Title
Opioid Systems and Depression: The Relationship Is Strengthening

Journal
Biological Psychiatry, 92(12)

ISSN
0006-3223

Authors
Dagher, Merel
Cahill, Catherine M
Evans, Christopher J

Publication Date
2022-12-01

DOI
10.1016/j.biopsych.2022.09.020

Peer reviewed

Biological Psychiatry

Commentary

Opioid Systems and Depression: The Relationship Is Strengthening

Merel Dagher, Catherine M. Cahill, and Christopher J. Evans

Prior to the mid-20th century, the acute euphoric effects of opioid drugs and their ability to alleviate depression were primary reasons for physician prescriptions of opioid drugs. This practice was abandoned and discouraged once it was recognized that tolerance, withdrawal, and dependence lead to iatrogenic addiction and opioid use disorder. Nevertheless, the field has far from discarded the connection of the opioid systems with depression [recently reviewed by Jelen *et al.* (1)], including evidence that nonmedical opioid use may precipitate new-onset depressive episodes (2). In the current issue of *Biological Psychiatry*, Carazo-Arias *et al.* (3) add one more piece to the evolving relationship by implicating the endogenous opioid system in the antidepressant effects of fluoxetine (Figure 1).

The opioid system consists of 4 receptors: mu, delta, kappa, and nociceptin/orphanin FQ. These opioid receptors are derived from different genes and are activated by a plethora of opioid peptides derived from distinct opioid precursors. The opioid peptides are enzymatically cleaved from various precursors, including proenkephalin (the precursor of enkephalins that can activate mu opioid receptors [MORs] and delta opioid receptors [DORs]) and prodynorphin (the precursor of the dynorphins and neoendorphins associated with kappa opioid receptor [KOR] activation) (4). The opioid receptor systems appear to modulate affect and anxiety, though in different and sometimes contrasting ways (Figure 1). Activating MORs is associated with the hallmark euphoric, respiratory depressant, and sedative effects of opioid therapeutics, as well as triggering the adaptations that lead to the dysphoric and anxiogenic effects experienced during opioid withdrawal. DOR activation, at least in preclinical models, has anxiolytic and antidepressant effects, whereas KOR activation elicits aversive and anxiogenic effects, which has driven the interest in developing KOR antagonists as potential antidepressant drugs (1). In reality, humans have a wide range of responses to agonists targeting different opioid receptors. For example, some people describe opioids such as oxycodone or hydrocodone as dysphoric, presumably because of intolerable side effects like nausea and constipation (5), while others find dysphoric kappa-targeting drugs such as salvinorin A (the hallucinogenic drug from the plant *Salvia divinorum*, also known as magic mint) pleasurable and will seek out and crave the drug for recreational use (6). Humans are surprisingly variable in experiencing different opioid drugs as inducing either positive or negative affect.

The affect-related pharmacology of opioid systems leads to this question: To what extent do endogenous opioid systems contribute to the etiology of mood disorders? Could differential activity of opioid systems, as implicated during the negative affect associated with opioid withdrawal, be causative of anxiety or depressive-like states? Noteworthy are genome-wide association studies implicating a functional variant of the MOR as being associated with heritability of opioid use disorder and an increased risk of depression (1), and these associations have been corroborated in more recent studies. The review by Jelen *et al.* (1) highlights the role of opioid receptor systems in various aspects of depressive states. For example, MOR activation reduces anxiety-like behavior, plays

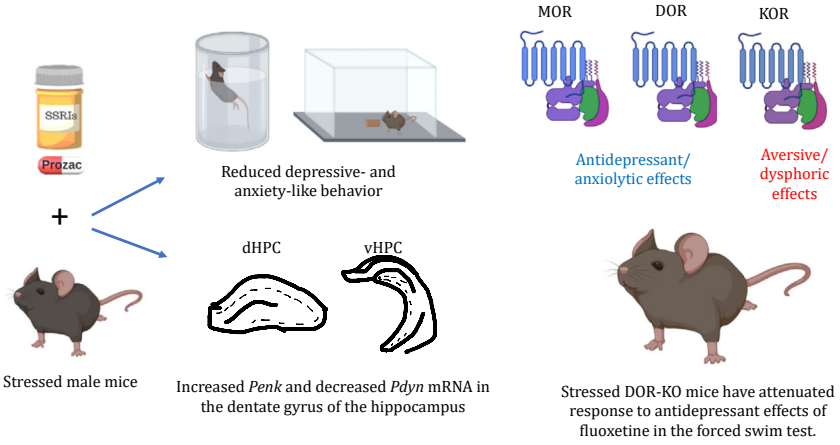

Figure 1. Regulation of fluoxetine by the endogenous opioid system. dHPC, dorsal hippocampus; DOR, delta opioid receptor; KO, knockout; KOR, kappa opioid receptor; MOR, mu opioid receptor; mRNA, messenger RNA; SSRI, selective serotonin reuptake inhibitor; vHPC, ventral hippocampus. Figure created with BioRender.com.

SEE CORRESPONDING ARTICLE ON PAGE 952

Biological Psychiatry December 15, 2022; 92:920–922 www.sobp.org/journal
https://doi.org/10.1016/j.biopsych.2022.09.020
ISSN: 0006-3223

Biological Psychiatry

a role in social interaction, and is involved in motivation for appetitive behavior. Constitutive DOR knockout mice have been reported to have increased anxiety- and depressive-like behaviors, although this phenotype was not observed in the stress-induced corticosterone paradigm used by Carazo-Arias *et al.* (3) Lastly, the KOR-dynorphin system has been dubbed the anti-reward system because activation of KORs and increased dynorphin activity observed in opioid withdrawal and chronic pain states elicits pro-depressive and anhedonic behaviors (7).

The neurobiology of depression and anxiety disorders is far from understood, and their etiology remains elusive. Still, selective serotonin reuptake inhibitors (SSRIs) are the most effective medications for treating these disorders and are more effective than placebos. Carazo-Arias *et al.* (3) ask if specific opioid receptors and endogenous ligands have a role in modulating the antidepressant effects of the SSRI fluoxetine (3). The authors used a stress assay characterized by a 5-week oral corticosterone exposure to induce heightened stress in male mice. In one group of mice, oral corticosterone was accompanied by an additional 4 weeks of fluoxetine treatment. In the other group, the mice received a vehicle solution for 4 weeks concomitant with oral corticosterone. The authors found that fluoxetine-treated mice had reduced immobility time in the forced swim test and reduced latency to feed in the novelty suppressed feeding test, two common behavior tests to assay affective-like behaviors. Moreover, the authors reported that in the fluoxetine-treated group, transcripts for *Penk*, the gene that encodes for proenkephalin, were significantly increased in the ventral and dorsal hippocampal dentate gyrus.

Using RNA transcript analysis, the researchers determined that *Penk* upregulation was high in a specialized population of hippocampal mature granule cells. Rene Hen's research team has previously demonstrated the importance of the dentate gyrus in the antidepressant response of SSRIs, particularly in the context of neurogenesis-dependent antidepressant efficacy [see the discussion in Carazo-Arias *et al.* (3)]. The Carazo-Arias *et al.* study also found that transcripts for *Pdyn*, the gene that encodes for dynorphin, were downregulated in the dentate gyrus. These findings are in line with the well-established literature that dynorphin upregulation and KOR activation correspond to dysphoric and aversive phenotypes.

Cleavage of proenkephalin produces [Met]enkephalin and to a lesser extent [Leu]enkephalin along with a host of endogenous peptide ligands with variable affinities for the different classical opioid receptors. The authors thus assessed the fluoxetine effects in mice with constitutive deletion of DOR or MOR (DOR-KO and MOR-KO, respectively). The DOR-KO mice were found to have attenuated responses to fluoxetine compared with wild-type control mice. However, the MOR-KO mice and control mice had similar responses to chronic fluoxetine exposure. These findings suggest that DORs, but not MORs, contribute to depressive-like behaviors produced by fluoxetine as measured in the forced swim test after the stress-induced corticosterone treatment. However, no differences were found between DOR-KO, MOR-KO, and wild-type mice in the fluoxetine effects on the novelty suppressed feeding test, suggesting that opioid systems may not modify all affect-related changes induced by SSRIs.

The findings of Carazo-Arias *et al.* (3) strengthen the relationship between antidepressant action and modulation of endogenous opioid systems. Previous research implicated endogenous opioid systems in the actions of tricyclic antidepressants as well as the analgesic effects of these drugs used for treatment of chronic pain (8). For example, in 1987, Hamon *et al.* reported that chronic treatment with the tricyclic antidepressants amoxapine or amitriptyline caused an increase in levels of immunoreactive leu-enkephalin and met-enkephalin immunoreactivity in several brain areas [discussed in (8)]. Pharmacology approaches subsequently indicated that both agmatine and fluoxetine antidepressant-like effects in preclinical models could be blocked by the nonselective opioid receptor antagonist naloxone as well as selective DOR or MOR antagonists but could not be blocked by KOR-selective antagonists (9). Tianeptine, prescribed in Europe for the treatment of depression, has been shown to be a full MOR/DOR agonist with tolerance-resistant properties, and in preclinical models requires MOR activation for antidepressant activity (1,10). Finally, opioid systems have also been implicated in the effects of the NMDA-targeting antidepressants ketamine and esmethadone, though the evidence is controversial (1).

As antidepressant treatments evolve, it is likely that the opioid systems will become one of the core modulatory systems to target, either directly using opioid ligands (MOR and DOR agonists or KOR antagonists) or indirectly via SSRIs or tricyclic antidepressants. Depression can undoubtedly have many different etiologies and will require different pharmacotherapies. Future research will need to assess if fluoxetine efficacy always requires endogenous opioid systems for alleviating negative affective states.

Another interesting finding from Carazo-Arias *et al.* (3) was the downregulation of *Pdyn* transcripts in the dentate gyrus as a result of fluoxetine treatment. Since SSRIs have a delayed therapeutic onset, a potential future strategy may combine SSRI treatment with initial, short-term treatment by KOR antagonists and MOR and/or DOR agonists, such as tianeptine, until the endogenous opioid system can adapt. Further research of the relationship between depression and endogenous opioid systems is most certainly warranted.

Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Shirley and Stefan Hatos Center for Neuropharmacology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, California.

Address correspondence to Christopher J. Evans, Ph.D., at cevans@ucla.edu.

Received Sep 20, 2022; accepted Sep 20, 2022.

References

1. Jelen LA, Stone JM, Young AH, Mehta MA (2022): The opioid system in depression. Neurosci Biobehav Rev 140:104800.
2. Li X, Fu Q, Scherrer JF, Humphrey D, Leigh I (2020): A temporal relationship between nonmedical opioid use and major depression in the U.S.: A prospective study from the National Epidemiological Survey on Alcohol and Related Conditions. J Affect Disord 273:298–303.

3. Carazo-Arias E, Nguyen PT, Kass M, Jee HJ, Nautiyal KM, Magalong V, *et al.* (2022): Contribution of the opioid system to the antidepressant effects of fluoxetine. Biol Psychiatry 92:952–963.
4. Le Merrer J, Becker JA, Befort K, Kieffer BL (2009): Reward processing by the opioid system in the brain. Physiol Rev 89:1379–1412.
5. Galer BS, Coyle N, Pasternak GW, Portenoy RK (1992): Individual variability in the response to different opioids: Report of five cases. Pain 49:87–91.
6. El-Khoury J, Baroud E (2018): Case series: *Salvia divinorum* as a potential addictive hallucinogen. Am J Addict 27:163–165.
7. Cahill CM, Lueptow L, Kim H, Shusharla R, Bishop A, Evans CJ (2022): Kappa opioid signaling at the crossroads of chronic pain and opioid addiction. Handb Exp Pharmacol 271: 315–350.
8. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M (2016): Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience 338:183–206.
9. Zomkowski AD, Santos AR, Rodrigues AL (2005): Evidence for the involvement of the opioid system in the agmatine antidepressant-like effect in the forced swimming test. Neurosci Lett 381:279–283.
10. Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, *et al.* (2017): The behavioral effects of the antidepressant tianeptine require the mu-opioid receptor. Neuropsychopharmacology 42:2052–2063.