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Opioids in Depression: Not Quite There Yet

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Abstract

Depression is a common mental disorder that affects people of all ages across the world. All current pharmacological interventions are based on the monoamine theory of depression and aim to increase the concentrations of monoamines in the brain. However, since many patients show no response or do not tolerate conventional therapies, there is an urgent need to identify new therapeutic targets, explore new molecular pathways and develop novel drugs against depression. Opioids, a class of compounds used against chronic pain, have major analgesic properties, but they are also well known for their anxiolytic and antidepressant effects. In preclinical and clinical studies, some opioids showed encouraging results to alleviate depression-like symptoms. Although our knowledge about the antidepressant effects of opioids stretches back to the late '70s, we still have a long way to cover. Predominantly, a clear understanding about their mode of action as well as the opioid-associated issues of addiction and convulsions, are the main challenges that need to be addressed before we will see opioid compound used in the clinic against depression.

1 Opioids and pain: an established relationship

Pain is a symptom associated with a number of conditions and diseases such as cancer or neuropathies, which remain a global public health concern due to the high percentage of documented undertreatment[1-4]. There are three types of pain; a classification that has been endorsed by the International Association for the Study of Pain (IASP): nociceptive pain, which is the stimulation of peripheral nerve fibres in response to noxious stimuli[5], neuropathic pain, which is based on neuronal damage or misfiring of peripheral or central nervous system due to toxins, metabolic disturbances or virus infection among other reasons[6], and combinatory pain that has both a nociceptive and neuropathic component, such as cancer pain[7]. Opioids are strong analgesics and the main drugs of choice in the treatment of moderate to severe acute pain, chronic pain and post-operative pain. These drugs essentially mimic the opiate action of endogenous ligands such as endomorphins, enkephalins and dynorphins, which activate the three classical $G_{i/o}$-coupled opioid receptors; mu- (MOP), delta- (DOP), kappa- (KOP)[8]. Basic classification, distribution, function, and pharmacology are summarized in Table 1. Although DOP and KOP receptor opioid binding plays a role in the modulation of pain signals, the MOP receptor is the major opioid receptor responsible for the analgesic effect of opioids, since MOP knock-out animals show abolished opioid-mediated analgesia[9]. A fourth receptor has been identified to exhibit a high degree of structural homology with the three opioid receptors, called nociceptin receptor (or NOP)[10], but has been characterised by the International Union of Basic and Clinical Pharmacology (IUPHAR) as an "opioid-like" receptor and not an actual opioid receptor, due to its distinct pharmacology and its irrelevance with analgesia.

Even though the MOP receptors are mostly found in the central nervous system (spinal cord dorsal horn, thalamus, cortex, midbrain)[11] where they inhibit nociceptive signals by intercepting ascending excitatory pathways and modulating the firing of GABAergic, serotonergic and dopanimergic neurons[12], the non-analgesic effects of opioids are very well documented in the literature[13]. Opioid receptors are found in peripheral tissues where MOP-ligand binding is responsible for a number of peripheral effects such as respiratory depression, constipation and immunodepression [14]. In addition, a number of behavioural non-analgesic opioid effects have also been documented in the literature. Long-term morphine treatment is associated with alternations of cellular signalling in the

reward centres that contribute to addiction and mood impairment[15]. MOP receptor desensitization has been shown to contribute to the development of physical dependence as a consequence of modulating inwardly rectifying K^+ conductance at a cellular level[16,17].

Gene knockout technology has provided consistent evidence for the absence of opioid addiction in MOP-receptor knockout rodents even after prolonged morphine treatment[18-20]. In parallel, opioid-induced behavioural non-analgesic effects such as sedation[21] and euphoria [22] have been also well documented in the literature, although usually noted as opioid side effects. Nevertheless, since the analgesic effects of opioids have attracted much of the attention, many other opioid receptor-mediated behavioural effects have been therapeutically underestimated or ignored.

2 Depression, Anxiety and Pain: more than a triangle

Clinical depression is a common mood disorder that is characterized by behavioural and cognitive symptoms such as disturbances in mood, sleep and eating behaviour, loss of interest, loss of pleasure (anhedonia), decreased energy, feelings of guilt, helplessness, worthlessness and general emotional instability. Depression affects more than 1 in 20 people in developed countries, and more than 350 million people worldwide in 2012[23]. The current antidepressant pharmacotherapies, which include the use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidation inhibitors (MAOIs) and tricyclic antidepressants (TCAs), are based on the *monoamine theory* of clinical depression, which links the development of depression with lower levels of dopamine, serotonin and noradrenalin levels in certain brain areas[24].

Table 1: Indicative tissue distribution of the three classical opioid receptor types (mu; MOP, delta; DOP, kappa; KOP), the respective effect upon activation and the relevant clinically-available opioid ligands

Opioid receptors	Tissue distribution	Linked effect	Clinical agonists	Clinical antagonists
MOP	Brain, spinal cord, peripheral-neural, GI tract, respiratory tract immune cells, CV endothelial cells	Analgesia, cytoprotection, Analgesia, GI transit, respiratory depression, itching, NO release, Anti-inflammatory	Morphine, codeine, oxycodone, fentanyl, tramadol, tapentadol, pethidine, methadone, dextropropoxyphene, nalbuphine, levorphanol, buprenorphine	Naloxone, naltrexone, butorphanol, pentazocine,
KOP	Brain	Analgesia, feeding, diuresis, neuroendocrine	Bremazocine, nalorphine, pethidine, pentazocine, nalbuphine	Naloxone, naltrexone, buprenorphine, butorphanol
DOP	Brain, spinal cord, peripheral-neural	Analgesia, cardioprotection, dopamine release, thermoregulation	None	Naloxone, naltrexone

However, current antidepressant therapy remains a challenge due to the high treatment failure rates among patients (63%) and the general negative attitude towards using these agents from both patients and their partners due to their potent behavioural side-effects [25]. Both of those issues justify the need to explore novel ideas that could explain the pathology of depression. They also highlight the urgent need to develop new antidepressants that do not rely on the monoamine theory.

Since the late '70s, a connection between untreated or undertreated chronic pain and the development of anxiety-related symptoms has been well established [26]. Today we know that the development of a number of different anxiety-related disorders can be caused by untreated and persistent chronic pain, which leads to mood disturbances due the reduced quality of life[27,28]. Anxiety and depression are usually reported as comorbid conditions, although they possess distinct characteristics[29], mainly due to the fact that they share common neurophysiological mechanisms of manifestation and sometimes even common interventions[30]. In parallel, depression has long been reported as a concomitant condition in chronic untreated pain, although there is a wide range of onset (between 10-90%) among neuropathic pain patients[31]. More than 75% of depressed patients display symptoms of some kind of untreated pain, whereas patients that suffer from persistent pain are more likely to develop depression[32]. A number of published reviews have quite accurately described the relationship between pain and depression in the literature at all levels of clinical science; diagnosis, symptomatology, clinical outcomes and treatment[23-36].

Although today, there is still a "chicken & egg" type of discussion regarding the causal relationship between pain, anxiety and depression, a significant clinical association between these three conditions is widely accepted (Figure 1). Their pharmacological treatments have attracted particular attention since they share common efficacies; effective anxiolytics show efficacy against depression and chronic pain, and vice versa[37-39]. Nevertheless, the use of clinically used opioids for the treatment of anxiety and depression in particular, has not been explored sufficiently, although the euphoric effects of opioids have been described since the late '70s[40].

3 Opioids as antidepressants: how close are we?

The antidepressant effects of opioids have been explored extensively during the last few decades as shown in Table 2 (for a detailed review see Berrocoso et al [41]). However, not much progress has been made towards developing novel opioids as antidepressants or even exploring the clinical use of currently available opioids for the treatment of mood disorders like depression. Despite a large volume of *in vitro* and *in vivo* studies in the literature regarding the effects of opioids on serotonergic and dopaminergic biology, only a few studies have explored the antidepressant potential of opioids in clinical trials.

Buprenorphine, a KOP receptor antagonist and a weak MOP agonist, is one such example. The role of the KOP receptors and its associated ligands in anxiety-related conditions has been studied extensively *in vitro* and *in vivo*[42]. A number of studies confirmed antidepressant effects of laboratory KOP receptor antagonists (such as norbinaltorphimine and JDtic) in various preclinical *in vivo* models of depressive-like behaviour, such as the force swimming test and the learned-helplessness paradigm[43-45]. In humans, low dose buprenorphine use exhibited antidepressant effects within the first 3 weeks of treatment in adults with treatment-resistant depression[46]. Currently two opioid ligands as one therapeutic regimen are tested in a Phase II clinical trial as an antidepressant treatment by the biopharmaceutical company Alkermes. The ALKS 5461 is a combination of buprenorphine and samidorphan (a selective MOP antagonist), in an effort to promote buprenorphine's KOP receptor antagonistic actions by simultaneously blocking it's MOP receptor specific action and therefore inhibiting it's potential addictive effects[47]. Another opioid that has been tested in clinical trials against depression is the atypical opioid tramadol (a MOP receptor agonist and a serotonin-noradrenaline reuptake inhibitor), which exhibited an antidepressant effect comparable to venlafaxine, a clinically-used serotonin-norepinephrine reuptake inhibitor for the treatment of depression[48]. Tramadol's mechanism of action as a weak MOP receptor agonist, which promotes analgesia, and as an agent that increases serotonin and noradrenaline concentrations in the brain, has been thought to be ideal to make it a first in the clinic as an antidepressant[49].

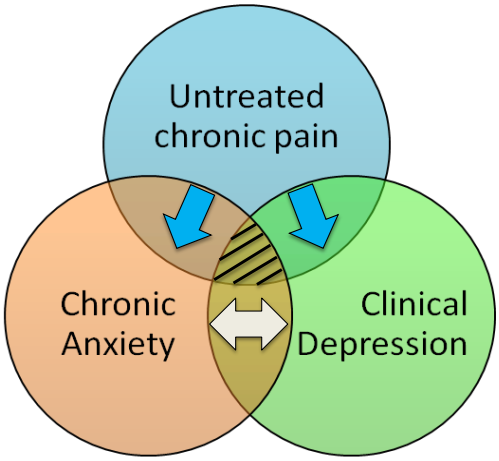

Fig 1 A simplified model for the proposed relationship among untreated chronic pain, chronic anxiety and clinical depression. Areas of overlap between two conditions represent comorbidity. In the case of concurrent pain and depression, the evidence in the literature suggests one-way causality (blue arrow), e.g. undertreating or untreating pain may lead to depression unlike the vice versa. A similar relationship exists between pain and anxiety. However, the relationship between anxiety and depression is described in the literature by a two-way causality (white arrow), e.g. chronic anxiety may lead to depression, as well as depressive episodes may lead to manifestation of anxiety. The triangle between pain, anxiety and depression represents the concurrent manifestation of all three conditions and a 'gray' area in the literature with many unanswered questions.

Since co-administration of tramadol with current antidepressants has been suggested to present an increased risk of manifested serotonergic syndrome[50], the therapeutic use of tramadol monotherapy in patients with depression has not been further explored extensively in double-blind clinical trials. In addition, other atypical opioids (like tapentadol; a MOP receptor agonist and a noradrenaline reauptake-inhibitor) have not been evaluated *in vivo* for any potential advantages as antidepressants. Although there is a large pool of preclinical studies that show a strong correlation between the MOP & DOP receptor activation and the increased activity of serotonergic/dopaminergic pathways [41], the clinical exploration of MOP and DOP receptor agonists as potential antidepressants has been quite slow. A limited number of studies have explored the clinical use of MOP agonists like oxycodone and oxymorphone in depression[51] whereas disturbance of beta-endorphin levels in depressed patients has been linked with specific clinical symptoms like severe anxiety, phobia and obsession [52]. Clinical studies using MOP agonists or antagonists against depression are scarce. Similarly, although there is a large number of preclinical *in vivo* studies that have confirmed the key role of DOP receptor agonism in the manifestation of antidepressant-like behaviour[53-56], clinical studies on DOP agonists are also rare.

Table 2: Clinically-used opioids that have been investigated for their their antidepressant effects in animal and human studies

Compound	MOP Activity	Clinical Study	Animal model	Reference
Morphine	Agonism	-	LH	63
Oxycodone	Agonism	Open label	-	64
Levorphanol	Agonism	-	TS	65
Codeine	Agonism	-	FST	66
Methadone	Agonism	-	TS	65
Buprenorphine	Agonism	Open label	-	67-69
Tramadol	Agonism	Case study	UCMS, FST, LH	70-73
Naloxone	Antagonism	Case study	LH	74-75
Naltrexone	Antagonism	Open label	LH	76-77

In addition, the pharmacological trend of turning away from peptidic opioids towards non-peptidic analogues, brought the limitations of manifested convulsions for some DOP receptor agonists to the surface, although these could be prevented by a slow dose-escalation strategy[57,58]. Overall, the unexplored molecular mechanisms of MOP and DOP receptor-mediated antidepressant effects remains a major hindrance for the development of novel opioids that will possess higher antidepressant efficacy.

The fact that latest epidemiological figures show that more than 50% of patients do not respond to current first-line antidepressant treatment, highlights the fact that there is an intense need for novel, more efficacious and fast-acting antidepressants that exploit new mechanisms of antidepressant activity[59]. Based on the current pipeline in commercial pharmaceutical development, it seems that there is the will to address this need. A significant number of non-monaminergic drugs are currently under investigation in in Phase II and III for depression, such as ifepristone (an antiprogestogen contraceptive by Corcept), lanicemine (an N-methyl-d-aspartate receptor antagonists by AstraZeneca), esketamine (a ketamine enantiomer and an NMDA antagonist by Janssen-Cilag), RG1578 (a negative modulator of metabotropic glutamate 2/3 receptor by Roche), MK-6096 (an orexin 1 & 2 antagonist by Merck) among others[47]. However, none of these are opioid or opioid-receptor mediated ligands. The only ligand which is currently in trials as a potential therapeutic agent for major depression and can be somehow linked to opioid action is the agent LY2940094 (a nociceptin antagonist by Lilly) with Phase-I pharmacokinetic studies being concluded in November 2011, followed by a Phase-II study (8-week administration, randomized, double-blinded, placebo-controlled, parallel-group, multi-centered) for the efficacy and safety of the ligand in patients with depressive disorder, concluded recently in March 2014. Although no results have been published yet from these studies, the company conducted a third Phase-I study looking at the occupancy of nociceptin receptors by the LY2940094 ligand in healthy subjects as well as a second Phase-II study looking at the efficacy of the drug to reduce alcohol dependency (both concluded in December 2014). Although the relationship between the nociceptin receptor and stress responses has been described in the literature and the use of nociceptin antagonists as antidepressant agents has been proposed based on data from animal studies[60-62], similarly to classical opioid ligands, there is still an obvious absence of novel opioid ligands in clinical trials for the treatment of depression.

4 Conclusion

Although a large volume of preclinical studies support the antidepressant activity of opioids, it does not appear that novel opioids are currently under development for the treatment of depression, let alone close to clinical trials. Even though there is a good amount of experimental *in vivo* evidence that supports the beneficial use of opioids in depression and anxiety, it is possible that the addictive properties of opioids as well as their tendency to produce tolerance of their resulted effect from long-term use, remains a point of concern that averts these agents from developed further. Perhaps the opioid research community needs time to reflect on recent advances in opioid pharmacology, both in non-addictive opioid ligands and opioid/non-opioid dual ligands, in order to set appropriate strategies in the future that will lead to the initiation of clinical studies, either as opioid monotherapies or as a co-treatment with current antidepressants.

5 Competing interest

None

6 Author's contributions

XY and ND researched the literature and drafted the manuscript. NG and ND provided conceptual input and proof read the manuscript.

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