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COMMENTARY

Nesfatin-1 could be a strong candidate obesity or diabetes medication, if blood pressure elevation can be controlled

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Nesfatin-1 is a metabolic polypeptide encoded in the N-terminal region of the protein precursor Nucleobindin 2 (NUCB2). Nesfatin-1 was discovered in 2006 by Dr Shimizu *et al.*, who is one of the authors of this investigation of the effects of peripheral nesfatin-1 administration on body weight and blood pressure in mice.[1] It is a naturally occurring protein produced by the brain.[2] There is growing evidence that nesfatin-1 may have an important role in the regulation of food intake (appetite), the production of body fat and glucose homeostasis.[3] Excess intracerebroventricular (ICV) nesfatin-1 administration leads to loss of appetite, a dose-dependent reduction of food consumption, less frequent hunger, a 'sense of fullness' and decreases in body fat and weight.[4] By contrast, a lack of nesfatin-1 in the brain leads to an increase of appetite, more frequent episodes of hunger, increases in body fat and weight, and the inability to 'feel full.'[4] This last condition can be artificially induced by injecting an anti-nesfatin-1 antibody into the brain. Therefore, several investigators have suggested possible treatment with nesfatin-1 for obesity-related diseases, such as metabolic syndrome and type 2 diabetes.

Nesfatin-1, originally identified as a hypothalamic neuropeptide, is also expressed in other areas of the brain and in the pancreatic islets of Langerhans, gastric endocrine cells and adipocytes. Nesfatin-1 can cross the blood–brain barrier without reaching saturation. An investigation by Unniappan and co-workers[5] showed that the nesfatin-1-induced inhibition of appetite may be mediated by the inhibition of anorexigenic neurons and stimulation of insulin secretion from pancreatic beta cells.[6] Riva *et al.*[7] has reported that nesfatin-1 is a novel glucagon-stimulatory peptide expressed in beta cells and that its expression is decreased in the islets of type 2 diabetes patients.

Both the peripheral (subcutaneous injection, intraperitoneal injection) and central (ICV) administration of nesfatin-1 suppressed food intake significantly but similarly. ICV nesfatin-1 administration has been shown to activate sympathetic nervous activity throughout the body,[8] indicating that the decrease in body fat following nesfatin-1 administration might be due to sympathetic activation. Heart rate (HR) or blood pressure (BP) might be elevated, but there are few published data on BP and HR during nesfatin-1 administration. Recently, Osaki and Shimizu[1] observed that the peripheral administration of nesfatin-1 increased BP without increasing HR. Pretreatment with propranolol (a β-blocker) abolished the BP elevation induced by peripheral nesfatin-1 administration, and HR was not affected (remained stable). However, pretreatment with phentolamine (an α-blocker) did not affect the BP elevation or HR. These findings suggest that the BP elevation caused by peripheral nesfatin-1 administration may occur through β-adrenergic receptors but not α-adrenergic receptors. The central administration of nesfatin-1 also resulted in BP elevation but no elevation in HR, similar to its peripheral administration. Importantly, both the peripheral and central administration of nesfatin-1 induces BP elevation, but neither affects HR. The BP elevation induced by central nesfatin-1 administration was abolished by pretreatment with phentolamine but not by propranolol, indicating that the central administration of nesfatin-1 activates sympathetic nervous activity in the brain, resulting in an increase in BP via α-adrenergic receptors.

Central and peripheral nesfatin-1 administration induces BP elevation through different adrenergic receptors (α- and β-adrenergic receptors, respectively). Shimizu *et al.* speculated that the mechanism of BP elevation through β-adrenergic activation results from a combination of cardiac and intra-renal β-adrenergic activation, and that peripheral administration of nesfatin-1 increased mean BP without increasing HR in mice indicates a direct action of nesfatin-1 on vascular smooth muscle.[1] However, a hypothalamic (brain) mechanism may not have a primary role in the regulation of systemic BP levels.[1]

Taken together, BP elevations induced by either the central or peripheral administration of nesfatin-1 may be controllable by α- or β-blockers. If the BP elevation can be controlled, nesfatin-1 will be a strong candidate medication for weight control or obesity-related diseases, similar to leptin, which was also recently investigated. In addition, the peripheral administration of nesfatin-1 is more practical for treating human diseases than its central administration.

Leptin, discovered in 1994, is an adipocyte-derived hormone that functions as an afferent signal that promotes the constancy of adipose tissue mass by regulating neuroendocrine and metabolic responses to alterations

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in the nutritional state. Hyperleptinemia (leptin resistance) in obese subjects reflects both increased adipose tissue mass and impairment of the anorectic effects of leptin to modulate appetite and energy expenditure, known as 'leptin resistance.' Leptin has an important role in obesity, hypertension and diabetes through either the central nervous system or the peripheral sympathetic nervous system, similar to nesfatin-1. These effects of leptin on sympathetic nervous system activity might lead to investigations showing that leptin administration has favorable effects as a therapy in leptin-resistant subjects, such as obese or diabetic subjects or those in a leptin-resistant state. Therefore, leptin analogs and leptin receptor blockers given in specific circumstances could optimize the beneficial actions of the hormone and minimize its deleterious effects. This is very similar to nesfatin-1. In the past decade, recombinant human leptin administration (pegylated polyethylene glycol recombinant human leptin, PEG-leptin; recombinant methionyl human leptin, r-metHuLeptin) has been developed as a potential obesity therapy to control resistant and morbid obesity. However, several investigators have reported that treatment with PEG-leptin protein modifies the subjective appetite at the given dosage, but induces no changes in body composition, energy expenditure or body mass loss relative to placebo treatment. Weekly injection of 60 mg of PEG-leptin in association with a low-calorie diet did not lead to additional weight loss after 8 weeks of treatment and did not alter the metabolic profile. No significant differences in the absolute or percent weight loss, percent body fat, sleeping metabolic rate or respiratory quotient were observed between the PEG-leptin and placebo groups, except for significant reductions in triglyceride levels in the PEG-leptin group. However, weight maintenance after PEG-leptin administration was primarily supported by dietary restraint, which was more effective in the placebo-treated group, resulting in a slower regain of body weight. These findings might be explained by the blunted sympathetic nervous sensitivity to leptin following physiological feeding (oral glucose loading) in obese individuals reported by Masuo *et al.*[9] Collectively, these studies have shown that treatment with PEG-leptin modifies subjective appetite but fails to induce weight loss. Therefore, nesfatin-1 may be a better candidate weight loss medication than PEG leptin.

Sympathetic nervous activation has an important role in energy expenditure and weight loss. Obesity is characterized by sympathetic nervous activation, insulin resistance and leptin resistance, although it has not been clarified whether the sympathetic nervous activation is a cause or consequence. There are several longitudinal studies showing different relationships between sympathetic nervous activity, insulin resistance, leptin resistance and weight changes between lean and obese individuals, and between a calorie restriction and exercise. However, during significant weight loss with any weight loss program (for example, lifestyle modifications, bariatric surgery), at least, significant reductions in sympathetic nervous system activation and normalized insulin sensitivity and hyperleptinemia are observed. When individuals modify their lifestyle with a low-calorie diet and exercise, sympathetic nervous system activation is suppressed or normalized, and BP reductions are observed. In addition, it has been reported that a weight loss protocol (very mild calorie-restricted diet and mild exercise) improves renal function and insulin sensitivity with a normalization or suppression of sympathetic nervous activation and resultant BP normalization even without significant weight loss.[10] These investigations may indicate the possibility of less BP elevation by nesfatin-1 administration with normalized or suppressed sympathetic nervous system activation caused by lifestyle modification. Recently, many reviews have examined the roles of nesfatin-1 in several obesity-related diseases, but further studies are needed to more precisely determine the physiological effects of nesfatin-1 in diabetes and obesity, the role of nesfatin-1 in weight loss trials and the possible use of nesfatin-1 as an anti-obesity medication.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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