## THE GLANDULAR CORNER: HYPOTHALAMUS

Linda Isaacs, MD, Discusses Hypothalamus Glandular Therapy, Including a Review of The Physiology of the Hypothalamus and Current Clinical Applications of Its Glandular

The hypothalamus makes up only 4 g of the 1,400 g of the adult human brain.<sup>1</sup> Despite its tiny size, it coordinates a remarkable number of physiologic activities: energy metabolism and expenditure, appetite and digestion, temperature control, fluid and electrolyte balance, sleep-wake cycles, and the various functions of the autonomic nervous system. It has two-way connecting pathways with all parts of the limbic system, the neuronal circuitry in the brain that controls emotional behavior and motivational drive.<sup>2</sup>

In addition to its interactions with the nervous system via the limbic pathways and the autonomic nervous system, the hypothalamus manages the endocrine response to stress via the hypothalamic-pituitary-adrenal-thyroid axis. The hypothalamus secretes hormones such as thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH), which then cause the pituitary to release thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH). These in turn cause the release of thyroxine from the thyroid, or cortisol from the adrenals.

As is common with the endocrine system, the functions of the hypothalamus were determined by study of humans whose hypothalamuses had been damaged by tumors or trauma, and by surgical procedures in animals. A 1940 book, The Hypothalamus and Central Levels of Autonomic Function, describes numerous cases of patients with hypothalamic tumors whose personalities had changed, or of intraoperative trauma to the base of the skull resulting in "outbursts of emotional activity and expression."<sup>3</sup> Other investigators found that when the hypothalamus of an animal was destroyed, "full expression of the patterns of emotional behavior did not occur."<sup>3</sup>

Given the hypothalamus' interactions with the limbic system; the autonomic nervous system; and the pituitary, adrenals, and thyroid, it is not surprising that the hypothalamus is believed to be involved when patients suffer from depression or anxiety.<sup>4</sup> For more than 20 years, I have been recommending the use of oral hypothalamus glandular products to patients with these conditions. In addition to finding the glandular beneficial in and of itself, patients tell me that adding it has led to other modalities, such as meditation or psychotherapy, becoming more effective. Taken at dinner or bedtime, hypothalamus glandular products can be helpful for occasional sleeplessness.

In my experience, most patients eventually no longer need the glandular, and it can cause headaches if taken when not needed.

How might it work? One possibility is oral tolerance: the damping down of autoimmunity by the ingestion of similar materials.<sup>5</sup> In a 2021 article, patients with chronic fatigue were tested for anti-hypothalamus antibodies.<sup>6</sup> The antibodies were found in 33% of the patients, and those with higher titers had more severe symptoms than those without such autoantibodies. Those with higher titers of antibodies also had depressed levels of ACTH and cortisol. My clinical experience is that hypothalamus and adrenal glandulars are helpful for patients with chronic fatigue.

Hypothalamus glandular products are typically from a bovine source, since tissue collection would not be feasible from smaller animals. Because nervous tissue raw materials could contain the prions that cause bovine spongiform encephalopathy (BSE), it is critically important to use high-quality materials. Australia and New Zealand have had strict restrictions on the importation of animals and animal products for many years, including prior to the discovery of BSE.<sup>7</sup> There have been no cases of BSE in Australia or New Zealand, and their governments are vigilant in the defense of their meat industries.<sup>8</sup>

Another theoretical concern is that TRH from oral hypothalamus product could produce hyperthyroidism. In a study of oral absorption of a synthetic TRH, 40 mg produced a measurable increase in TSH and triiodothyronine (T3), but no symptoms associated with hyperthyroidism.<sup>9</sup> The concentration of TRH in hypothalamic tissue is extremely small, around 126 pg/ mg.<sup>10</sup> The amount of TRH in a capsule of hypothalamus glandular product is orders of magnitude less than what would be needed to produce hyperthyroidism.

Overall, I have found hypothalamus glandular products to be invaluable in my practice—they are well tolerated, and especially helpful for my patients needing support around chronic fatigue and mood concerns.

SEE P. 19 FOR REFERENCES

The hypothalamus makes up only 4 g of the 1,400 g of the adult human brain. Despite its tiny size, it coordinates a remarkable number of physiologic activities.

- Murbach TS, et al. A toxicological evaluation of a fulvic and humic acids preparation. Toxicol Rep. 2020 Sep 14;7:1242-54.
- 9. Kell DB, et al. The biology of lactoferrin, an iron-binding protein that can help defend against viruses and bacteria. Front Immunol. 2020 May 28;11:1221.
- Ali AS, et al. Lactoferrin reduces the risk of respiratory tract infections: a meta-analysis of randomized controlled trials. Clin Nutr ESPEN. 2021 Oct;45:26-32.
- Hussein OM. Efficacy of lactoferrin as adjunct therapy for pneumonia in children and adolescents. ClinicalTrials.gov Identifier: NCT05431023.
- 12. Santus P, et al. Oxidative stress and respiratory system: pharmacological and clinical reappraisal of N-acetylcysteine. COPD. 2014 Dec;11(6):705-17.
- Kalyuzhin OV. Effect of N-acetylcysteine on mucosal immunity of respiratory tract. Ter Arkh. 2018 Apr 19;90(3):89-95.
- Aldini G, et al. N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why. Free Radic Res. 2018 Jul;52(7):751-62.
- Zhang Q, et al. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia. Medicine (Baltimore). 2018 Nov;97(45):e13087.
- Sharafkhah M, et al. Safety and efficacy of N-acetyl-cysteine for prophylaxis of ventilator-associated pneumonia: a randomized, double blind, placebo-controlled clinical trial. Med Gas Res. 2018 Apr 18;8(1):19-23.
- Chen Y, et al. Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages. Mediators Inflamm. 2014;2014:426740.
- Hunt C, et al. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. Int J Vitam Nutr Res. 1994;64(3):212-19.

## References from p. 13, Soothing a Post-Infectious Cough"

- 1. Chung KF, et al. Semantics and types of cough. Pulm Pharmacol Ther. 2009 Apr;22(2):139-42.
- Irwin RS, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):1S-23S.
- 3. Kwon NH, et al. Causes and clinical features of subacute cough. Chest. 2006 May;129(5):1142-7.
- Braman SS. Postinfectious cough: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):138S-46S.
- 5. Welsh EJ, et al. Caffeine for asthma. Cochrane Database Syst Rev. 2010;(1):CD001112.
- Paul IM, et al. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007 Dec;161(12):1140-6.
- Raeessi MA, et al. Honey with coffee: a new finding in the treatment of persistent postinfectious cough. Iran J Oto Rhino Laryng. 2011;23(2):1-8.
- Raeessi MA, et al. Honey plus coffee versus systemic steroid in the treatment of persistent post-infectious cough: a randomised controlled trial. Prim Care Respir J. 2013 Sep;22(3):325-30.
- 9. Nosáľová G, et al. Antitussive arabinogalactan of Andrographis paniculata demonstrates synergistic effect with andrographolide. Int J Biol Macromol. 2014 Aug;69:151-7.
- Hu XY, et al. Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: a systematic review and meta-analysis. PLoS One. Aug 2017;12(8):e0181780.

## References from p. 16, "The Glandular Corner: Hypothalamus"

- 1. Saper CB, Lowell BB. The hypothalamus. Curr Biol. 2014;24(23):R1111-R1116.
- Hall JE, Hall ME. The Limbic System and the Hypothalamus Behavioral and Motivational Mechanisms of the Brain. Guyton and Hall Textbook of Medical Physiology. 14th ed. Philadelphia, PA: Elsevier; 2021.
- Brooks CM. The history of thought concerning the hypothalamus and its functions. Brain Res Bull. 1988;20(6):657-67.
- Bao AM, et al. The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev. 2008;57(2):531-53.
- Rezende RM, et al. Mucosal tolerance therapy in humans: Past and future. Clin Exp Neuroimmunol. 2019;10(S1):20-31.
- De Bellis A, et al. Hypothalamic-pituitary autoimmunity and related impairment of hormone secretions in Chronic Fatigue Syndrome. J Clin Endocrinol Metab. 2021;106(12):e5147-e5155.

- Bakaev VV, Duntau AP. Ascorbic acid in blood serum of patients with pulmonary tuberculosis and pneumonia. Int J Tuberc Lung Dis. 2004 Feb;8(2):263-6.
- Zhou YF, et al. The association between vitamin D deficiency and community-acquired pneumonia. Medicine (Baltimore). 2019 Sep;98(38):e17252.
- Remmelts HHF, et al. Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. Clin Infect Dis. 2012 Dec;55(11):1488-94.
- Holter JC, et al. Vitamin D status and long-term mortality in community-acquired pneumonia: secondary data analysis from a prospective cohort. PLoS One. 2016;11(7):e0158536.
- Yang C, et al. Efficacy of high-dose vitamin D supplementation as an adjuvant treatment on pneumonia: systematic review and a meta-analysis of randomized controlled studies. Nutr Clin Pract. 2021 Apr;36(2):368-84.
- 24. Bhat MH, et al. Zinc levels in community acquired pneumonia in hospitalized patients; a case control study. Egypt J Chest Dis Tuberc. 2016;65(2);485-89.
- Saleh P, et al. Relationship between plasma levels of zinc and clinical course of pneumonia. Tanaffos. 2017;16(1):40-5.
- 26. Kiabi FH, et al. Zinc supplementation in adult mechanically ventilated trauma patients is associated with decreased occurrence of ventilator-associated pneumonia: a secondary analysis of a prospective, observational study. Indian J Crit Care Med. 2017;21(1):34-9.
- Wang L, Song Y. Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: a meta-analysis of randomized, double-blind and placebo-controlled trials. Clin Respir J. 2018;12(3):857-64.
- Mamber SW, McMichael J. Microdose DNA for the treatment of acute and chronic respiratory diseases and otitis media. JANA. 2006;9(1):13-22.
- Sieben A, et al. Alpha-hederin, but not hederacoside C and hederagenin from Hedera helix, affects the binding behavior, dynamics, and regulation of beta 2-adrenergic receptors. Biochemistry. 2009;48:3477-82.
- Wolf A, et al. Pre-treatment with α-hederin increases β-adrenoceptor mediated relaxation of airway smooth muscle. Phytomedicine. 2011;18(2-3):214-8.
- 14. Greunke C, et al. A systematic study on the influence of the main ingredients of an ivy leaves dry extract on the  $\beta$ 2-adrenergic responsiveness of human airway smooth muscle cells. Pulm Pharmacol Ther. 2015;31:92-8.
- 15. Schaefer A, et al. A randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a liquid containing ivy leaves dry extract (EA 575 ®) vs. placebo in the treatment of adults with acute cough. Pharmazie. 2016 Sep 1;71(9):504-9.
- Kemmerich B, et al. Efficacy and tolerability of a fluid extract combination of thyme herb and ivy leaves and matched placebo in adults suffering from acute bronchitis with productive cough. A prospective, double-blind, placebo-controlled clinical trial. Arzneimittelforschung. 2006;56(9):652-60.
- Kardos P, et al. Effectiveness and tolerability of the thyme/ivy herbal fluid extract BNO 1200 for the treatment of acute cough: an observational pharmacy-based study. Curr Med Res Opin. 2021 Oct;37(10):1837-44.
- Maxwell J. A history of livestock quarantine in Australia. Anim Husb Dairy Vet Sci. 2018;2(2):1-4.
- Agriculture Victoria. Bovine spongiform encephalopathy (Mad Cow Disease) [Internet]. Victoria, Australia: Victoria State Government; 2022 [cited 30 May 2022]. Available from: https://agriculture.vic.gov.au/biosecurity/animal-diseases/beef-and-dairy-cattle/bovinespongiform-encephalopathy-mad-cow-disease
- Vogt P, et al. Thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) response to intravenous and oral stimulation with synthetic thyrotropin-releasing hormone (TRH) in young healthy adults. Klin Wochenschr. 1978;56(1):31-5.
- Fuse Y, et al. Distribution of thyrotropin-releasing hormone (TRH) and precursor peptide (TRH-Gly) in adult rat tissues. Endocrinol. 1990;127(5):2501-5.