Mini Review　　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Comorbidity of Depression and Pain: A review of shared contributing mechanisms

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Article Info

ABSTRACT

Pain and depression are two major health issues that we are currently facing. Chronic pain is the main reason that people seek medical care; and numerous people commit suicide each year because of depression. These two pathological conditions often coexist. Chronic pain patients are more likely to develop major depressive symptoms, while depressed patients reported more pain symptoms than normal healthy population. Understanding the common mechanisms associated with depression and pain is important for developing the effective strategy to treat this comorbidity. In this review, the potential mechanisms that contribute to both depression and pain are discussed from four perspectives, the morphological changes in the brain, monoamine deficiency, brain-derived neurotrophic factor (BDNF) reduction in the hippocampus, and the hypothalamic-pituitary-adrenocortical (HPA) axis dysfunction.

Introduction

Both chronic pain and major depression (MD) are important health issues. Pain is the leading reason that patients seek medical care. The annual cost pf pain (combining the health care cost and loss of productivity) in United States ranges from $560 to 635 billion, which is greater than the annual costs of heart disease, cancer, and diabetes[1,2]. Depression now is the leading cause of disability worldwide and is estimated to affect 350 million people[3]. These two conditions often coexist. The prevalence of pain in patients with MD and the prevalence of depression in chronic pain patients are higher than the prevalence of pain or depression in general population[4]. Moreover, the condition of one can exacerbate the other. Chronic pain patients with depression are more likely to have higher severity and longer duration of pain, and the presence of pain is associated with increased depressive symptoms and possible relapses[4–7]. The detailed epidemiological information about the comorbidity of pain and depression was reviewed by Bair et al., (2003). It is important to treat pain and depression concurrently in comorbid populations. By targeting the common mechanisms shared by both pain and depression, we can better treat these comorbid conditions. This review discusses the potential mechanisms that contribute to both depression and pain from four perspectives, the morphological changes in the brain, monoamine, brain-derived neurotrophic factor (BDNF), and the hypothalamic-pituitary-adrenocortical (HPA) axis dysfunction. The animal models for pain and depression are also briefly reviewed.

Morphological changes in the brain

Morphological changes in depression

Brain imaging studies and post-mortem studies showed that patients with depression had abnormal morphology in many brain structures[8]. Grey matter reduction is one of the major reasons. Left anterior cingulate cortex (ACC), which is ventral to the corpus collosum and is also called subgenual prefrontal cortex (SGPFC), showed prominent grey matter reduction in depressed patients[9]. Reduction of this area was found both in young women with early onset MD and middle aged women with recurrent MD[10]. The reduction in left posterior SGPFC is more prominent in MD patients compared with patients with other psychotic disorders, such as schizophrenia[11]. Decreased blood flow and activity in this area may contribute to the decrease in volume[12]. Hippocampus also exhibited volume reduction in depressed patients[13,14]. Reduction in hippocampus was seen in patients with a history of early-life adversity[15,16] and subjects with multiple depressive episodes[17]. Basal ganglia is another brain area showed grey matter reduction in depressed patients, more specifically the reduction was seen in putamen[18,19] and caudate nuclei[20,21]. Besides grey matter reductions, white matter abnormalities have been observed in depressed patients[22,23].

Morphological changes in pain

Chronic pain patients showed grey matter reduction in many brain areas. The most common areas that have grey matter decrease in chronic pain patients are the frontal cortex, ACC, insula, some areas in the temporal lobe[24–30]. Other areas, such as the thalamus, amygdala, motor cortex, and cerebellum, etc., also showed a decrease of grey matter depending on the type of chronic pain and disability the patients have[31–33]. The decreased grey matter was reversible in some cases after the pain was gone or was successfully treated[28,30,34]. Areas with increased grey matter were also noticed in some studies, such as the increased grey matter in the somatosensory cortex of migraine patients[35], which is probably related to its crucial role of processing noxious and innocuous sensory information.

Structural changes of brain areas involved in both depression and pain appears to be consequences of these pathological conditions instead of causes, because these changes were reversible once the depression[36] or chronic pain[28,30,34] has been treated. Overall, the brain areas that are mostly affected by both depression and pain are ACC, and the hippocampus in the temporal lobe. ACC is directly or indirectly connected to many other brain areas[37], and is involved in the integration of emotion, cognition, autonomic function and conflict resolution[38]; these functions are disturbed during depression[39]. Additionally, ACC is highly involved in the affective component of pain[40]. The

hippocampus in the temporal lobe is important in learning and memory, which are impaired in both depressed patients[41] and some chronic pain patients[42]. Therefore, abnormality of ACC and hippocampus can contribute to the symptomology of both pain and depression.

Monoamine

Monoamine and depression

There are two major classes of antidepressants: the tricyclic antidepressants which block the plasma membrane transporter for serotonin (5-HT) and/or noradrenaline, and monoamine oxidase inhibitors which reduce the enzymatic breakdown of 5-HT and noradrenaline. Both categories increase the level of monoamine, which leads to the hypothesis that depression is caused by a deficiency of monoamines, such as noradrenaline, 5-HT, or both[36,43]. Therefore, based on this hypothesis, monoamine depletion was utilized to study the direct effects of monoamine on mood. However, conflicting results were found in heterogeneous populations. The monoamine depletions only had an effect in subjects with a family history of major depressive disorder (MDD) or in drug-free patients with MDD in remission, but did not decrease mood in healthy humans[44]. Additionally, it requires weeks of treatment with antidepressants to produce mood changes in clinical population, despite the relatively immediate increase of monoamine transmission after the administration of these drugs. Therefore, it was hypothesized that acute increase of monoamine induced by antidepressants produces secondary neuroplastic changes which takes longer time and alleviate depression[43]. In line with this hypothesis, studies have found antidepressants increased calpactin I light chain/annexin II (p11) which could increase serotonin 1B receptor (5-HT$_{1B}$) receptors at the cell surface[45] and upregulate the transcription factor cAMP response element-binding protein (CREB)[46].

Monoamine and pain

Monoamines play an important role in pain, especially in the descending inhibition of pain. The spinal cord is innervated by noradrenergic nuclei located in the brain stem[47]. The noradrenergic projections to the dorsal horn modulate nociceptive signals before their transmissions to higher centers. Both stimulation of locus coeruleus[48] and direct administration of noradrenaline to the spinal cord[49,50] were antinociceptive. The release of noradrenaline acts predominantly on α_2-adrenoceptor subclass and can inhibit transmitter release from primary afferent terminal and therefore suppress the activation of projection neurons in dorsal horn[47]. Serotonergic projections to the spinal cord mostly derives from rostral ventromedial medulla (RVM) and the dorsal raphe nucleus[47]. Both acute and chronic exposure to noxious stimuli can activate serotonergic

neurons in the rostral ventromedial medulla (RVM) and facilitate the turnover of 5-HT in the spinal cord, therefore inhibit nociceptive transmission at the spinal cord[51]. 5-HT$_3$ receptors has been discovered to mediate the inhibitory effect of 5-HT on dorsal horn neurons upon periaqueductal grey (PAG) stimulation[52].

Overall, monoamines are highly implicated in both pain and depression. The brain stem nuclei send descending projections to spinal cord to modulate pain transmission and ascending projections to different brain areas to modulate mood, cognition and physiological function. The disruption of serotonergic and noradrenergic systems can contribute to the comorbidity of pain and depression.

BDNF

BDNF and depression

BDNF is the most prevalent growth factor in the central nervous system. It is known to be involved in survival and synaptic plasticity of central and peripheral nervous system. In human, the BDNF was significantly lower in depressed patients without antidepressant than those who were treated or control group[53]; and the BDNF was increased by antidepressant therapies[54] and electroconvulsive therapy[55]. Similar phenomena were seen in animals[46,56]. Furthermore, direct administration of BDNF in the hippocampus can produce an antidepressant-like effect in animals. A single bilateral infusion of BDNF into the dentate gyrus of the hippocampus produced an antidepressant effect which lasted for at least 10 days in both learned helplessness and forced swim test (FST) paradigms[57]. This antidepressive effect of BDNF was comparable in magnitude with repeated systemic administration of chemical antidepressant[57]. BDNF was able to promote the function and growth of 5-HT containing neurons and increase the turnover of 5-HT and levels of noradrenaline in many forebrain areas[58]. Given the important role of 5-HT and noradrenaline in treating depression, the effect of BDNF on serotonergic neuron and serotonin suggested a potential link between BDNF and depression.

BNDF and Pain

Similar to depression, reduction of BDNF in the hippocampus was observed during pain[59,60]. But BDNF increased in spinal cord dorsal horn[60,61] and periphery[62,63] under pain conditions. Spinal administration of BDNF resulted in decreased nociceptive threshold[64] and allodynia[61]. The binding of BDNF to tropomyosin receptor kinase B (TrkB) receptor is possibly involved in the pronociceptive effect of BDNF, because the sequestration of BDNF by TrkB receptor chimera protein suppressed nerve injury-induced thermal hyperalgesia and tactile allodynia[61,65]. In addition, BDNF induced phosphorylation of N-Methyl-D aspartic acid (NMDA) receptors on the

spinal cord neurons, which is necessary for maintaining pain hypersensitivity after nerve injury[66].

Although the BDNF changes differently at different location under pain condition, both pain and depression had reduction of BDNF in the hippocampus. It is interesting that the induction of BDNF by intracerebroventricular injection of 4-methycatechol (4-MC) reduced both the pain and depression response in rats caused by chronic constriction injury (CCI) of sciatic nerve, and this effect was blocked by anti-BDNF antibody[67]. This implies that the enhancement of BDNF in the brain may be a new treatment strategy for chronic pain associated with depression.

Dysfunction of HPA axis in depression and pain

The HPA axis is involved in the "flight or fight" response to stress. It consists of hypothalamus, pituitary and adrenal gland. External stressor activates hypothalamus to release corticotropin-releasing factor (CRF) which is delivered to and stimulate pituitary gland to release adrenocorticotropin hormone (ACTH). ACTH reaches adrenal gland through circulation and activate it to release glucocorticoids, such as cortisol which is involved in glucose metabolism[68]. Glucocorticoid, in turn, can suppress the production of CRH and ACTH to serve as the negative feedback mechanism for the HPA axis. Activation of the HPA axis is an adaptive process and enables organisms to respond to various challenges. However, continued and prolonged stress may disturb the HPA axis to such an extent that the negative feedback mechanism is disrupted; and the adaptive response of HPA axis then becomes maladaptive[69].

Depression and HPA axis

Dexamethasone (DST) has been used to detect the HPA abnormalities in melancholic patients[70–72]. DST is an exogenous steroid that can suppress the ACTH release by binding to the glucocorticoid receptors (GR) in the anterior pituitary gland. Depressed patients did not show such inhibition of HPA axis by DST, and some patients showed hypersecretion of cortisol at baseline[70,72]. Interestingly, not everyone who undergoes trauma develops abnormal HPA activity, only those who actually develop depression[73].

This loss of inhibition of HPA axis or maladaptive of HPA negative feedback mechanism has been attributed to the glucocorticoid receptors (GRs) which play an important role in the negative feedback regulation of the HPA axis. Patients with bipolar or major depressive disorders, as well as first-degree relatives of those patients, displayed GRα mRNA reduction[74], which indicates the genetic involvement. Genetic manipulation of GR expression in mice made animals more prone to develop depression-like behavior by under-expressing GR or more resistant to depression by over-expressing GR[75]. Antidepressants can also modify GR mRNA concentrations in primary

culture of rat hypothalamic or cortical neurons[76], elevate GR concentration in hypothalamus[77], and reduce basal, as well as stress-induced plasma ACTH and corticosterone[77]. Therefore, antidepressant may alleviate depression through increasing the number of the corticosteroid receptors and restore susceptibility of HPA axis to negative feedback by cortisol[78]. It is true that drugs specifically targeting HPA axis have shown promise in ameliorating depression symptoms[69].

Pain and HPA axis

Unlike the depression for which the hypercortisolism is a common phenomenon, hypocortisolism is more common in chronic pain patients[79-81]. No escape from DST was observed in fibromyalgia (FMS) patients[81]. However, not all pain patients are associated with low cortisol level. Women with shoulder and neck pain had a tendency to develop higher elevated cortisol levels, and this hypercortisolism was suggested to represent an intermediate stage towards the development of a hypocortisolism in wide spread musculoskeletal pain[80].

In summary, both pain patients and depressed patients showed maladaptive HPA function. However, depressed pain patients are more likely to develop hyperacitivity of HPA axis and result in hypercortisolism, while pain patients develop hypocortisolism.

Animal models for depression and pain

Animal models are great surrogates to study human disease in basic and preclinical research. They are pivotal for understanding the underlying pathophysiological mechanisms of disease and development of effective therapy. Therefore, the animal models of depression and pain are briefly summarized in this section to better understand how the animal models can be used to study the comorbidity of depression and pain (for more comprehensive and thorough reviews of depression models see[82-84], and pain models see[85-87]).

Some depression models are used to screen for the efficacy of antidepressants. These tests are easy, low-cost, and highly reproducible; such as FST and tail suspension test (TST), in which animal is forced to swim in a confined space or is suspended by its tail respectively[82-84]. In these tests, animal becomes immobile after the initial struggle. The total immobility time is sensitive to anti-depressive treatment. Some other depression models incorporate stress as the major determinant. Learned helplessness introduces the uncontrollable and unpredictable stress, and results in the loss of motivation to escape in animals[82-84,88]. For example, a rat is placed in a chamber divided into two halves, with one of them is equipped with the floor which can deliver electric shock. Animal learns to escape to the safe side when hears a warning tone preceding the shock.

However, if the animal is confined to the side with shock and receives several unavoidable and uncontrolled shocks, animal will subsequently fail to escape when he is allowed to[84]. In the chronic mild stress (CMS) model, animals are exposed to a series of mild and unpredictable stressors for at least 2 weeks, such as isolation or crowded housing, food or water deprivation, disruption of dark-light cycle, tilted home cages, dampened bedding, etc[82-84]. And sucrose intake is used as readout of anhedonia in this model. Additionally, social stress is adopted in depression models by introducing an intruder to the stable social group or mixing different social groups; and maternal separation is used as an early life stressor. Furthermore, there are depression models based on the putative pathophysiological mechanism, such as the deficiency of monoamine. Reserpine, a vesicular monoamine transporter blocker, has been used to deplete synaptic monoamines in depression models[82-84]. Others employ genetic manipulation to create mutant lines that display depressive symptoms[82,83].

Animal pain models have been created in an attempt to recapitulate clinical conditions. To create inflammatory pain, irritant inflammatory agents are injected into different parts of the body, such as cutaneous and subcutaneous tissue, joint, and muscle, etc[89]. For example, formalin can be injected subcutaneously in the hind paw of rodents to induce biphasic pain responses. The initial phase lasts about 5 min after the injection, and then after quiescent period, a second phase persists for about 45 min. The spontaneous pain behaviors, such as flinching, shaking, or jerking of the injected paw, are quantified to indicate the present pain induced by formalin[85,89]. Other commonly used irritant algogenic agents are capsaicin, Freund's adjuvant, and carrageenan, etc. When these agents are injected intraperitoneally or directly into the hollow organs, such as colon, visceral pain is produced and writing response can be measured[85]. Another major type of pain is the neuropathic pain which results from the injury or dysfunction of the nervous system. Many surgical variations have been invented to injure the nerve. For example, there are complete transection of the sciatic nerve, tight ligation of dorsal one third to half of the common sciatic nerve, tight ligation of L5 spinal nerve, tight ligation of peroneal and tibial nerve while leaving sural nerve intact, or spinal cord contusion, etc[86,87]. Inflammatory agent, such as zymosan, can also be applied to the nerve to induce neuropathic pain[86]. Additionally, chemotherapy-induced neuropathic pain is commonly seen in patients who receive chemotherapeutic drugs. Therefore, chemotherapeutic agents, such as vincristine, cisplatin and paclitaxel, have been repeatedly injected to animals to produce chemotherapy-induced peripheral neuropathy. Other disease-induced neuropathy models are diabetes- and cancer-induced neuropathy[86]. Many of the pain models can result in the peripheral hypersensitivity

which can be measured by the reduced threshold to thermal or mechanical stimuli. To measure the hypersensitivity to mechanical stimuli, a pressure of increasing intensity is applied to the hind paw until the paw withdrawal. For example, a series of von Frey filaments of different diameters (producing different pressure when bent) are applied to the ventral or dorsal surface of the hind paw. The lowest pressure that produces withdrawal response is regarded as the mechanical threshold. Similarly, the thermal hypersensitivity can be measured by the reaction time of certain behavior when exposed to a thermal stimulus. An example of such test is the Hargreaves test in which a radiant heat is directed toward the plantar surface of the hind paw and the latency of paw withdrawal is recorded as the thermal threshold[90]. Sometimes, animal's response to cold is also measured. Vocalization is another parameter that is measured as the reaction to painful stimuli, and the stimulus intensity necessary to elicit a vocal response is determined[85,89].

To study the comorbidity of depression and pain in animal models, it is necessary to evaluate the pain hypersensitivity in depression models and depressive proneness in pain models, and find the optimal model for the comorbidity of depression and pain. It can imagine that not every model will produce the same degree of comorbidity based on the differences in the etiologies and pathophysiological mechanisms for each model. Because the comorbidity was mostly seen in patients with chronic pain, it is more appropriate to incorporate chronic pain such as neuropathic pain, as opposed to the relatively transient pain such as formalin injection-induced pain. Furthermore, depression models with higher face validity involving stress as major determinant can better mimic clinical conditions as compared to the FST or TST.

Summary

As discussed above, there are common factors involved in both depression and pain: the grey matter decrease in ACC and hippocampus, deficiency in monoamine and reduction of BDNF in hippocampus. Although both depression and pain are associated with the malfunction of HPA axis, they differ in the direction of changes in HPA axis activity. Targeting at these shared mechanisms for pain and depression may increase the efficiency of treating patients with comorbidity of pain and depression. More research needs to be done in a comorbidity model to study the efficacy of targeting these factors in treating pain and depression. For example, does the increase of monoamine or BDNF level ameliorate both pain and depression? There is one study which has shown increased BDNF can increase pain threshold and alleviate depression in CCI model[67], but more research needs to be done. Studies have shown that increased glucocorticoids and ACTH was able to increase monoamine oxidase activity to reduce monoamine

level[91,92]. Decreased BDNF level could lead to changes of neuroplasticity and volume in critical brain areas[46], such as the prefrontal cortex, ACC and hippocampus, which can result in the dis-regulation of mood and changed pain perception. Therefore, we also want to know how these mechanisms interact with each other and how they play as a whole in the comorbidity of depression and pain.

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