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Original article

Neurobiological basis of chiropractic manipulative treatment of the spine in the care of major depression

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Abstract. *Background and aim:* Major depressive disorder is associated with an autonomic nervous system imbalance. All the symptoms of depression (high cortisol, high adrenalin, insomnia, agitation, anxiety) can probably be attributed to over-activation of the sympathetic nervous system. We performed this review in order to highlight the possible links between chiropractic intervention, its potential molecular effects and its possible outcomes on patients with depression. *Methods:* We performed a literature search for all the relevant manuscript regarding the effects of chiropractic and depression on the autonomic nervous system. *Results:* Chiropractic care and spinal manipulation regulate the autonomic nervous system at peripheral level and its projections to the central nervous system. In particular, they may activate the parasympathetic system to counterbalance the activity of the sympathetic system. Vagal parasympathetic stimulation is also considered an effective therapy for major depression as it releases neurotrophins essential for anti-depressive therapies, including brain-derived neurotrophic factor and nerve growth factor. *Conclusion:* Chiropractic and spinal manipulative therapies along with vagal nerve stimulation may therefore be regarded as treatment options for depression. (www.actabiomedica.it)

Key words: chiropractic, depression, neurtrophin

Introduction

Major depressive disorder (MDD) is the fourth main cause of disability worldwide, according to the World Health Organization (1). It causes severe mental distress and dysregulation of the autonomic nervous system and the neuroendocrine system. Autonomic functional imbalance associated with loss of vagal or parasympathetic activation and over-reactivity of the sympathetic system are regularly observed in MDD (2). These dysfunctions may contribute to comorbidities of MDD like early coronary artery disease and osteoporosis (1). The main symptoms of MDD include anxiety, continuous depressed mood, anhedonia, poor concentration, feelings of guilt, loss of appetite, insomnia and frequent suicidal thoughts (3).

Autonomic nervous system in depression

The autonomic nervous system consists of two systems, sympathetic and parasympathetic, which usually have opposite effects on tissues, so that an increase in one system's activity concurrently decreases the other system's activity in a very precise control of tissue function (4).

The sympathetic nervous system predominantly enhances the activity of effector organ through catecholamines like dopamine, adrenalin and noradrenalin release at neuroeffector junctions, whereas the parasympathetic nervous system is concerned with conservation of vegetative energy and facilitation of processes like digestion and rest, lowering the heart rate and enhancing gut motility (5).

Most depressive symptoms such as high cortisol, anxiety, insomnia, high adrenalin and agitation can be attributed to changes in the sympathetic system. Autonomic control along with interoceptive feedback predominantly contribute to emotional processing. The activity of sympathetic nerves increases under the influence of physical or emotional trauma. Failure to re-establish homeostasis over-exposes the subject to chronic stress (6). This dysregulation leads to intolerance of the emotional and physiological stressors linked to trauma, prompting dysfunctional behaviors, like depression (5).

In MDD, autonomic function is assessed by analyzing blood pressure regulation, gastric motility, pupil variations, skin conductance and heart rate variability (7). Recent research has shown an association of MDD with genetic and non-genetic factors like biochemical alterations, affective trauma, stress, viral infections and abnormal brain development (8-10). Early research showed a reduction in parasympathetic function during MDD. In 2007, Rottenberg critically reviewed this evidence of parasympathetic dysregulation during depressive disorders in a cross-sectional meta-analysis that covered 13 studies (11). More recent studies report an association of MDD with lowered heart rate variability. The sympathetic and parasympathetic nervous systems both affect heart rate and low frequency fluctuations in heart rate variability (12).

Other autonomic functions such as pupil variations are controlled by the sympathetic and parasympathetic branches. Indeed, pupil light reflex is used to detect autonomic imbalance. Interestingly, changes in pupil fluctuations have been reported in persons suffering from MDD (13).

Another study explored the functions of different branches of the autonomic nervous system for insights into the role of sympathetic and parasympathetic system modulation in MDD. Untreated MDD patients and controls matched for age, gender and body mass index were evaluated for heart rate variability, blood pressure variability, baroreflex sensitivity, skin conductance, pupil unrest index, respiration and pupil diameter. The results showed a substantial difference between the pupil diameter, pupil unrest index, skin conductance and its fluctuations between untreated MDD patients and controls (7).

Latvala et al. performed a longitudinal study recruiting more than 1 million men and established that blood pressure and heart rate may help predict MDD. In a follow-up study over 45 years, the risk of depressive disorders increased by up to 6% in individuals with a resting heart rate of more than 82/min with respect to those having a heart rate of less than 62/min (14).

A fundamental neurotransmitter for MDD onset is serotonin. Serotonin regulates emotional and behavioral responses. The serotonin transporter is involved in transporting excess serotonin from the synaptic cleft to presynaptic neurons and in the regulation of serotonin concentrations and activity, with significant antidepressant effects. Significant alterations in serotonin transporter availability have been reported in MDD patients (15). The correlation between serotonin and autonomic nervous system activity is demonstrated by serotonin precursor levels (tryptophan), depletion of which may lower heart rate variability and enhance other depressive symptoms (16).

Numerous studies have revealed that plasma concentrations of norepinephrine are elevated in MDD patients. Norepinephrine is a neurotransmitter and its plasma concentrations usually reflect sympathetic nervous system activity. Elevated plasma concentrations of norepinephrine among depressed patients suggest enhanced activity of the sympathetic nervous system (17). This was confirmed in a study on a cohort of 17 depressed patients and 36 controls. These observations were also supported by other studies that established an association between increased plasma concentrations of norepinephrine and severe depression or elevated hypothalamic-pituitary-adrenal activity, suggesting an increase in sympathetic nervous system activity (17). Furthermore, increased norepinephrine and epinephrine levels stimulate proinflammatory cytokines. The resulting neuroinflammation may cause neurotoxic changes in the brain of patients affected with depression (18).

Similarly, high sympathetic nervous system tone in MDD is associated with a high risk of mortality from cardiovascular dysfunction. In fact, the activity level of the cardiac sympathetic nervous system is raised in MDD patients and may be considered as a key player in the high cardiovascular morbidity and mortality in MDD. Increased activity of the sympathetic nerv-

ous system may also play a role in depression-related weight loss, because the sympathetic nervous system is an important constituent of neuroendocrine systems involved in the regulation of energy metabolism (19).

In 1984, Nemeroff and co-workers found elevated concentrations of corticotropin-releasing factor in cerebrospinal fluid of MDD patients, leading to the suggestion that elevated activity of this factor in the central nervous system could explain hypothalamic-pituitary-adrenal hyperactivity in MDD (20), leading in turn to increased sympathetic nervous system activity (17).

All this evidence supports a strong relation between the autonomic nervous system and depression. Hence autonomic regulation at peripheral level through manipulative adjustments and spinal massage may have a positive effect on patients suffering from MDD.

Brain-derived neurotrophic factor and nerve growth factor as key modulators in depression

According to the neurotrophic hypothesis, there is a significant association between MDD with reduced neurotrophin expression and aberrant neurogenesis in different parts of the brain (3). Many clinical and preclinical studies have proposed that several neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), are involved in the pathogenesis of MDD. These neurotrophic proteins contribute to the survival and plasticity of serotonergic, dopaminergic and cholinergic neurons in the central nervous system (21).

Brain-derived neurotrophic factor is an important neuronal growth factor that regulates neuronal maturation, neurogenesis, synaptic plasticity and survival. Reduced BDNF levels have been observed in the prefrontal cortex and hippocampus of stressed animals, suicidal subjects and depression patients. A recent review established the role of BDNF in numerous neurological and psychiatric disorders. Inadequate levels of BDNF can be improved by treatment with antidepressants and physical therapy in depressed patients and animal models (22).

Nerve growth factor is another important neurotrophin recognized for its role in the survival of cholinergic and sympathetic neurons in the basal forebrain. Dysfunction of NGF may lead to depression in stressed and peripheral-nerve-damaged animal models (3). Nerve growth factor acts as a modulator of the hypothalamic-pituitary-adrenal axis and contributes to maintaining the neuroendocrine and immune systems. Many studies have observed functional abnormalities of the hypothalamic-pituitary-adrenal axis in MDD (23).

Lower NGF levels were observed in the hippocampus of suicidal individuals than in healthy controls. In line with this, NGF proved to have antidepressant properties, while acute and chronic stress reduced NGF expression in the mouse, shrew and rat hippocampus, an effect that is reversed by antidepressant treatment. These observations suggest the possibility of a new strategy for the prevention and treatment of MDD consisting in increasing BDNF and NGF levels in the corresponding brain regions (3).

Chiropractic manipulative therapy stimulates the release of various neurotrophins, and some of them, like BDNF and NGF, are essential for the treatment of depression. Non-noxious mechanical stimulation of the skin leads to release of NGF in rats, thereby promoting neuron survival and function. Thoracic spinal manipulative therapy stimulates different responses related to the sympathetic nervous system, the hypothalamic-pituitary axis and the endocrine system. The theory of an association between spinal manual therapy and spinal cord neuroplasticity is being explored and several studies have shown such a connection. Chiropractic therapy works on the nervous system, stimulating it to release various chemicals and hormones that regulate blood pressure and flow, calm the brain and reduce inflammation (24).

Similarly, vagal nerve stimulation may influence cell differentiation and survival through BDNF expression, which is low in most mood disorders like MDD, and antidepressant treatments increase its levels. The efficacy of vagal nerve stimulation might be explained by the hypothesis of an link between monoamines and neuroplasticity mechanisms. As the hippocampus has rich serotonergic and noradrenergic innervation, changes in neurotransmitter concentrations may affect regional plasticity (25). A study by Revesz et al. showed that vagal nerve stimulation enhances cell proliferation in the hippocampus and dentate gyrus regions, whereas acute medication with conventional

antidepressants was not associated with any increase in neurogenesis (26).

The neurotrophic hypothesis of depression states that expression of neurotrophic factors (i.e. BDNF and its receptor, TrkB) in brain circuits linked to mood regulation is inversely proportional to the effects of stress and antidepressants, whereas the neurogenesis hypothesis states that increase in expression of neurotrophins by antidepressant treatment may stop or even reverse the neuronal loss associated with depression (27).

Another study explored the effects of chronic vagal nerve stimulation on hippocampal neurogenesis in a bulbectomized mouse depression model, and showed that vagal nerve stimulation prevented loss of differentiated proliferating cells in the dentate gyrus while sham stimulation showed no such effect (28). Interestingly, chronic treatment (21 days) with conventional antidepressants increased the expression of BDNF and TrkB mRNAs in the hippocampus. The same increase in BDNF and TrkB mRNA expression in the hippocampus and cortex has also been observed after acute (3 hours) vagal nerve stimulation (27). However, it would be ill-conceived to draw conclusions on the basis of changes in BDNF mRNA or protein levels, while ignoring factors like release, proteolytic cleavage and translation (29).

Furthermore, vagal nerve stimulation may influence several brain regions, neurotransmitters and signal transduction mechanisms affected by traditional antidepressant medications. Substantial improvements in MDD can be observed after 3-12 months of vagal nerve stimulation therapy (27,30).

Chiropractic therapy and autonomic nervous system

The parasympathetic nervous system regulates the upper cervical region, so a cervical manipulation or adjustment results in a parasympathetic response (lowering of heart beat, reduction of blood pressure, pupil constriction) (4), whereas manual adjustment of spinal regions with significant sympathetic innervation, i.e. the upper thoracic and lumbar regions, produces a sympathetic response (heart beat stimulation, blood pressure increase, pupil dilation). Many studies have explored chiropractic cranial and vertebral adjustments, and spinal manipulative therapy in relation to autonomic functions (31).

Interestingly, depression seems to be correlated with pain probably because of their common neurological pathways. In fact, 50-65% of patients with chronic pain are also diagnosed with depression. For instance, autonomic dysfunction is linked to tension-type headache (TTH) and depression. Spinal adjustments for TTH stimulate a parasympathetic response and improve TTH and associated mental disorders like depression (18,32). One study recruited TTH patients and tested the benefits of manual adjustment on depression and anxiety. The results confirmed that vertebral manipulative techniques were very effective in improving TTH and depression (33). An interesting case report of a 44 year-old teacher showed long-lasting relief from TTH and MDD after chiropractic manipulative therapy. These effects are a first clue linking chiropractic therapy for pain with treatment for MDD (18).

Parasympathetic vagal nerve stimulation in major depression

The vagal nerve is located in the cervical region between the jugular vein and the carotid artery. About 85% of the cervical vagal nerve consists of unmyelinated, slow-conducting, afferent C fibers with projections to the brain. Stimulation of the vagal nerve is considered a treatment option for severe depressive disorders. It is performed with bipolar electrodes on the vagus nerve in the left cervical region. Since 2005, more than 3000 preclinical and clinical research studies exploring the effects of vagal nerve stimulation in depression and epilepsy have been published (25).

The first studies by Bohning and colleagues into the effects of vagal nerve stimulation on the brain of treatment-resistant depression patients revealed that acute stimulation activates brain regions affected by MDD, like the amygdala, parieto-occipital cortex, bilateral orbitofrontal cortex, left temporal cortex and hypothalamus (34). Further studies revealed significant blood flow changes in many brain regions involved in MDD, like the anterior insular cortex, inferior frontal gyrus, bilateral anterior cingulate cortex, and posterior and frontal orbital cortices, after vagal nerve stimula-

tion. Later studies showed that subacute vagal nerve stimulation decreases regional cerebral blood flow in subcortical and cortical regions like the amygdala and increases regional cerebral blood flow in the left inferior frontal gyrus (35).

A study by Nahas and colleagues linked brain imaging studies and found that acute vagal nerve stimulation initially activates the right medial prefrontal gyrus but after 30 weeks of stimulation this activation switches to deactivation of the right medial prefrontal gyrus, coinciding with improvement in depressive symptoms. A similar activation-deactivation switching pattern was found in the right anterior insular cortex. The authors therefore established a correlation between attenuated depression and activation of the right anterior insular cortex. They also observed a significant correlation between early activation of the right anterior insular cortex and severity of depression (36,37).

Likewise, Conway and colleagues conducted brain imaging studies in patients with treatment-resistant depression undergoing vagal nerve stimulation. After 3-12 months of stimulation, the images showed a response in 9 out of 13 patients, while and 5 out of 13 patients no longer show clinical signs of depression (38).

Animal studies have demonstrated that vagal nerve stimulation increases serotonergic and noradrenergic neurotransmission in brain areas that are critical for mood regulation, like the amygdala, hippocampus and prefrontal cortex (39). Chronic vagal nerve stimulation has also been demonstrated to be involved in neuronal birth, neuroplasticity, migration, survival and synaptogenesis. Both long- and short-term vagal nerve stimulation increases the length of dendrites and hippocampal neuronal complexity (25,40).

Finally, there have also been long-term studies into the effects of vagal nerve stimulation on major depression. Fifty-nine patients followed up for 2 years showed an increase in response rate from 31% at 3 months to 44% at 24 months. The remission rate was about 25% after 2 years. Most patients who responded well after 3 months maintained their good response after 2 years (37,41). In a subsequent larger cohort study with 205 patients, 76.7% maintained their good response from 3 to 24 months. Interestingly, 65% of those who did not respond at 12 months began to respond well to vagal nerve stimulation at 24 months (42). In another study, 91 out of 160 patients received transcutaneous vagal nerve stimulation for 3 months; 69 of them first received 1 month of sham stimulation, then 2 months of transcutaneous vagal nerve stimulation. After 1 month, patients receiving transcutaneous vagal nerve stimulation showed a significant reduction in Hamilton Depression Rating Scale scores as compared to the patients that received sham stimulation. By the end of the first month, 27% patients receiving transcutaneous vagal nerve stimulation were found to be good responders. This improvement in response continued for a further 2 to 3 months (43).

In conclusion, vagal nerve stimulation acts on the same brain regions, signal transduction mechanisms and neurotransmitters as conventional antidepressants, and has similar effects, which however take longer to manifest.

Conclusion

Major depression may depend largely on imbalances in autonomic nervous system activity. All symptoms of depression, such as high cortisol, high adrenalin, insomnia, agitation and anxiety, can be attributed to excessive activity of the sympathetic system. Furthermore, neuroendocrine factors like dopamine, BDNF and NGF have roles in the pathophysiology of MDD. Although not yet definitely confirmed, chiropractic therapy and vagal nerve stimulation may possibly regulate the autonomic nervous system through activation of the parasympathetic nervous system, reduction of sympathetic nervous system activity, and synthesis of neuroendocrine factors. In this review we show evidence that MDD may be a symptom of autonomic imbalance and that chiropractic manipulation, spinal manipulative therapy and vagal nerve stimulation, which elicit sympathetic and parasympathetic responses, may improve autonomic imbalance and the symptoms of MDD.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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