

# Neurobiological Mechanisms in Depression and Chronic Pain: A Mini Review



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## Abstract

Depressive disorders affect approximately 322 million people around the world. People affected by chronic pain are more likely to develop depression. This occurs because depression and chronic pain share some neurobiological mechanisms that may overlap. The objective of this study is to perform a review of the common neurobiological and pathophysiological factors between depression and chronic pain.

**Keywords:** Depression; Pain; Neurotransmitters

**Abbreviations:** IC: Insular Cortex; CCA: Anterior Cingulate Cortex; HPA: Hypothalamic-Pituitary-Adrenal Axis; CRH: Corticotropin Releasing Hormone; ACTH: Adrenocorticotrophic Hormone

## Introduction

According to the World Health Organization, depression is a disorder characterized by sadness, loss of interest, feelings of guilt, disturbed sleep and appetite, feelings of tiredness and poor concentration. Depressive disorders can be longlasting and occur recurring, impairing an individual's ability to perform their daily activities [1]. It is estimated that approximately 322 million people suffer from depression in the world [1], being a common comorbidity in people affected by pain [2]. Approximately 52% of patients with pain are susceptible to developing depression and 85% of patients with chronic pain are affected by severe depression, being three times more likely to be suffering from distress [2,3]. Patients suffering from depression induced by chronic pain have a worse prognosis than those who only suffer from chronic pain; and chronic pain and depression are correlated in terms of occurrence and development [3]. Studies have shown that the interactions between chronic pain and depression occur because they have pathophysiological and neurobiological similarities [4]. The objective of this study is to perform a review of the common neurobiological and pathophysiological factors between depression and chronic pain.

## Discussion

### Anterior Cingulate Cortex (CCA) and Insular Cortex (IC)

People with chronic pain present activation of limbic areas, as well as cerebral changes similar to those observed in depression. In these individuals occurs activation of the medial prefrontal cortex, the hippocampus, the anterior cingulate cortex (CCA) and insular cortex (IC) [5,6]. The ACC interconnects neurons of the frontal cortex, the thalamus and the amygdala, integrating cognitive, emotional and autonomic functions. Studies have shown that ACC is recruited in pain processing [7] and that ACC injuries reduce pain sensitivity [5]. The IC is another cortical area recruited in both acute pain and chronic pain [7]. The posterior portion of the IC participates in somatosensory characteristics of the pain while the anterior portion is related to affective aspects. Clinical evidence shows that chronic pain can lead to anatomical and functional changes in IC that are correlated with cognitive and affective disorders [8]. The ACC and CI develop functional and morphological alteration in depressive states such as decreased connectivity, altered glucose metabolism and reduced ACC volume [7]. When

compared to healthy individuals, people with depression present a higher recruitment of the rostral and dorsal ACCs in an attempt to attenuate negative stimuli. It has been suggested that people with depression need greater cognitive effort to inhibit negative information [9]. Thus, ACC can be the target of studies aiming to discover precise cellular and molecular bases of the changes that occur in depression induced by chronic pain [7].

### Neurotransmitters

Pain and mood are controlled by common neurotransmitters such as serotonin, glutamate and  $\gamma$ -aminobutyric acid (GABA) [10]. The biochemical theory of depression suggests that a neurochemical imbalance of monoamines occurs. These neurotransmitters also play an important role in the modulatory pathways of pain, which could lead to changes in pain perception. These neural mechanisms common to pain and depression are also linked to humoral areas of the brain, such as the IC and amygdala, which also play an important role in modulating pain [11]. When a painful stimulus occurs some mechanisms inhibit nociceptive transfer to the upper brain center, one of these mechanism is a mediated pathway by serotonin (5-HT) that plays an important role in suppressing painful stimuli causing analgesic effects. In individuals with chronic pain serotonin is reduced [6].

GABA and glutamate are the major inhibitory and excitatory neurotransmitters, respectively, an imbalance between them can cause psychiatric and neurological disorders. In individuals with depression, a hypofunction of the GABAergic system and hyperfunction of the glutamatergic system were observed. Regarding the development of pain, it is believed that the loss of GABA inhibitory neurotransmission in the dorsal horn of the spinal cord is an important mechanism that leads to the development of neuropathic pain [12]. Thus, pain and depression share neurotransmitters that are part of an overlapping pain system, suggesting that they could respond to similar pharmacological treatments [10].

### Hypothalamic-Pituitary-Adrenal Axis (HPA)

Depression and chronic pain cause hyperactivity of the hypothalamic-pituitary-adrenal axis. People with chronic pain and depression present increased activity of the hypothalamus inducing the release of corticotropin releasing hormone (CRH) leading to secretion of the adrenocorticotrophic hormone (ACTH) by the anterior pituitary. ACTH binds to adrenal cortex receptors stimulating glucocorticoid secretion. Glucocorticoids act by regulating the HPA axis, however, in individuals with chronic pain and depression this regulation does not occur resulting in increased glucocorticoids in the blood [6]. HPA axis hyperactivity is related to both chronic pain and depression states. In individuals with depression, the HPA axis can be stimulated if the same individual has chronic pain by stressors such as nociceptive stimuli [6,13].

### Inflammation

Inflammation is another common pathway between depression and chronic pain. Studies have shown that inflammatory markers such as reactive-C-protein and proinflammatory cytokines such as IL-6 are increased in individuals with depression [14].

Depression and chronic pain have a high prevalence in patients with chronic levels of inflammation [15]. Studies show that high levels of inflammation increase the risk factor for depression [16]. Other studies suggest that an increase in inflammatory signaling deregulates the neurotransmitter metabolism and alters neural activity in regions brain mood-related. The released cytokines reach the brain and increase inflammation in the central nervous system by altering the production, metabolism and transport of neurotransmitters including serotonin, dopamine and glutamate affecting mood [17].

Inflammatory cytokines also promote dysregulation of the HPA axis by increasing the release of glucocorticoid. In people with depression the feedback mechanism is inactive increasing the glucose levels in the blood. However, inflammation can cause resistance to glucocorticoid resulting in uncontrolled inflammation which increases these symptoms [18]. Studies suggest that chronic pain is associated with elevated levels of inflammation and that such inflammation generates hyperalgesia or increased sensitivity to pain. In this context, it is notable that chronic pain has also been found in individuals with depression [19], since it generates an amplified sensitivity that can cause depressive symptoms. The association between pain and depression seems to be reciprocal: greater pain is associated with a higher prevalence of depression, and improvements in depression levels are related to the decline of pain [18].

### Conclusion

In conclusion, the clinical importance in early identification of the mechanisms of chronic pain and depression aim at a better psychosocial rehabilitation, allowing the integrated treatment, reducing the administration of more than one type of medicament contributing to the improvement of life quality of patients.

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