Research article

N-palmitoylethanolamide attenuates negative emotions induced by morphine withdrawal in mice

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Abstract

Depression and anxiety are prominent symptoms of withdrawal syndrome, often caused by the abuse of addictive drugs like morphine. N-palmitoylethanolamide (PEA), a biologically active lipid, is utilized as an anti-inflammatory and analgesic medication. Recent studies have highlighted PEA's role in mitigating cognitive decline and easing depression resulting from chronic pain. However, it remains unknown whether PEA can influence negative emotions triggered by morphine withdrawal. This study seeks to explore the impact of PEA on such emotions and investigate the underlying mechanisms. Mice subjected to morphine treatment underwent a 10-day withdrawal period, followed by assessments of the effect of PEA on anxiety- and depression-like behaviors using various tests. Enzyme-linked immunosorbent assay was conducted to measure levels of monoamine neurotransmitters in specific brain regions. The findings indicate that PEA mitigated anxiety and depression symptoms and reduced 5-hydroxytryptamine, noradrenaline, and dopamine levels in the hippocampus and prefrontal cortex. In summary, PEA demonstrates a significant positive effect on negative emotions associated with morphine withdrawal, accompanied with the reduction in levels of monoamine neurotransmitters in key brain regions. These insights could be valuable for managing negative emotions arising from morphine withdrawal.

Introduction

The behavioral manifestations of opioid addiction are linked to positive affective experiences, while withdrawal stages are associated with negative emotional symptoms such as anxiety, depression, and anhedonia. These symptoms can intensify the motivation to seek drugs, leading to relapse and craving [1], [2]. The neural basis of drug dependence

involves adaptive changes in neurocircuitry, which may persist even after drug exposure is discontinued, contributing to withdrawal syndromes [3]. The opponent-process theory of emotion suggests that when the opioid stimulus causing the new balance of homeostasis is removed, a reversal of emotional valence is experienced [4]. Epidemiological data indicate that 20 % of Americans with substance use disorder also have comorbid anxiety or depressive disorders [5]. It is important to explore the effectiveness of antidepressant treatments in managing the negative emotions associated with opioid abstinence, considering the high prevalence of comorbidity. Additionally, it is noteworthy that classic antidepressants have shown contrasting results in this patient population [6].

Clinical studies have shown reductions in the volumes of the hippocampus and prefrontal cortex (PFC), as well as changes in the number of neurons and glial cells in the brains of individuals suffering from major depression [7]. Reports suggest that the volume of the left hippocampus is correlated with depression rating scores in males [8], which is supported by findings of specific atrophy in the left hippocampal region in depressed patients [9]. Similarly, recent studies have shown that patients exhibit reduced ventral PFC brain activity [10], with depressive behavior strongly correlated to dendritic atrophy and synaptic remodeling in the PFC and hippocampus [11].

Furthermore, preliminary research suggests that depression is linked to decreased levels of neurotransmitters such as 5-hydroxytryptamine (5-HT), noradrenaline (NE), and dopamine (DA) [12]. Inhibition of 5-HT neurons leads to decreased neuronal activity in the reward circuit, contributing to the development and progression of negative emotions. Antidepressants may enhance 5-HT, NE or DA neurotransmission in the PFC, impacting cognitive and depressive symptoms in individuals at risk of psychosis [13]. Additionally, research by Dunn KE. et al. has highlighted the involvement of various neurotransmitter systems including 5-HT, NE and DA, in opioid withdrawal [14].

More recently, the endogenous bioactive lipid N-palmitoylethanolamide (PEA), used as a dietary supplement, has shown potential in reducing pro-inflammatory tumor necrosis factor-α and lipid peroxidation [15], [16], [17]. Studies have also demonstrated PEA's ability to mitigate stress responses, offering significant protection against stress and anxiety [18]. Activation of peroxisome proliferator-activated receptor α by PEA has been found to induce significant changes in 5-HT levels in the basal forebrain [19]. Hence, it can be postulated that the effect of PEA could be linked to its ability to regulate the levels of monoamine neurotransmitters involved in emotional control in specific brain regions.

To explore this further, we utilized morphine withdrawal mice as a model to examine whether PEA could mitigate anxiety- and depression-like behaviors triggered by morphine

withdrawal by modulating the levels of monoamine neurotransmitters in PFC and hippocampus, thereby elucidating the underlying mechanisms.