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Noninvasive Vagus Nerve Stimulation in the Treatment of Methamphetamine Use Disorder: A Review Article

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Abstract

Context: Methamphetamine (MA) use and the mortality it causes are increasing worldwide. The neurobiological mechanisms underlying the destructive effects of MA use are complex; however, there is much evidence that MA induces the dysfunction of monoaminergic transmission and causes oxidative stress, neuroinflammation, gliosis, and apoptosis. These toxic effects are associated with cardiotoxicity and neurotoxicity and with an imbalance in the autonomic nervous system, which altogether manifest themselves in clinical symptoms, such as neuropsychiatric disorders and cardiovascular diseases.
Evidence Acquisition: There is no approved treatment for methamphetamine use disorder (MUD) despite all efforts made to date. The behavioral and pharmacological approaches currently used for the treatment of MUD are not completely effective. In this study, it is hypothesized that the stimulation of the vagus nerve and biological pathways underlying the processes of this stimulation might be effective as adjunctive therapy.
Results: Despite the potential effects of vagus nerve stimulation (VNS) to improve MUD, no study has yet examined the clinical potential effects of VNS in patients with the disorder.
Conclusions: Therefore, further studies, including experimental and clinical trials, are needed to examine the effects of VNS on MUD.

Keywords: Cardiotoxicity, Methamphetamine Use Disorder, Neuroinflammation, Neurotoxicity, Vagus Nerve Stimulation

1. Context

The use of amphetamine-type stimulants (i.e., methamphetamine (MA), amphetamine, and methylenedioxy-methamphetamine) is on the rise worldwide. According to the United Nations Office on Drugs and Crime report, there were an estimated 27 million individuals using amphetamine-type stimulants in 2019 (1). Meanwhile, MA is the most widely used in the amphetamine-type stimulants group (2). A pernicious social wonder with far-reaching mental, familial, and economic adversities, which contribute to robbery, murder, suicide, aggression, and divorce, has been attributed to this drug (3).

1.1. Neurobiology, Clinical Symptoms, Diagnosis, and Treatment of Methamphetamine Use Disorder

The MA, due to its lipophilic nature, easily passes the blood-brain barrier, where it stimulates the excessive release of monoamines (i.e., dopamine, norepinephrine, and serotonin) in the monoaminergic nerve terminals. There are several mechanisms that contribute to this release of neurotransmitters, including (a) the redistribution of monoamines from synaptic vesicles to the cytosol; (b) the reversal of monoaminergic transporter function and release of neurotransmitters into the extraneuronal space; and (c) the reduction of metabolism of monoamines by the suppression of monoamine oxidase function. Collectively, elevated neurotransmitters in nerve terminals promote neurotoxicity through the degeneration of monoaminergic terminals, apoptosis, oxidative stress, and neuroinflammation (4-6).

The MA, known as a sympathomimetic agent, acts rigorously on the central and peripheral nervous systems and the cardiovascular system (7, 8). The clinical signs depend on the duration, dose, and route of drug use. In general, the clinical picture of acute MA use is eupho-

ria, decreased need for sleep and food, increased alertness and energy, and overactivation of the sympathetic nervous system, producing a fight-or-flight response (9, 10). In a study of emergency department referrals, seizures, chest pain, tachycardia, palpitations, hypertension, tachypnea, visual hallucinations, auditory hallucinations, paranoia, grandiosity, talkativeness, suicidal ideation, homicidal ideation, violence, and disorientation have been significantly more common in patients who tested positive for MA (11).

The repeated use of MA causes tolerance; therefore, some MA users in order to re-experience the pleasure effect take higher doses; as a result, long-term consumption, along with increasing the dose of the drug, can exacerbate the symptoms. The excessive release of dopamine by MA has destructive effects on nerve endings of dopaminergic neurons in the brain. Neuroimaging studies of chronic MA users have shown a greater number of blood flow defects and ischemic lesions (12) and severe functional and structural changes in brain regions related to memory and mood. The most common symptoms of chronic abuse include mood disturbances, anxiety, depression, hallucinations, paranoid ideas, homicidal ideas, violence, out-of-control rages, psychosis, relapse tendency, and neurocognitive dysfunction (3). The discontinuation of MA is also associated with withdrawal syndromes, such as somnolence, craving, depression, anxiety, suicidal ideation, anhedonia, and cognitive impairment (13-15).

The diagnosis of methamphetamine use disorder (MUD) is characterized by the diagnostic and statistical manual of mental disorders, fifth edition, and includes the escalation of drug use, tolerance, withdrawal, and drug craving in users (16). Currently, there is no Food and Drug Administration (FDA)-approved effective intervention to prolong abstinence and prevent relapse from MA (17). A systematic review surveyed the efficacy of numerous medications for the treatment of MUD, including dopamine agonists, antidepressants, anticonvulsants, antipsychotics, and opioid antagonists. This review showed that none of these medications was successful in treating MUD (18). Other approaches, such as behavioral therapies, have been associated with promising results; however, few studies have examined these interventions, and further studies are needed to clarify the effectiveness of these approaches (19).

The vagus nerve is known as the major part of the autonomic nervous system and involves in the maintenance of homeostasis by the regulation of the neuroendocrine-immune axis and cardiovascular system (20, 21). The disturbance of the balance between the sympathetic and parasympathetic nervous systems and overactivation of the sympathetic and immune systems have been reported in MUD (8, 9). The current study hypothesizes the role of potential neuroprotective mechanisms of noninvasive vagus nerve stimulation (VNS) and the neurobiological pathways underlying the processes in the treatment of MUD.

2. Evidence Acquisition

2.1. Vagus Nerve Stimulation Methods

Currently, invasive vagus nerve stimulation (iVNS) is approved by FDA for the treatment of refractory epilepsy and drug-resistant depression. Transcutaneous vagus nerve stimulation (tVNS) is another technique for vagal electrical stimulation that is known as a noninvasive method and, unlike iVNS, does not require surgery and has better safety and tolerability among users. The tVNS is performed in two ways; one is via the cervical branch of the vagus nerve in the neck, and the other is via the auricular branch of the vagus nerve in the outer ear. The common side effects of tVNS are tingling, redness, itching, and less pain around the site of stimulation (22, 23). The tVNS is used to treat various disorders, such as depression (24), migraines (25), tinnitus (26), chronic pain (27), and epilepsy (28).

3. Results

3.1. Neuroimmune Mechanisms of Vagus Nerve Stimulation in the Control of Inflammatory Response

The MA induces neurotoxicity through the hyperactivation of the neuroimmune system and produces pro-inflammatory cytokines (e.g., interleukin-1 beta, interleukin-6, and tumor necrosis factor α (TNF-α)). Exposure to MA promotes the disruption of blood-brain barrier integrity and infiltration of pro-inflammatory cytokines from microglia and astrocytes, which might lead to neurodegeneration. In addition, excessive monoamines induce oxidative stress and subsequently mitochondrial damage and endoplasmic reticulum stress. The repeated use of MA leads to the depletion of monoamine stores, damage to nerve terminals, and apoptosis. Therefore, these neurotoxic mechanisms might contribute to neuropsychiatric complications and cognitive dysfunction and prolong addictive behavior (29-33).

Recent documents have suggested anti-inflammatory effects for VNS, which might be central and peripheral (34, 35). Neuroimmune and neuroendocrine systems are involved in vagal anti-inflammatory pathways (36). Two pathways are activated by vagal afferent fibers through peripheral inflammatory mediators. These mediators, such as endotoxins and pro-inflammatory cytokines, stimulate vagal afferent fibers and, subsequently, vagal afferents send inflammatory information to the dorsal vagal

complex which consists of the nucleus tractus solitarii (NTS), the area postrema (AP), and the dorsal motor nucleus of the vagus (37, 38). After the dorsal vagal complex receives inflammatory input, two distinct mechanisms are initiated: The hypothalamic-pituitary-adrenal (HPA) axis and the cholinergic anti-inflammatory pathway (CAP). In the HPA axis, vagal inputs activate NTS neurons from the A2 noradrenergic group, which projects to neurons in the hypothalamus that contain corticotropin-releasing factor. These neurons stimulate the release of adreno-corticotrophin hormone by the pituitary gland, a hormone that activates the release of glucocorticoids from the adrenal glands and suppresses peripheral inflammation (36, 39). The HPA axis can also be centrally activated by pro-inflammatory cytokines reaching the AP, a circumventricular organ that lacks a normal blood-brain barrier (40). The second mechanism, known as the CAP, is activated by vagal efferent fibers that project to enteric neurons in the gut and release acetylcholine near macrophages. This neurotransmitter binds to alpha-7 nicotinic acetylcholine receptors located on the membrane of macrophages and suppresses the release of TNF-α (39, 41, 42).

3.2. Role of Vagus Nerve Stimulation in Balancing the Autonomic Nervous System and Regulating Cardiovascular Function

The acute consumption of MA causes a rapid release of central and peripheral monoamine neurotransmitters and a marked increase in sympathetic tone, causing vasoconstriction, hypertension, tachycardia, bronchodilation, and hyperthermia (30). In addition, MA overdose is associated with sudden cardiac death and is the second leading cause of death, especially among young consumers (43). Furthermore, the chronic consumption of MA is associated with vagal tone dysfunction and a decrease in heart rate variability (HRV), cardiovascular tissue damage induced by an inflammatory response, pulmonary hypertension, cardiac arrhythmias, and heart failure due to electrical remodeling of cardiac tissue (44, 45). It has been reported that VNS alters the balance between the activation of sympathetic and parasympathetic nervous systems toward the dominance of parasympathetic tone (46-48). Therefore, it might be an effective approach to various disorders characterized by sympathetic hyperactivity, such as MUD.

Noninvasive VNS has been shown to increase HRV in healthy participants, which is a biomarker for enhancing vagus nerve outflow to the heart and inhibiting sympathetic hyperactivity (49). Numerous studies have shown that iVNS is a novel intervention to improve patients with heart failure. Similar to autonomic system dysfunction in MA users, heart failure is characterized by a decrease in vagal tone and an increase in sympathetic outflow (50-53). Several mechanisms have been described for the clinical benefits of VNS in heart failure, including heart rate reduction, antiarrhythmic effects, and suppression of proinflammatory cytokines (54-56).

3.3. Role of Vagus Nerve Stimulation in Modulating Mood Disturbances

Mood/affective disturbances, such as anxiety and depression, are characteristic withdrawal symptoms during abstinence from the chronic abuse of MA, which might persist for 2 - 5 years after discontinuation of the drug (57, 58). Chronic MA use leads to structural and functional changes in the monoaminergic system in the reward circuit, including the limbic system, striatum, and paralimbic regions, which are associated with anxiety and depressive symptoms (9, 59). Therefore, improving affective withdrawal symptoms might reduce the risk of MA relapse.

Numerous studies have demonstrated the antidepressant and anxiolytic effects of VNS on depressive and anxiety disorders through the modulation of monoaminergic neurotransmitters, alteration of neuronal activity, suppression of neuroinflammatory responses, neurogenesis in the hippocampus, and control of the gut-microbiota-brain axis (60-64). The effect of VNS on the treatment of mood disturbances is partly related to the innervation of afferent fibers to the NTS in the medulla oblongata. These fibers are directly and indirectly further projected to other brain regions, such as the orbitofrontal cortex, thalamus, insula, hypothalamus, amygdala, and reticular formation, responsible for the control of anxiety and depression (61, 62, 65). According to these findings, neuroimaging studies have shown that VNS can improve depressive symptoms by altering the activity of cortical-limbic-thalamic-striatal neural circuits that are disrupted in depression (61, 62, 66-68). Anatomically, the vagus nerve sends direct afferent sensory information to the NTS and from this region to the locus coeruleus (LC) and the dorsal raphe nucleus (DRN). As previously mentioned, the LC and NTS project numerous mood-regulating limbic and cortical brain structures (69). Therefore, VNS can increase the concentration of noradrenaline from noradrenergic neurons in the LC and serotonin from the DRN (60, 70, 71). These events could restore the depletion of monoamines, which are a major cause of depressive and anxiety symptoms in chronic MA users.

The effect of VNS on biogenic amines is consistent with the mechanism of action of antidepressants. The electrophysiological recordings and microdialysis studies of neurons in the DRN and the LC show an increase in neuronal activation and release of serotonin and norepinephrine after acute and chronic VNS therapy (72). An animal study has shown that the lesion of noradrenergic and serotonergic

systems by 6-hydroxydopamine abolishes the antidepressant and anxiolytic-like effects induced by VNS (73).

There are controversial findings regarding the dopaminergic system and its relationship to VNS. Positron emission tomography performed by Conway et al. (66) showed that long-term VNS therapy increases the cerebral metabolic rate of glucose in the ventral tegmental area (VTA), the primary brainstem area of dopamine. This finding is consistent with the findings of a study by Carpenter et al. who demonstrated an increase in homovanillic acid in the cerebrospinal fluid (CSF) of patients with chronic major depression following VNS treatment (60). In contrast to these findings, a preclinical study using electrophysiological recordings has shown a decrease in neuronal firing rate in the VTA after 2 weeks of VNS therapy (71).

The neurogenesis theory in depression describes that stress causes the impairment of neurogenesis in the hippocampus, which can also be restored by antidepressants (74, 75). Preclinical studies have shown that VNS enhanced the proliferation of neural progenitor cells in the dentate gyrus of the hippocampus in an animal model of depression (63, 76). A similar effect was also observed after the chronic administration of fluoxetine (77). Chronic MA consumption is associated with impairments in the proliferation, differentiation, and survival of neural progenitor cells in the dentate gyrus. These impairments contribute to memory impairment, mood disorders, drug seeking-behavior, and drug taking-behavior (78-80). The current study suggests that VNS might reverse the negative effects of MA on hippocampal neurogenesis and reduce relapse during MA abstinence.

The growing evidence elaborated that targeting of gut microbiome ameliorates mood disorders in patients with depression and anxiety (81, 82). The influence of the microbiota on brain function and the modulation of mood and behavior is achieved through the vagus nerve (64). Animal studies have revealed that MA causes gut dysbiosis, which can be associated with anxiety-like behaviors (83, 84). Therefore, the present study hypothesizes that VNS reverses MA-induced gut dysbiosis and improves depression and anxiety in drug users. The microbiota components can activate vagus nerve afferent fibers directly or indirectly through gut endocrine cells. Activated vagus nerve afferent fibers stimulate the central nervous system via the central autonomic network and, in this way, affect psychiatric disorders and other stress-induced and inflammatory diseases. As previously mentioned, vagus nerve afferent fibers stimulate efferent fibers via inflammatory reflex and decrease gut inflammation and intestinal permeability by tight junction reinforcement, restoring dysbiosis. Studies have reported a low vagal tone in inflammatory bowel disease. Therefore, VNS can increase vagal tone and improve homeostasis in the gut-microbiota-brain axis (37, 85).

The concentrations of pro-inflammatory cytokines are increased in the peripheral circulation and the CSF in patients with depression (86). Similarly, the serum levels of pro-inflammatory cytokines are increased in MA abusers (87). Therefore, VNS might have a protective effect on the treatment of depression via the inhibition of pro-inflammatory cytokines.

4. Conclusions

The treatment of MUD by clinicians is difficult because it is associated with repeated relapses after abstinence from drugs. Moreover, intensive MA use is accompanied by physiological deficits, such as cardiovascular pathologies and mood disorders. Some of the disorders might even lead to death. The hypothesis of this study suggests that noninvasive VNS, auricular tVNS, might be effective as a complementary therapy in combination with current treatments in the management of MUD, especially during withdrawal from MA abstinence. Given the broad spectrum of MA adverse effects, there is an urgent need to develop new interventions for the treatment of MUD.

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Footnotes

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References

1. United Nations Office on Drugs and Crime. *Booklet 2 - Global overview of drug demand and drug supply*. 2021. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr-2021_booklet-2.html.
2. Perez-Mana C, Castells X, Torrens M, Capella D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. *Cochrane Database Syst Rev*. 2013;(9). CD009695. [PubMed ID: 23996457]. https://doi.org/10.1002/14651858.CD009695.pub2.

3. Zarghami M. Methamphetamine Has Changed the Profile of Patients Utilizing Psychiatric Emergency Services in Iran. *Iran J Psychiatry Behav Sci*. 2011;**5**(1):1–5.
4. Yang X, Wang Y, Li Q, Zhong Y, Chen L, Du Y, et al. The Main Molecular Mechanisms Underlying Methamphetamine- Induced Neurotoxicity and Implications for Pharmacological Treatment. *Front Mol Neurosci*. 2018;**11**:186. [PubMed ID: 29915529]. [PubMed Central ID: PMC5994595]. https://doi.org/10.3389/fnmol.2018.00186.
5. Chiang M, Lombardi D, Du J, Makrum U, Sitthichai R, Harrington A, et al. Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options. *Hum Psychopharmacol*. 2019;**34**(5). e2710. [PubMed ID: 31441135]. https://doi.org/10.1002/hup.2710.
6. Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug Alcohol Depend*. 2014;**143**:11–21. [PubMed ID: 25176528]. [PubMed Central ID: PMC4164186]. https://doi.org/10.1016/j.drugalcdep.2014.08.003.
7. Yu S, Zhu L, Shen Q, Bai X, Di X. Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. *Behav Neurol*. 2015;**2015**:103969. [PubMed ID: 25861156]. [PubMed Central ID: PMC4377385]. https://doi.org/10.1155/2015/103969.
8. Kaye S, McKetin R, Duflou J, Darke S. Methamphetamine and cardiovascular pathology: a review of the evidence. *Addiction*. 2007;**102**(8):1204–11. [PubMed ID: 17565561]. https://doi.org/10.1111/j.1360-0443.2007.01874.x.
9. Cruickshank CC, Dyer KR. A review of the clinical pharmacology of methamphetamine. *Addiction*. 2009;**104**(7):1085–99. [PubMed ID: 19426289]. https://doi.org/10.1111/j.1360-0443.2009.02564.x.
10. Schep LJ, Slaughter RJ, Beasley DM. The clinical toxicology of metamfetamine. *Clin Toxicol (Phila)*. 2010;**48**(7):675–94. [PubMed ID: 20849327]. https://doi.org/10.3109/15563650.2010.516752.
11. Hadinezhad P, Zarghami M, Montazer H, Moosazadeh M, Ghaderi F. Study of Methamphetamine Use in Patients Referred to Emergency Ward of a General Hospital at North of Iran in 2017. *Addict Health*. 2019;**11**(1):18–25. [PubMed ID: 31308906]. [PubMed Central ID: PMC6612239]. https://doi.org/10.22122/ahj.v11i1.222.
12. Alaee A, Zarghami M, Farnia S, Khademloo M, Khoddad T. Comparison of brain white matter hyperintensities in methamphetamine and methadone dependent patients and healthy controls. *Iran J Radiol*. 2014;**11**(2). e14275. [PubMed ID: 25035700]. [PubMed Central ID: PMC4090641]. https://doi.org/10.5812/iranjradiol.14275.
13. Zorick T, Nestor L, Miotto K, Sugar C, Hellemann G, Scanlon G, et al. Withdrawal symptoms in abstinent methamphetamine-dependent subjects. *Addiction*. 2010;**105**(10):1809–18. [PubMed ID: 20840201]. [PubMed Central ID: PMC3071736]. https://doi.org/10.1111/j.1360-0443.2010.03066.x.
14. McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM. The nature, time course and severity of methamphetamine withdrawal. *Addiction*. 2005;**100**(9):1320–9. [PubMed ID: 16128721]. https://doi.org/10.1111/j.1360-0443.2005.01160.x.
15. Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *J Neuropsychiatry Clin Neurosci*. 2003;**15**(2):215–20. [PubMed ID: 12724464]. https://doi.org/10.1176/jnp.15.2.215.
16. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: American Psychiatric Association; 2013.
17. Paulus MP, Stewart JL. Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder: A Review. *JAMA Psychiatry*. 2020;**77**(9):959–66. [PubMed ID: 32267484]. [PubMed Central ID: PMC8098650]. https://doi.org/10.1001/jamapsychiatry.2020.0246.
18. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018;**191**:309–37. [PubMed ID: 30173086]. https://doi.org/10.1016/j.drugalcdep.2018.06.038.
19. Lee NK, Rawson RA. A systematic review of cognitive and behavioural therapies for methamphetamine dependence. *Drug Alcohol Rev*. 2008;**27**(3):309–17. [PubMed ID: 18368613]. [PubMed Central ID: PMC4445690]. https://doi.org/10.1080/09595230801919494.
20. Howland RH. Vagus Nerve Stimulation. *Curr Behav Neurosci Rep*. 2014;**1**(2):64–73. [PubMed ID: 24834378]. [PubMed Central ID: PMC4017164]. https://doi.org/10.1007/s40473-014-0010-5.
21. Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. *Headache*. 2016;**56**(1):71–8. [PubMed ID: 26364692]. https://doi.org/10.1111/head.12647.
22. Yap JYY, Keatch C, Lambert E, Woods W, Stoddart PR, Kameneva T. Critical Review of Transcutaneous Vagus Nerve Stimulation: Challenges for Translation to Clinical Practice. *Front Neurosci*. 2020;**14**:284. [PubMed ID: 32410932]. [PubMed Central ID: PMC7199464]. https://doi.org/10.3389/fnins.2020.00284.
23. Broncel A, Bocian R, Klos-Wojtczak P, Kulbat-Warycha K, Konopacki J. Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. *Brain Res Bull*. 2020;**155**:37–47. [PubMed ID: 31790720]. https://doi.org/10.1016/j.brainresbull.2019.11.011.
24. Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. *Biol Psychiatry*. 2016;**79**(4):266–73. [PubMed ID: 25963932]. [PubMed Central ID: PMC4838995]. https://doi.org/10.1016/j.biopsych.2015.03.025.
25. Grazzi L, Usai S, Bussone G. Gammacore Device For Treatment Of Migraine Attack: Preliminary Data (I9-2.005). *Neurology*. 2014;**82**(10 Suppl):I9–2.005.
26. Lehtimaki J, Hyvarinen P, Ylikoski M, Bergholm M, Makela JP, Aarnisalo A, et al. Transcutaneous vagus nerve stimulation in tinnitus: a pilot study. *Acta Otolaryngol*. 2013;**133**(4):378–82. [PubMed ID: 23237096]. https://doi.org/10.3109/00016489.2012.750736.
27. Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception–an experimental study. *Brain Stimul*. 2013;**6**(2):202–9. [PubMed ID: 22621941]. https://doi.org/10.1016/j.brs.2012.04.006.
28. Liu A, Rong P, Gong L, Song L, Wang X, Li L, et al. Efficacy and Safety of Treatment with Transcutaneous Vagus Nerve Stimulation in 17 Patients with Refractory Epilepsy Evaluated by Electroencephalogram, Seizure Frequency, and Quality of Life. *Med Sci Monit*. 2018;**24**:8439–48. [PubMed ID: 30467307]. [PubMed Central ID: PMC6266629]. https://doi.org/10.12659/MSM.910689.
29. Loftis JM, Janowsky A. Neuroimmune basis of methamphetamine toxicity. *Int Rev Neurobiol*. 2014;**118**:165–97. [PubMed ID: 25175865]. [PubMed Central ID: PMC4418472]. https://doi.org/10.1016/B978-0-12-801284-0.00007-5.
30. Rusyniak DE. Neurologic manifestations of chronic methamphetamine abuse. *Neurol Clin*. 2011;**29**(3):641–55. [PubMed ID: 21803215]. [PubMed Central ID: PMC3148451]. https://doi.org/10.1016/j.ncl.2011.05.004.
31. Ghazvini H, Tirgar F, Khodamoradi M, Akbarnejad Z, Rafaiee R, Seyedhosseini Tamijani SM, et al. Ovarian hormones prevent methamphetamine-induced anxiety-related behaviors and neuronal damage in ovariectomized rats. *Neurosci Lett*. 2021;**746**:135652. [PubMed ID: 33482310]. https://doi.org/10.1016/j.neulet.2021.135652.
32. Seyedhosseini Tamijani SM, Beirami E, Ahmadiani A, Dargahi L. Thyroid hormone treatment alleviates the impairments of neurogenesis, mitochondrial biogenesis and memory performance induced by methamphetamine. *Neurotoxicology*. 2019;**74**:7–18. [PubMed ID: 31075280]. https://doi.org/10.1016/j.neuro.2019.05.003.
33. Beirami E, Oryan S, Seyedhosseini Tamijani SM, Ahmadiani A, Dargahi L. Intranasal insulin treatment alleviates methamphetamine induced anxiety-like behavior and neuroinflammation. *Neurosci Lett*. 2017;**660**:122–9. [PubMed ID: 28917981]. https://doi.org/10.1016/j.neulet.2017.09.026.
34. Kwan H, Garzoni L, Liu HL, Cao M, Desrochers A, Fecteau G, et al. Va-

gus Nerve Stimulation for Treatment of Inflammation: Systematic Review of Animal Models and Clinical Studies. *Bioelectron Med*. 2016;**3**:1–6. [PubMed ID: 29308423]. [PubMed Central ID: PMC5756070].
35. Payne SC, Furness JB, Burns O, Sedo A, Hyakumura T, Shepherd RK, et al. Anti-inflammatory Effects of Abdominal Vagus Nerve Stimulation on Experimental Intestinal Inflammation. *Front Neurosci*. 2019;**13**:418. [PubMed ID: 31133776]. [PubMed Central ID: PMC6517481]. https://doi.org/10.3389/fnins.2019.00418.
36. Bonaz B, Sinniger V, Pellissier S. The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract. *Front Immunol*. 2017;**8**:1452. [PubMed ID: 29163522]. [PubMed Central ID: PMC5673632]. https://doi.org/10.3389/fimmu.2017.01452.
37. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders. *Front Psychiatry*. 2018;**9**:44. [PubMed ID: 29593576]. [PubMed Central ID: PMC5859128]. https://doi.org/10.3389/fpsyt.2018.00044.
38. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;**405**(6785):458–62. [PubMed ID: 10839541]. https://doi.org/10.1038/35013070.
39. Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. *J Physiol*. 2016;**594**(20):5781–90. [PubMed ID: 27059884]. [PubMed Central ID: PMC5063949]. https://doi.org/10.1113/JP271539.
40. Buller KM. Circumventricular Organs: Gateways to the Brain Role Of Circumventricular Organs In Pro-Inflammatory Cytokine-Induced Activation Of The Hypothalamic– Pituitary–Adrenal Axis. *Clin Exp Pharmacol Physiol*. 2001;**28**(7):581–9. https://doi.org/10.1046/j.1440-1681.2001.03490.x.
41. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med*. 2003;**9**(5-8):125–34. [PubMed ID: 14571320]. [PubMed Central ID: PMC1430829].
42. Tracey KJ. The inflammatory reflex. *Nature*. 2002;**420**(6917):853–9. [PubMed ID: 12490958]. https://doi.org/10.1038/nature01321.
43. Darke S, Duflou J, Kaye S. Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study. *Drug Alcohol Depend*. 2017;**179**:174–9. [PubMed ID: 28787694]. https://doi.org/10.1016/j.drugalcdep.2017.07.001.
44. Henry BL, Minassian A, Perry W. Effect of methamphetamine dependence on heart rate variability. *Addict Biol*. 2012;**17**(3):648–58. [PubMed ID: 21182570]. [PubMed Central ID: PMC3117088]. https://doi.org/10.1111/j.1369-1600.2010.00270.x.
45. Kevil CG, Goeders NE, Woolard MD, Bhuiyan MS, Dominic P, Kolluru GK, et al. Methamphetamine Use and Cardiovascular Disease: In Search of Answers. *Arterioscler Thromb Vasc Biol*. 2019;**39**(9):1739–46. [PubMed ID: 31433698]. [PubMed Central ID: PMC6709697]. https://doi.org/10.1161/ATVBAHA.119.312461.
46. Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex–linking immunity and metabolism. *Nat Rev Endocrinol*. 2012;**8**(12):743–54. [PubMed ID: 23169440]. [PubMed Central ID: PMC4082307]. https://doi.org/10.1038/nrendo.2012.189.
47. Kampusch S, Kaniusas E, Szeles JC. Modulation of Muscle Tone and Sympathovagal Balance in Cervical Dystonia Using Percutaneous Stimulation of the Auricular Vagus Nerve. *Artif Organs*. 2015;**39**(10):E202–12. [PubMed ID: 26450637]. https://doi.org/10.1111/aor.12621.
48. Deuchars SA, Lall VK, Clancy J, Mahadi M, Murray A, Peers L, et al. Mechanisms underpinning sympathetic nervous activity and its modulation using transcutaneous vagus nerve stimulation. *Exp Physiol*. 2018;**103**(3):326–31. [PubMed ID: 29205954]. [PubMed Central ID: PMC5887928]. https://doi.org/10.1113/EP086433.
49. Clancy JA, Mary DA, Witte KK, Greenwood JP, Deuchars SA, Deuchars J. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul*. 2014;**7**(6):871–7. [PubMed ID: 25164906]. https://doi.org/10.1016/j.brs.2014.07.031.
50. Klein HU, Ferrari GM. Vagus nerve stimulation: A new approach to reduce heart failure. *Cardiol J*. 2010;**17**(6):638–44. [PubMed ID: 21154273].
51. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J*. 2011;**32**(7):847–55. [PubMed ID: 21030409]. https://doi.org/10.1093/eurheartj/ehq391.
52. Nearing BD, Anand IS, Libbus I, Dicarlo LA, Kenknight BH, Verrier RL. Vagus Nerve Stimulation Provides Multiyear Improvements in Autonomic Function and Cardiac Electrical Stability in the ANTHEM-HF Study. *J Card Fail*. 2021;**27**(2):208–16. [PubMed ID: 33049374]. https://doi.org/10.1016/j.cardfail.2020.10.003.
53. Nearing BD, Libbus I, Carlson GM, Amurthur B, KenKnight BH, Verrier RL. Chronic vagus nerve stimulation is associated with multi-year improvement in intrinsic heart rate recovery and left ventricular ejection fraction in ANTHEM-HF. *Clin Auton Res*. 2021;**31**(3):453–62. [PubMed ID: 33590355]. [PubMed Central ID: PMC8184538]. https://doi.org/10.1007/s10286-021-00780-y.
54. Kuschyk J, Borggrefe M. [Vagus stimulation. Mechanisms and current clinical importance in heart failure]. *Herzschrittmacherther Elektrophysiol*. 2011;**22**(1):21–6. German. [PubMed ID: 21365469]. https://doi.org/10.1007/s00399-011-0119-0.
55. Subramanian M, Edwards L, Melton A, Branen L, Herron A, Sivasubramanian MK, et al. Non-invasive vagus nerve stimulation attenuates proinflammatory cytokines and augments antioxidant levels in the brainstem and forebrain regions of Dahl salt sensitive rats. *Sci Rep*. 2020;**10**(1):17576. [PubMed ID: 33067477]. [PubMed Central ID: PMC7567801]. https://doi.org/10.1038/s41598-020-74257-9.
56. De Ferrari GM, Schwartz PJ. Vagus nerve stimulation: from preclinical to clinical application: challenges and future directions. *Heart Fail Rev*. 2011;**16**(2):195–203. [PubMed ID: 21165697]. https://doi.org/10.1007/s10741-010-9216-0.
57. Rawson RA, Huber A, Brethen P, Obert J, Gulati V, Shoptaw S, et al. Status of methamphetamine users 2-5 years after outpatient treatment. *J Addict Dis*. 2002;**21**(1):107–19. [PubMed ID: 11831496]. https://doi.org/10.1300/j069v21n01_09.
58. Zweben JE, Cohen JB, Christian D, Galloway GP, Salinardi M, Parent D, et al. Psychiatric symptoms in methamphetamine users. *Am J Addict*. 2004;**13**(2):181–90. [PubMed ID: 15204668]. https://doi.org/10.1080/10550490490436055.
59. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;**3**(8):760–73. [PubMed ID: 27475769]. [PubMed Central ID: PMC6135092]. https://doi.org/10.1016/S2215-0366(16)00104-8.
60. Carpenter LL, Moreno FA, Kling MA, Anderson GM, Regenold WT, Labiner DM, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biol Psychiatry*. 2004;**56**(6):418–26. [PubMed ID: 15364040]. https://doi.org/10.1016/j.biopsych.2004.06.025.
61. Conway CR, Sheline YI, Chibnall JT, Bucholz RD, Price JL, Gangwani S, et al. Brain blood-flow change with acute vagus nerve stimulation in treatment-refractory major depressive disorder. *Brain Stimul*. 2012;**5**(2):163–71. [PubMed ID: 22037127]. [PubMed Central ID: PMC3270206]. https://doi.org/10.1016/j.brs.2011.03.001.
62. Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher JW, Mintun MA. Cerebral blood flow changes during vagus nerve stimulation for depression. *Psychiatry Res*. 2006;**146**(2):179–84. [PubMed ID: 16510266]. https://doi.org/10.1016/j.pscychresns.2005.12.007.
63. Gebhardt N, Bar KJ, Boettger MK, Grecksch G, Keilhoff G, Reichart R, et al. Vagus nerve stimulation ameliorated deficits in one-way active avoidance learning and stimulated hippocampal neurogenesis in bulbectomized rats. *Brain Stimul*. 2013;**6**(1):78–83. [PubMed ID: 22405742]. https://doi.org/10.1016/j.brs.2012.01.009.
64. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour.

Nat Rev Neurosci. 2012;**13**(10):701–12. [PubMed ID: 22968153]. https://doi.org/10.1038/nrn3346.
65. Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. *J Psychiatr Res*. 2002;**36**(4):219–27. [PubMed ID: 12191626]. https://doi.org/10.1016/s0022-3956(02)00013-4.
66. Conway CR, Chibnall JT, Gebara MA, Price JL, Snyder AZ, Mintun MA, et al. Association of cerebral metabolic activity changes with vagus nerve stimulation antidepressant response in treatment-resistant depression. *Brain Stimul*. 2013;**6**(5):788–97. [PubMed ID: 23485649]. [PubMed Central ID: PMC3954813]. https://doi.org/10.1016/j.brs.2012.11.006.
67. Kosel M, Brockmann H, Frick C, Zobel A, Schlaepfer TE. Chronic vagus nerve stimulation for treatment-resistant depression increases regional cerebral blood flow in the dorsolateral prefrontal cortex. *Psychiatry Res*. 2011;**191**(3):153–9. [PubMed ID: 21306877]. https://doi.org/10.1016/j.pscychresns.2010.11.004.
68. Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. *Trends Cogn Sci*. 2012;**16**(1):61–71. [PubMed ID: 22197477]. https://doi.org/10.1016/j.tics.2011.12.011.
69. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci*. 2000;**85**(1-3):1–17. [PubMed ID: 11189015]. https://doi.org/10.1016/S1566-0702(00)00215-0.
70. Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *J Pharmacol Exp Ther*. 2006;**318**(2):890–8. [PubMed ID: 16690723]. https://doi.org/10.1124/jpet.106.104166.
71. Manta S, El Mansari M, Debonnel G, Blier P. Electrophysiological and neurochemical effects of long-term vagus nerve stimulation on the rat monoaminergic systems. *Int J Neuropsychopharmacol*. 2013;**16**(2):459–70. [PubMed ID: 22717062]. https://doi.org/10.1017/S1461145712000387.
72. Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. *J Psychiatry Neurosci*. 2009;**34**(4):272–80. [PubMed ID: 19568478]. [PubMed Central ID: PMC2702444].
73. Furmaga H, Shah A, Frazer A. Serotonergic and noradrenergic pathways are required for the anxiolytic-like and antidepressant-like behavioral effects of repeated vagal nerve stimulation in rats. *Biol Psychiatry*. 2011;**70**(10):937–45. [PubMed ID: 21907323]. https://doi.org/10.1016/j.biopsych.2011.07.020.
74. Miller BR, Hen R. The current state of the neurogenic theory of depression and anxiety. *Curr Opin Neurobiol*. 2015;**30**:51–8. [PubMed ID: 25240202]. [PubMed Central ID: PMC4293252]. https://doi.org/10.1016/j.conb.2014.08.012.
75. Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology*. 2001;**25**(6):836–44. [PubMed ID: 11750177]. https://doi.org/10.1016/S0893-133X(01)00358-X.
76. Yuan TF, Li A, Sun X, Arias-Carrion O, Machado S. Vagus nerve stimulation in treating depression: A tale of two stories. *Curr Mol Med*. 2016;**16**(1):33–9. [PubMed ID: 26695696]. https://doi.org/10.2174/1566524016666151222143609.
77. Wang JW, David DJ, Monckton JE, Battaglia F, Hen R. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. *J Neurosci*. 2008;**28**(6):1374–84. [PubMed ID: 18256257]. [PubMed Central ID: PMC6671574]. https://doi.org/10.1523/JNEUROSCI.3632-07.2008.
78. Takashima Y, Mandyam CD. The role of hippocampal adult neurogenesis in methamphetamine addiction. *Brain Plast*. 2018;**3**(2):157–68. [PubMed ID: 30151340]. [PubMed Central ID: PMC6091036]. https://doi.org/10.3233/BPL-170058.
79. Singhakumar R, Boontem P, Ekthuwapranee K, Sotthibundhu A, Mukda S, Chetsawang B, et al. Melatonin attenuates methamphetamine-induced inhibition of neurogenesis in the adult mouse hippocampus: An in vivo study. *Neurosci Lett*. 2015;**606**:209–14. [PubMed ID: 26366944]. https://doi.org/10.1016/j.neulet.2015.09.011.
80. Mandyam CD, Wee S, Crawford EF, Eisch AJ, Richardson HN, Koob GF. Varied access to intravenous methamphetamine self-administration differentially alters adult hippocampal neurogenesis. *Biol Psychiatry*. 2008;**64**(11):958–65. [PubMed ID: 18490002]. [PubMed Central ID: PMC2587157]. https://doi.org/10.1016/j.biopsych.2008.04.010.
81. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*. 2013;**6**(1):39–51. [PubMed ID: 23320049]. [PubMed Central ID: PMC3539293]. https://doi.org/10.1177/1756283X12459294.
82. Sanchez B, Delgado S, Blanco-Miguez A, Lourenco A, Gueimonde M, Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. *Mol Nutr Food Res*. 2017;**61**(1):1600240. [PubMed ID: 27500859]. https://doi.org/10.1002/mnfr.201600240.
83. Forouzan S, Hoffman KL, Kosten TA. Methamphetamine exposure and its cessation alter gut microbiota and induce depressive-like behavioral effects on rats. *Psychopharmacology (Berl)*. 2021;**238**(1):281–92. [PubMed ID: 33097978]. https://doi.org/10.1007/s00213-020-05681-y.
84. Ning T, Gong X, Xie L, Ma B. Gut Microbiota Analysis in Rats with Methamphetamine-Induced Conditioned Place Preference. *Front Microbiol*. 2017;**8**:1620. [PubMed ID: 28890714]. [PubMed Central ID: PMC5575146]. https://doi.org/10.3389/fmicb.2017.01620.
85. Bonaz B, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front Neurosci*. 2018;**12**:49. [PubMed ID: 29467611]. [PubMed Central ID: PMC5808284]. https://doi.org/10.3389/fnins.2018.00049.
86. Suarez EC, Krishnan RR, Lewis JG. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. *Psychosom Med*. 2003;**65**(3):362–8. [PubMed ID: 12764208]. https://doi.org/10.1097/01.psy.0000035719.79068.2b.
87. Yang X, Zhao H, Liu X, Xie Q, Zhou X, Deng Q, et al. The Relationship Between Serum Cytokine Levels and the Degree of Psychosis and Cognitive Impairment in Patients With Methamphetamine-Associated Psychosis in Chinese Patients. *Front Psychiatry*. 2020;**11**:594766. [PubMed ID: 33362607]. [PubMed Central ID: PMC7759545]. https://doi.org/10.3389/fpsyt.2020.594766.