

Review

Short but continuous natural pain for depression treatment and beyond

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Abstract

The correlation and comorbidity between depression and chronic pain have been observed for a long time. Generally, it is considered that the two conditions reinforce each other, whereas the causal relationship between them is not clear. However, some evidence suggested that chronic pain may reverse the progression of depression in some cases. This article presents a selective review of clinical and pharmacological relationship between depression and pain, and their interactions at neurochemical and neurobiological levels. In addition, we open a discussion on a recent case report of repeated success of using short but continuous pain (SCP) during meditation as the only treatment for depression, compared to initial success but no remission with other conventional antidepressants on the same patient. Together this review proposes an updated model for depression and its various treatments that is based on synaptic and system homeostasis. More importantly, it suggests that SCP may benefit depression recovery through its properties that are different from either acute or chronic pain and represents a novel research area that has been largely neglected to date.

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Major depressive disorder (MDD) is a common psychiatric disorder, which leads to usually seriously impaired condition in the patients and great global disability burden (1, 2). Current treatments for depression often take weeks or months to demonstrate full effect, not all patients have a good response, relapse rate is high even for those effective treatment, and only a subset of patients achieved remission, raising the question of either the complexity of the disease or the effectiveness of the currently available treatments (3, 4).

In light of its diverse etiologies, comorbidity with many other diseases, and complex underlying pathology, it is challenging to understand the physiological basis of MDD, which may be a complex of related diseases, rather than a single one. In addition to the incomplete understanding of MDD, the individual heterogeneities among patients may render it an elusive goal to develop a universal treatment for MDD. But studying the effectiveness of each current treatment can help stratify patients into different subtypes for customized treatments as an ultimate goal (5).

Recently, we published the first report of repeated success of using meditation as the only treatment of MDD, whereas other conventional antidepressants achieved initial success but no remission on the same patient (6). We hypothesized that *the Short but Continuous natural Pain (SCP) during meditation sittings has the therapeutic effect to treat depression in the case of this patient and potentially others with MDD*. The special opportunity to eliminate individual heterogeneity has enabled us to probe deeply into the potential mechanisms of depression treatments and the intricate physiology of depression itself, providing profound implications in the treatment of other MDD patients. More importantly, the case report helps us dissect one specific component of meditation for its long-known and well-established benefits against depression (7, 8).

However, our proposed hypothesis is counterintuitive to the current understanding of the relationship between depression and chronic pain. Chronic pain is generally detrimental, whereas acute pain is usually useful to trigger reflex to prevent injury. SCP may exhibit different properties from those two types of pain and represent an exciting novel research area that has been largely neglected to date. In this review we will present the links between depression and pain and discuss potential mechanisms of our hypothesis. Due to space constraints, we have not attempted a comprehensive review but focused on selected areas that are closely related to the interface between depression and pain. We will start with some clinical and pharmacological observations, which suggest some fundamental connections between these two conditions.

Depression and chronic pain

Depression and chronic pain are usually closely associated, but their causal relationship is not clear (9, 10). However, it was noted that a substantial minority of treatment seekers for chronic pain do not seem depressed, and even lower

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rates of depression in community samples of people with persistent pain, where the modest relationship is proposed to be mediated by cognitive factors (catastrophizing, self-efficacy, sense of control/helplessness), physical functioning, medication variables, and psychological factors (resilience and flexibility) (11). Thus, chronic pain may not have a simply causal effect on depression, but instead might exert some antagonistic function.

In a study that prospectively examined depression response to chronic pain over a course of six years in a nationally representative middle-aged sample of 2,172 individuals, the resilience group (no or minimal depression symptoms prior to and following pain onset) was much larger than the post-pain depression group (low depression at baseline but increasing symptoms following pain onset) (72.0% compared to 11.4%). More strikingly, gradually declining depression symptoms were observed in a higher number of patients with initially high depression following the onset of chronic pain, compared to patients with similar depression before and after the onset of chronic pain (9.8% vs 6.8%) (12). These data provide support to our hypothesis, but the complex relationship between depression and pain, and multiple involving factors demands more rigorous research.

Chronic pain patients show reduced levels of serotonin and dopamine, deficient working memory, and impaired decision making, which are also typical symptoms of depression (13). Even though SCP is not exactly the same as chronic pain, their shared pain pathways may act on the same targets involved in depression with different outcomes due to their different properties.

Drugs in depression and pain

Conventional antidepressants

One major difficulty with the monoamine theory of depression for conventional antidepressants is that the antidepressant effect usually takes weeks to develop whereas the monoamine activity increases quickly (14). Thus additional theories, such as neurotrophic and neurogenic hypotheses, have been proposed to explain the pathophysiology of depression and corresponding antidepressant responses (5). In the case report, slowly-building antidepressant effect was not observed for multiple conventional antidepressants and/or their combinations (6). Instead, there were two times of fast recovery through antidepressant(s) that took place within several or 36 hours after administration of the new medications. One possible explanation for this discrepancy might lie in the ability of monoamines to serve as analgesics, since descending pain pathways utilize monoamine neurotransmitters and conventional antidepressants may actually work through enhancing the analgesic activity of those pathways (14).

In the clinics, The tricyclic antidepressants (TCAs) have been used to treat chronic pain and one TCA, amitriptyline, is commonly prescribed off label for the

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treatment of shingles pain (14). The serotonin/norepinephrine reuptake inhibitor (SNRI) duloxetine is approved for the treatment of fibromyalgia pain and also efficacious to treat pain in diabetic peripheral neuropathy (15). If this is the mechanism behind the recovery from depression using conventional antidepressants, the fast-acting effect of psilocybin may be also exerted through monoamine related pain pathways, since it primarily functions as an agonist of serotonin (5-HT) receptors (16, 17).

Ketamine

Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist, is a well-established anesthetic and generates “dissociative anesthesia”, which includes hypnosis, intense anti-nociception, increase sympathy, and maintenance of respiration (18). Sub-anesthetic dosing of ketamine has shown rapid clinical antidepressant effect in both MDD and bipolar depression (17–27). The hypnotic effect of ketamine is largely mediated through inhibition of NMDA and HCN1 receptors, its sedation and analgesia effects are modulated by cholinergic, aminergic (serotonergic and noradrenergic activation and inhibition of re-uptake), and opioid systems, whereas its effects in chronic pain and depression are likely achieved through glutamate neurotransmission and secondary changes in synaptic plasticity (18, 29). Additionally, ketamine acts on different levels of inflammation to confer an overall anti-inflammatory effect, limiting exacerbation of systemic inflammation but not disrupting local healing processes (30), which could also be an important aspect of its antidepressant function. The responses or part of the responses of our body to the SCP could be similar to some of the physiological changes caused by ketamine and thus contribute to relief in depression symptoms.

Inflammation in depression and pain

In the case report, allergic reaction to seasonal pollens correlated with depression symptoms and the relief of allergic response marked the beginning of depression recovery triggered by SCP perception (6). These observations agree well with the close association of inflammation with both depression and pain and suggest possible causal relationships. Peripheral immune modulators could induce psychiatric symptoms in animal models and human, and in psychiatric patients, peripheral immunological abnormalities are also more prevalent compared to healthy control (31–34). It is proposed that neuroinflammation and cytokines are at least a contributing factor to the pathological development of depression (35–38).

The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis have long been closely associated with the pathophysiology of depression, but the causal relationship is far from clear (38). The overdrive of the HPA axis, hypersecretion of cortisol, dysfunctional feedback mechanisms, and/or cytokine over-secretion are most consistently seen in patients with more severe

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depression, such as melancholic or psychotic depression (38, 39). In the case report, SCP could serve as a sustained stressor and stimulate the HPA axis and the SNS, leading to glucocorticoid (GC) release from the adrenal glands and further anti-inflammatory effects, or acting through the parasympathetic nervous system and the cholinergic anti-inflammatory pathway (reduced production of inflammatory cytokines and relief of allergic responses) (29, 31–33). This may be similar to what occurs during vagus nerve stimulation, which is a promising treatment for drug-resistant depression, likely due to its ability to increase the vagal tone and to inhibit cytokine production (42, 43).

Pain activation and long-lasting effect

The multiple dimensions of pain experience (sensory, emotional, and cognitive) involve activation of different regions of brain (pain matrix), which are also involved in other functions of the brain and likely affected by depression. The brain network for acute pain, most consistently revealed through functional imaging studies, include primary and secondary somatosensory cortices (S1 and S2), insular cortex (IC), anterior cingulate cortex (ACC), prefrontal cortex (PFC), and thalamus (Th), out of which clinical chronic pain conditions more frequently involve PFC and are often associated with decreased baseline activity or decreased stimulus related activity in Th (44–46). Also abnormalities of the white matter structures connecting the medial PFC and the nucleus accumbens were observed in chronic pain patients (47).

With a significant overlap with pain matrix, structural and functional abnormalities in PFC, ACC, hippocampus, basal ganglia, and amygdala have been documented in MDD (48, 49). However, meditation, where SCP was first implicated in our case report, can to certain degree reverse these abnormalities, as well as other neurochemical, neuroendocrinal, neurobiological, and immune/inflammatory changes associated with depression (7, 8). Last but not least, Meditation associated pain has also been described by others (50). Thus, it is reasonable to postulate that SCP may activate certain pathways or brain areas, and lead to depression relief through a mechanism that has not be revealed yet.

Possible system mechanisms for the antidepressant effects of SCP

As illustrated above, pain and depression are inter-connected at many different levels through the endocrine, immune, and nervous systems. The same systems communicate with each other to achieve a dynamic equilibrium and system homeostasis, which are exemplified at different levels, such as Th1/2 balance and synaptic plasticity (41, 51). However, dysregulations triggered by stress result in shifts in balance and the system may not be able to return to homeostasis and exemplified again at different levels, such as Th1/2 imbalance

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and synaptic malfunctions (31). In this vein, depression is not a simple disease caused by one or several factors, but a disrupted system homeostasis. Multiple factors that influence the function of the immune and nervous systems, such as monoamines and neural synapses, can be the triggering factors that initiate the development of depression (5, 31, 37, 38, 52). Eventually, the system reaches maladaptive states that have symptomatic presentations. This could help explain the increased sensitivity to pollen during the depression and remarkably decreased allergic response as the start of recovery from depression observed in the case report (6).

Interestingly, in a recent transcriptomic profiling of molecular brain-based phenotypes across major psychiatric disorders, including autism, schizophrenia, bipolar disorder, depression, and alcoholism, shared molecular neuropathology (demonstrated in transcriptional dysregulation) parallels polygenic (single-nucleotide polymorphism-based) overlap, suggesting a substantial genetic causal component and pathways of molecular convergence, despite the distinct features and specificity of each condition (34). Using the analogy of a rugged funnel-like energy landscape proposed in protein folding (53), the ideal stable state of homeostasis is in the center and other less stable maladaptive states can be widely spreading across an infinite field, where the depth can also vary from person to person and change at different stages of life. Depression and other psychiatric or somatic illnesses are all individual maladaptive states and can potentially be cured by disrupting the system in a controlled way and subsequent guiding towards the center, similar to protein refolding.

Each body system is under constant stimulations of environmental and internal changes and reacting to each stimulation is neither practical nor beneficial. Thus, a balance of inhibition and perception needs to be maintained and the presentation of the balance is homeostasis at both system and synapse levels. Conventional antidepressants and psilocybin may exert their fast antidepressant effect through their ability to manipulate body's response to external and internal stimuli. Ketamine as well as other new fast acting antidepressants might function through similar mechanisms. However, shifted homeostatic states of the body make it an elusive goal to achieve remission.

During the repeated recovery from depression in the case report (6), SCP likely restored the homeostasis of neuronal synapses and networks, demonstrating plasticity as one of their most fundamental and intrinsic properties. The inability to adapt is one unique property of pain sensation from other senses, which would be dampened by constant stimulations (13). In this sense, SCP lasts long enough to trigger significant changes in the pain pathways and potentially benefit depression recovery despite shifting homeostatic states of the body system, through fine tuning the inter-connected endocrine, immune, and nervous systems. Similarly, exercise, fish oil consumption, controlled breathing, and other relaxation therapies increase vagus nerve activities and decreasing pro-inflammatory cytokine release, in agreement with observed clinic benefits of vagus nerve stimulation against depression (41–43, 54).

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Possible cellular/molecular mechanisms for the antidepressant effects of SCP

The aforementioned transcriptomic study on several major psychiatric disorders also identified genes up-regulated specifically in MDD that are enriched for G protein-coupled receptors, cytokine-cytokine interactions, and hormone activity pathways, which indicate the direct involvement of inflammation and HPA axis dysregulation in depression (34). In another study that investigated the overlap between genes with robust changes in expression caused by the antidepressant Mianserin (a noradrenaline uptake inhibitor) and genes involved in depressive symptoms of an aging non-psychiatric population discovered through a genome-wide association (GWAS) approach, the top gene based on relevance to mood disorders and stress response was identified as *ANK3* (55). The protein encoded by *ANK3*, ankyrin-G, has been found as a critical regulator of synapses and strongly associated with schizophrenia, depression, anxiety disorders, and autism (56, 57). These data support the critical role of neuronal signaling and synapses in depression (52, 58). Potentially SCP functions through the same pathway(s) to counteract the damaging effect of depression.

Neuron plasticity as one of their most fundamental and intrinsic properties requires neurons to change their cellular behaviors and intracellular functions upon signaling triggered by stimulations. Integration of cellular history with current environment determines the response of cells at certain space and time. Based on our limited literature studies, at the center of the link between SCP and depression is the hypothalamus, the neuroendocrine 'headquarters' in the body (59). First of all, the hypothalamus plays critical roles in nociceptive processing and pain modulation (60, 61). Secondly, the hypothalamus controls various endocrine systems through synthesizing and secreting specific hormones that modulate the secretion of pituitary hormones, which further control a wide range of physiological processes (62).

Physical stressors such as SCP convey excitatory information through ascending aminergic pathways toward the paraventricular nucleus (PVN) of the hypothalamus, which synthesizes corticotrophin-releasing factor (CRH) to drive sympathetic and behavioral fight-or-flight response and to activate the HPA axis (63). The end product of HPA axis, glucocorticoids, can reach every organ by way of circulation and has a profound effect on the whole body and brain functions. Depression has been known to be associated with elevated levels of cortisol and dysfunctional feedback mechanisms within the HPA axis (39).

The complex actions of glucocorticoids mediated by a dual receptor systems, mineralocorticoid (MR) and glucocorticoid receptors (GR), as well their roles in mental health are comprehensively reviewed elsewhere (40). Here we will just emphasize several pertinent points: 1) the HPA axis and glucocorticoids coordinate both the initial fight-or-flight stress reactions and later recovery/adaptations, in concert with catecholamines (adrenal hormones) and neuropeptides; 2) the molecular signaling pathways that underlies neuroendocrine communication which integrates body and brain functions are

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extremely complex and dependent on time, space, and context; 3) the balance of MR/CR function is critical and the relevant genetic variations and epigenetic modulations are implicated in stress response, HPA axis responsiveness, and depressive feelings; 4) a three-hit hypothesis was proposed that a combination of risk/plasticity genes with early adversity and later stressful life events generates a state vulnerable for mental disorders.

There are two other important examples for the capacity of hypothalamus's control over the whole body, hypothalamic-pituitary-thyroid (HPT) axis and hypothalamic-pituitary-gonadal (HPG) axis, the latter of which, together with gonadotropin-releasing hormone (GnRH), has been extensively implicated in ageing and longevity. A lot of related studies have been focused on ageing and longevity, but behavior and mood can just be the other aspects of one integral system (64). Mediobasal hypothalamus (MBH) modulates immune responses and endocrine systems (59) and is the most sensitive brain region to nuclear factor- κ B (NF- κ B) activation, which stimulates immune responses during the ageing process (62). In the glial cells of MBH, NF- κ B activation results in the production and secretion of the inflammatory cytokine tumor necrosis factor (TNF)- α , which then leads to the activation of NF- κ B in GnRH neurons and reduced production of GnRH (62, 65). Of note, GnRH travels within in the brain to promote brain-wide adult neurogenesis independently of a specific sex hormone (59). There is a strikingly similar pattern of cross-talk between glial cells and neurons in studies of ATM (A-T mutated) and neurodegeneration in *Drosophila melanogaster*. ATM mutations cause neurodegeneration by activating a specific Nuclear Factor- κ B (NF- κ B) transcription factor, Relish, in glial cells, which regulates the immune deficiency (Imd) innate immune response (IIR) signaling pathway and leads to neuron and glial cells (66, 67).

However, how activation of HPA/HPT/HPG pathway is triggered at the molecular level has not been fully illustrated. Here, we propose that enhanced perception and neuronal activity upon exposure to sustained stressors lead to unusually high levels of DNA double strand break (DSB), which subsequently activate DNA damage responses (DDR) in an overwhelming way that triggers inflammation in the nervous system. The long-term effect depends on the subsequent responses, where efficient repair would restore the system and potentially enhance plasticity, but impaired capacity to repair (for example, ATM mutants) contributes to cell death, neurodegeneration, and/or other pathological conditions. For example, SCP may sequentially trigger strong neuronal activity within certain areas of the brain (such as hypothalamus), induce DNA DSBs and DDR in the neural cells, and/or activate innate immune response (IIR) in glial cells, and ultimately modulates immune and endocrine systems through the mammalian HPA axis. Alternatively, the higher neuronal activity in the first place is sufficient to cause downstream effects, such as neuroendocrine regulation through hypothalamus.

It is only in recent years that DNA DSBs and DDR have been recognized to have a much wider presence and a much more profound involvement in normal cellular functions, especially in the nervous system. For example, DDR signaling

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is required for efficient RNA polymerase II (Pol II) pause release and transcriptional signaling (68). Physiological neural activity, such as during learning and exploring a novel environment, has been shown to cause DNA DSBs in mice neurons (69). A more recent study found that neuronal activity stimulation triggers DNA DSBs in the promoters of some early-response genes, including *Fos*, *Npas4*, and *Egr1*, to induce gene expression (70). These studies as well as others not mentioned here due to limited space, suggest that activity-induced DSB formation by Topo II might be a conserved mechanism to rapidly respond to stimulations (71). DNA strand breaks (either single strand or double strand break) activate Poly (ADP-ribose) polymerase (PARP) for DNA repair, whereas excessive activation of PARP depletes tissue stores of its substrate, nicotinamide adenine dinucleotide (NAD), and results in depletion of ATP and cell death (72). More intriguingly, PARP inhibitors provide broad protection from DNA damage-involved tissue damages in animal models of diseases as diverse as diabetes, vascular stroke, and ischaemic injury (72).

Our hypothesis on the involvement of DNA DSB and DDR agrees well with the newly emerging field of neuroepigenetics, where DNA and histone modifications are closely associated with neuronal activity-induced gene expression regulation, plasticity, and survival, whereas alterations in these neuroepigenetic mechanisms are linked to neurodevelopmental, psychiatric, and neurodegenerative disorders (71). For example, ATM helps to recruit Sirt1 to DSBs, which in return enhances ATM activity and stimulates the neuroprotective class I histone deacetylase HDAC1 (73). The collaboration between Sirt1, ATM, and HDAC1 is required for DSB repair through the nonhomologous end-joining pathway (NHEJ) to maintain genomic stability in post-mitotic neurons (74). In line with the close relationship between neuronal activity-triggered DSBs, DDR, and neuroepigenetic pathways, chromatin accessibility landscape was found to be modified 1h after neuronal activation, with enrichment of gained-open regions at active enhancers and at binding sites of AP-1 complex subunits, including *Fos* and *FosB*, both of which also have identified DNA DSBs within their respective promoters (70, 75).

Sirt1, as well as other members of sirtuins (the silent information regulator 2 (Sir2) family of NAD⁺-dependent protein deacetylases and deacylases), plays critical roles in the brain, especially in the hypothalamus, in regulating diverse functions that includes feeding behavior, endocrine modulation, physiological rhythms, and emotions (62). The hypothalamic-pituitary axis (such as HPA, HPT, and HPG), as discussed earlier, is modulated by Sirt1 through the synthesis and secretion of hormones in the hypothalamus and pituitary gland (62), whereas Sirt2 could specifically function as an inhibitor of microglia-mediated inflammation and neurotoxicity (76). Since NAD⁺ is required for all the enzymatic activities, sirtuins can also function as sensors of the cellular energy status (62).

In diseases like A-T, defects in DDR cause neurodegeneration, whereas chronic pain leads to cortisol de-sensitization and other immune- and neuro-malfunctions. Thus, it seems that maintaining a balanced DDR is critical for the

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nervous system, where SCP can stimulate the system in a controlled manner to activate the functionality of immune, nervous, and endocrine modulations, which counteracts both the initial local neuro-inflammatory imbalance caused by SCP and also the systematically maladaptive states of depression as a beneficial byproduct.

Deep brain stimulation (DBS), which is an established treatment for movement disorders and Parkinson's disease, has also been actively explored for its effectiveness in the management of treatment-resistant depression (TRD). An integrated review by Dandekar et al. provides useful insights that 1) stimulation of pertinent brain regions displayed differential effects on mood transition in TRD patients, 2) stimulation parameters and neuroanatomical locations affected DBS-associated antidepressant effects, and 3) modulatory influence on monoamine neurotransmitters in target regions or interconnected brain network could be the potential mechanism (77).

In a recent study to investigate the mechanisms of DBS benefits using a mouse model of Rett syndrome (RTT), a neurodevelopmental disorder caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) (78), genes involved in synaptic function, cell survival, and neurogenesis are upregulated and about 25% of the genes differentially expressed in *Mecp2*-null mice are normalized upon 45 min of forniceal DBS with a 20 min recovery period (79). Interestingly, a significant portion of genes induced by DBS are involved in apoptosis regulation, which is an important part of DDR (80, 81), suggesting that DNA DSBs likely take place and trigger those transcriptional changes during DBS. More intriguingly, 17% of the genes downregulated in post-mortem human brain tissues from patients with MDD are found in the DBS-upregulated genes, whereas 35% of the genes upregulated by treatment with antidepressant fluoxetine, a selective serotonin reuptake inhibitor, overlap with genes upregulated by forniceal DBS (79). Compared to DBS, SCP represents a natural option that is likely more precisely targeting and much less invasive, and thus can potentially apply to a wider population of MDD patients for better outcomes.

Conclusions and future directions

SCP likely exhibit different properties from acute or chronic pain and represent an exciting new research area. Our hypothesis, at both system and molecular levels, remains to be verified and the proposed potential mechanisms merit future investigation. Even though there won't be a silver bullet, the knowledge gained through future studies will further support and advance our understanding of the amazing plasticity of the brain, as well as help devise personalized lifestyle/medicine strategy to prevent and cure diseased brains.

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