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CORRESPONDENCE

Peripheral administration of nesfatin-1 increases blood pressure in mice

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Anorexigenic protein, nesfatin-1, processed from its precursor protein, nesfatin/nucleobindin-2 (NUCB2), by prohormone convertases, is found in the paraventricular nucleus of the hypothalamus.[1] Peripherally administered nesfatin-1 or its mid-segment section also inhibits feeding behavior.[2] On the other hand, nesfatin/NUCB2 is ubiquitously expressed in peripheral tissues, including the white adipose tissue.[3,4] Production of nesfatin/NUCB2 in the white adipose tissue is regulated by the sympathetic nervous system.[4] Bioactive substances released from adipose tissue are involved in the central regulation of metabolism.[5] Nesfatin/NUCB2 and nesfatin-1, released from the adipose tissue, appear to be involved in the transmission of the anorexigenic signal from the periphery to the brain. Recently, intracerebroventricular infusion of nesfatin-1 was demonstrated to activate sympathetic nerve activities;[6] intracerebroventricular administration of nesfatin-1also increases mean blood pressure (MBP).[6] However, the issue of whether nesfatin/NUCB2, produced in the peripheral tissues, is physiologically involved in regulating blood pressure remains to be clarified. We have demonstrated a physiological role of nesfatin/NUCB2 in regulating blood pressure.

Male ICR (Institute of Cancer Research) mice were obtained from Charles Rivers Japan, Tokyo, Japan. Recombinant murine nesfatin-1 (25 nmol per dose; Bachem AG, Bubendorf, Switzerland) was subcutaneously injected into male ICR mice. Mice were pretreated with intraperitoneal administration of 10 mg kg^{-1} phentolamine (Sigma-Aldrich, St Louis, MO, USA)[7] or 1 μg kg^{-1} propranolol (Sigma-Aldrich)[8] 30 min prior to the administration of 25 nmol nesfatin-1. A non-invasive blood pressure monitor (Model MK-2000ST, Muromachi Kikai,

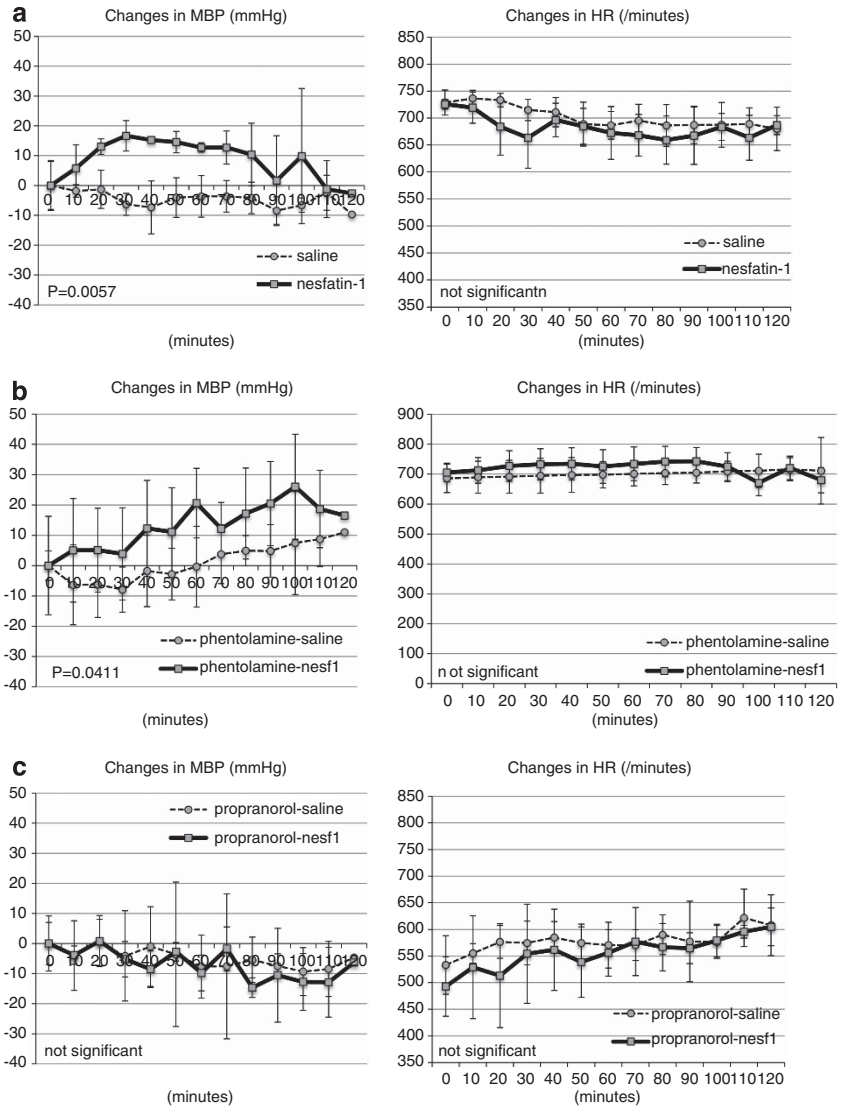

Figure 1 Changes of mean blood pressure (MBP; left panel) and heart rate (HR; right panel) after peripheral administration of 25 nmol nesfatin-1 in mice without (**a**) or with intraperitoneal administration of 10 mg kg^{-1} phentolamine (**b**) or 1 μg kg^{-1} propranolol (**c**) 15 min prior to the experiment. $N=3$ in each treatment group.

Tokyo, Japan) was used for the measurement of blood pressure and heart rate (HR).[9,10] All the data are expressed as mean ± s.d. Statistical analysis of the mean values was performed by analysis of variance, followed by a Tukey test for comparisons of individual means. $P<0.05$ was considered statistically significant.

Peripheral administration of 25 nmol of nesfatin-1 significantly increased MBP in male ICR mice by 100 min after injection, but HR remained unaffected (Figure 1a). Pretreatment by subcutaneous injection of 10 mg kg^{-1} body weight phentolamine 15 min before nesfatin-1 had no effect on this increase in MBP by nesfatin-1, and HR remained unaffected (Figure 1b). In contrast, the increase in MBP was completely abolished by pretreatment with subcutaneous injection of 1 μg kg^{-1} body weight propranolol (Figure 1c), indicating that the β-adrenergic receptor is involved in the elevation of MBP caused by peripherally administered nesfatin-1.

Central infusion of nesfatin-1 activates the sympathetic nervous system in the brain, resulting in an increase in MBP via the α-adrenoreceptor, although intracerebroventricular infusion of nesfatin-1 does not affect HR.[6] Peripheral nesfatin-1 is supposed to cross the blood–brain barrier and reach the brain by nonsaturable mechanism.[11,12] Peripherally administered nesfatin-1 significantly suppressed food intake in mice fed *ad libitum*,[2] as did nesfatin-1 infused into the third ventricle.[1] Therefore, peripherally administered nesfatin-1 could directly activate the sympathetic nervous system, a phenomenon that is in agreement with observations on feeding behavior.[2] Pretreatment with phentolamine blocked MBP elevation by central nesfatin-1,[6] but had no effect on MBP elevation induced by peripherally administered nesfatin-1; pretreatment with propranolol abolished MBP elevation, indicating an involvement of the β-adrenergic system in MBP elevation by peripherally administered nesfatin-1. As it is supposed that the mechanism of blood pressure elevation by β-adrenergic activation is based upon a combination of cardiac (increase of cardiac output) and intra-renal β-adrenergic activation, a hypothalamic mechanism may not have a main role in the regulation of systemic blood pressure. Although renal tubular sodium and water reabsorption is regulated by the β-adrenergic system, the effect of β-adrenergic receptor on the kidney may usually require many hours to develop. In addition, nesfatin-1 was recently found to specifically impair sodium nitroprusside-induced relaxation of vascular smooth muscle by inhibiting cyclic GMP production in rats.[13] The present finding that peripheral administration of nesfatin-1 increased MBP without increasing HR in mice indicates a direct action of nesfatin-1 on vascular smooth muscle *in vivo*. In the future study, those possibilities should be clarified.

It is concluded that nesfatin/NUCB2 and/or nesfatin-1, released from the brain and peripheral tissues, is involved in the regulation of blood pressure *in vivo*, and it acts by modifying vascular contractility, in addition to the central mechanism. Nesfatin-1 or its precursor protein, nesfatin/NUCB2, may have a role on hypertension in the patients with type 2 diabetes or metabolic syndrome. Nesfatin-1 may probably be a new key molecule involved in hypertension, and can be used as an anti-obesity and anti-T2DM medications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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