate the complex pathways mediated by DOR activation that with further investigations might lead to a better understanding of the molecular basis of DOR roles and potentially provide therapeutic targets in the control and management of ischemic heart diseases (IHD).

3. DELTA OPIOID RECEPTOR ANXIOLYTIC/ANTIDEPRESSANT POTENTIALS

Besides from the general observations of antidepressant-like effects of exogenous opioids, experimental investigations were directed towards the possible emotional effects of DOR. As it was found in earlier studies that mice with mutant DOR phenotype had persistent anxiety and depression symptoms; in addition to, the observed antidepressant effects of enkephalinase inhibitors\(^{(24)}\). To determine the effects of DOR expressed in the amygdala nucleus, which has key roles in emotional modulation, the selective DOR agonist SNC80 was tested against yohimbine-induced anxiety using the elevated zero maze, SNC80 had significant anxiolytic effects on test rats\(^{(25)}\). Another study was conducted to evaluate the selective DOR agonist KNT-127 anxiolytic effects; using the light/dark box and elevated maze tests, DOR activation had significant anxiolytic effects comparable to diazepam-treated group without causing the typical-benzodiazepine side effects as evident by locomotor functions in the Y-maze\(^{(26)}\). DOR can be classified into two major receptor subtypes; DOR1 and DOR2; despite less than clear differences between the two subtypes, a study evaluating the receptor-subtype selective effects of KNT-127 has shown that the anxiolytic effects were mediated by the DOR2 subtype through the use of subtype-selective antagonists\(^{(27)}\). Furthermore, KNT-127 has been additionally investigated for antidepressant effects, a study has shown that in addition to the anxiolytic effects of KNT-127, it also has antidepressant and hyperalgesia preventative properties\(^{(28)}\). In a more recent study, KNT-127 chronic administration antidepressant effects were investigated against the standard antidepressant SSRI (Selective Serotonin Reuptake Inhibitor) fluoxetine; in a 14-days period following excision of the olfactory bulb as an animal model of depression in two groups of rats; in addition to the significant antidepressant effects of the DOR agonist, it was more prominent and more effective than fluoxetine-treated group; KNT-127 had faster onset as well as lower side effects\(^{(29)}\). Another selective DOR agonist AZD-2327 has been clinically investigated as potential therapeutic agent for mixed anxiety depression disorder (MADD); AZD-2327 exhibited more anxiolytic than antidepressant effects measure through HAM-A and HAM-D scores respectively. Despite statistically insignificant responses, various DOR agonists have shown differential effects which could be attributed to DOR subtype selectivity\(^{(30)}\). Thus, DOR agonists have huge potential in the management of anxiety and depression.
4. CONCLUSION

Ultimately, the peptide-related pharmacokinetic hurdles of DOR agonists have been resolved through the development of synthetic receptor-subtype selective ligands. Together with DOR agonists improved side effects profile compared to mu receptors, especially in the case of respiratory depression and constipation. DOR-dependent tissue specific functions can be established through in vivo studies and direct clinical monitoring. Despite incomplete understanding of the molecular basis governing the observed DOR activation physiological effects, current research findings revealed the potent and promising potentials of DOR agonists in improving the management of chronic and clinically-challenging acute ischemic conditions; in addition to, various psychiatric disorders such as anxiety, major depressive disorder and potentially MADD which is associated with more severe and treatment-resistant symptoms.

REFERENCES


