[9] Date, Y.; Murakami, N.; Kojima, M.; Kuroiwa, T.; Matsukura, S.; Kangawa, K.; Nakazato, M. Central effects of a novel acylated peptide, ghrelin, on growth hormone release in rats. *Biochem. Biophys. Res. Commun.*, **2000**, *275*, 477-480.

[10] Tschop, M.; Smiley, D.L.; Heiman, M.L. Ghrelin induces adiposity in rodents. *Nature,* **2000**, *407*, 908-913.

[11] Wren, A.M.; Small, C.J.; Ward, H.L.; Murphy, K.G.; Dakin, C.L.; Taheri, S.; Kennedy, A.R.; Roberts, G.H.; Morgan, D.G.; Ghatei, M.A.; Bloom, S.R. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology*, **2000**, *141*, 4325-4328.

[12] Unniappan, S.; Lin, X.; Cervini, L.; Rivier, J.; Kaiya, H.; Kangawa, K.; Peter, R.E. Goldfish ghrelin: molecular characterization of the complementary deoxyribonucleic acid, partial gene structure and evidence for its stimulatory role in food intake. *Endocrinology,* **2002**, *143*, 4143-4146.

[13] Furuse, M.; Tachibana, T.; Ohgushi, A.; Ando, R.; Yoshimatsu, T.; Denbow, D.M. Intracerebroventricular injection of ghrelin and growth hormone releasing factor inhibits food intake in neonatal chicks. *Neurosci. Lett.*, **2001**, *301*, 123-126.

[14] Saito, E.S.; Kaiya, H.; Tachibana, T.; Tomonaga, S.; Denbow, D.M.; Kangawa, K.; Furuse, M. Inhibitory effect of ghrelin on food intake is mediated by the corticotropin-releasing factor system in neonatal chicks. *Regul. Pept.*, **2005**, *125*, 201-208.

5] Shousha, S.; Nakahara, K.; Kojima, M.; Miyazato, M.; Hosoda, H.; Kangawa, K.; Murakami, N. Different effects of peripheral and central ghrelin on regulation of food intake in the Japanese quail. *Gen. Comp. Endocrinol.*, **2005**, *141*, 178-183.

[16] Wren, A.M.; Small, C.J.; Abbott, C.R.; Dhillo, W.S.; Seal, L.J.; Cohen, M.A.; Batterham, R.L.; Taheri, S.; Stanley, S.A.; Ghatei, M.A.; Bloom, S.R. Ghrelin causes hyperphagia and obesity in rats. *Diabetes*, **2001**, *50*, 2540-2547.

[17] Schwartz, M.W.; Woods, S.C.; Porte, D. Jr.; Seeley, R.J.; Baskin, D.G. Central nervous system control of food intake. *Nature*, **2000**, *404*, 661-671.

[18] Schwartz, M.W.; Seeley, R.J.; Campfield, L.A.; Burn, P.; Baskin, D.G. Identification of targets of leptin action in rat hypothalamus. *J. Clin. Invest.*, **1996**, *98*, 1101-1106.

[19] Mercer, J.G.; Hoggard, N.; Williams, L.M.; Lawrence, C.B.; Hannah, L.T.; Morgan, P.J.; Trayhurn, P. Coexpression of leptin receptor and preproneuropeptide Y mRNA in arcuate nucleus of mouse hypothalamus. *J. Neuroendocrinol.*, **1996**, *8*, 733-735.

[20] Broberger, C.; Johansen, J.; Johansson, C., Schalling, M., Hökfelt, T. The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 15043-15048.

[21] Schwartz, M.W.; Seeley, R.J.; Woods, S.C.; Weigle, D.S.; Campfield, L.A.; Burn, P.; Baskin, D.G. Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. *Diabetes*, **1997**, *46*, 2119-2123.

[22] Kristensen, P.; Judge, M.E.; Thim, L.; Ribel, U.; Christjansen, K.N.; Wulff, B.S.; Clausen, J.T.; Jensen, P.B.; Madsen, O.D.; Vrang, N.; Larsen, P.J.; Hastrup, S. Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature*, **1998**, *393*, 72-76.

[23] Lawrence, C.B.; Snape, A.C.; Baudoin, F.M.; Luckman, S.M. Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers. *Endocrinology*, **2002**, *143*, 155-162.

[24] Tamura, H.; Kamegai, J.; Shimizu, T.; Ishii, S.; Sugihara, H.; Oikawa, S. Ghrelin stimulates GH but not food intake in arcuate nucleus ablated rats. *Endocrinology*, **2002**, *143*, 3268-3275.

[25] Kamegai, J.; Tamura, H.; Shimizu, T.; Ishii, S.; Sugihara, H.; Wakabayashi, I. Central effect of ghrelin, an endogenous growth hormone secretagogue, on hypothalamic peptide gene expression. *Endocrinology*, **2000**, *141*, 4797-4800.

[26] Shintani, M.; Ogawa, Y.; Ebihara, K.; Aizawa-Abe, M.; Miyanaga, F.; Takaya, K.; Hayashi, T.; Inoue, G.; Hosoda, K.; Kojima, M.; Kangawa, K.; Nakao, K. Ghrelin, an endogenous growth hormone secretagogue, is a novel orexigenic peptide that antagonizes leptin action through the activation of hypothalamic neuropeptide Y/Y1 receptor pathway. *Diabetes*, **2001**, *50*, 227-232.

[27] Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.M.; Tanaka, H.; Williams, S.C.; Richardson, J.A.; Kozlowski, G.P.; Wilson, S.; Arch, J.R.; Buckingham, R.E.; Haynes, A.C.; Carr, S.A.; Annan, R.S.; McNulty, D.E.; Liu, W.S.; Terrett, J.A.; Elshourbagy, N.A.; Bergsma, D.J.; Yanagisawa, M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, **1998**, *92*, 573-585.

[28] Toshinai, K.; Date, Y.; Murakami, N.; Shimada, M.; Mondal, M.S.; Shimbara, T.; Guan, J.L.; Wang, Q.P.; Funahashi, H.; Sakurai, T.; Shioda, S.; Matsukura, S.; Kangawa, K.; Nakazato, M. Ghrelin-induced food intake is mediated via the orexin pathway. *Endocrinology*, **2003**, *144*,1506-1512.

[29] Qu, D.; Ludwig, D.S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M.A.; Cullen, M.J.; Mathes, W.F.; Przypek, R.; Kanarek, R.; Maratos-Flier, E. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature*, **1996**, *380*, 243-247.

[30] Szentirmai, E.; Hajdu, I.; Obal, F.. Jr, Krueger, J.M. Ghrelin-induced sleep responses in ad libitum fed and food-restricted rats. *Brain Res.*, **2006**, *1088*, 131-140.

[31] Szentirmai, E.; Kapás, L.; Krueger, J.M. Ghrelin microinjection into forebrain sites induces wakefulness and feeding in rats. Am J Physiol Regul Integr *Comp Physiol.*, **2007**, *292*, R575-R585.

[32] Date, Y.; Nakazato, M.; Murakami, N.; Kojima, M.; Kangawa, K.; Matsukura, S. Ghrelin acts in the central nervous system to stimulate gastric acid secretion. *Biochem. Biophys. Res. Commun.*, **2001**, *280*, 904-907.

[33] Mano-Otagiri, A.; Ohata, H.; Iwasaki-Sekino, A.; Nemoto, T.; Shibasaki, T. Ghrelin suppresses noradrenaline release in the brown adipose tissue of rats. *J. Endocrinol.*, **2009**, 201, 341-349.

[34] Asakawa, A.; Inui, A.; Kaga, T.; Yuzuriha, H.; Nagata, T.; Ueno, N.; Makino, S.; Fujimiya, M.; Niijima, A.; Fujino, M.A.; Kasuga, M. Ghrelin is an appetite-stimulatory signal from stomach with structural resemblance to motilin. *Gastroenterology*, **2001**, *120*, 337-345.

[35] Jerlhag, E.; Egecioglu, E.; Landgren, S.; Salomé, N.; Heilig, M.; Moechars, D.; Datta, R.; Perrissoud, D.; Dickson, S.L.; Engel, J.A. Requirement of central ghrelin signaling for alcohol reward. *Proc. Natl. Acad. Sci. USA*, **2009**, *106*, 11318-11323.

[36] Leggio, L. Role of the ghrelin system in alcoholism: Acting on the growth hormone secretagogue receptor to treat alcohol-related diseases. *Drug News Perspect.*, **2010**, *23*, 157-166.

[37] Wren, A.M.; Small, C.J.; Fribbens, C.V.; Neary, N.M.; Ward, H.L.; Seal, L.J.; Ghatei, M.A.; Bloom, S.R. The hypothalamic mechanisms of the hypophysiotropic action of ghrelin. *Neuroendocrinology*, **2002**, *76*, 316-324.

[38] Asakawa,.A.; Inui, A.; Kaga, T.; Yuzuriha, H.; Nagata, T.; Fujimiya, M.; Katsuura, G.; Makino, S.; Fujino, M.A.; Kasuga, M. A role of ghrelin in neuroendocrine and behavioral responses to stress in mice. *Neuroendocrinology*, **2001**, *74*, 143-147.

[39] Carlini, V.P.; Monzón, M.E.; Varas, M.M.; Cragnolini, A.B.; Schiöth, H.B.; Scimonelli, T.N.; de Barioglio, S.R. Ghrelin increases anxiety-like behavior and memory retention in rats. *Biochem. Biophys. Res. Commun.*, **2002**, *299*, 739-743.

[40] Stevanović, D.; Milosević, V.; Starcević, V.P.; Severs, W.B. The effect of centrally administered ghrelin on pituitary ACTH cells and circulating ACTH and corticosterone in rats. *Life Sci.*, **2007**, *80*, 867-872.

[41] Wren, A.M.; Small, C.J.; Ward, H.L.; Murphy, K.G.; Dakin, C.L.; Taheri, S.; Kennedy, A.R.; Roberts, G.H.; Morgan, D.G.; Ghatei, M.A.; Bloom, S.R. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology*, **2000**, *141*, 4325-4328.

[42] Cowley, M.A.; Smith, R.G.; Diano, S.; Tschop, M.; Pronchuk, N.; Grove, K.L.; Strasburger, C.J.; Bidlingmaier, M.; Esterman, M.; Heiman, M.L.; Garcia-Segura, L.M.; Nillni, E.A.; Mendez, P.; Low, M.J.; Sotonyi, P.; Friedman, J.M.; Liu, H.; Pinto, S.; Colmers, W.F.; Cone, R.D.; Horvath, T.L. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron*, **2003**, *37*, 649-661.

[43] Silva, J.E. Thyroid hormone control of thermogenesis and energy balance. *Thyroid*, **1995**, *5*, 481-492.

[44] Kokkinos, A.; Mourouzis, I.; Kyriaki, D.; Pantos, C.; Katsilambros, N.; Cokkinos, D.V. Possible implications of leptin, adiponectin and ghrelin in the regulation of energy homeostasis by thyroid hormone. *Endocrine*, **2007**, *32*, 30-32.

[45] Casanueva, F.F.; Dieguez, C. Ghrelin: the link connecting growth with metabolism and energy homeostasis. *Rev. Endocr. Metab. Disord.*, **2002**, *3*, 325-338.

[46] Riis, A.L.; Hansen, T.K.; Møller, N.; Weeke, J.; Jørgensen, J.O. Hyperthyroidism is associated with suppressed circulating ghrelin levels. *J. Clin. Endocrinol. Metab.*, **2003**, *88*, 853-857.

[47] Caminos, J.E.; Seoane, L.M.; Tovar, S.A.; Casanueva, F.F.; Dieguez, C. Influence of thyroid status and growth hormone deficiency on ghrelin. *Eur. J. Endocrinol.*, **2002**, *147*, 159-163.

[48] Sosić-Jurjević, B.; Stevanović, D.; Milosević, V.; Sekulić, M.; Starcević, V. Central ghrelin affects pituitary-thyroid axis: histomorphological and hormonal study in rats. *Neuroendocrinology*, **2009**, *89*, 327-336.

[49] Wren, A.M.; Small, C.J.; Abbott, C.R.; Dhillo, W.S.; Seal, L.J.; Cohen, M.A.; Batterham, R.L.; Taheri, S.; Stanley, S.A.; Ghatei, M.A.; Bloom, S.R. Ghrelin causes hyperphagia and obesity in rats. *Diabetes*, **2001**, *50*, 2540-2547.

[50] Broglio, F.; Benso, A.; Castiglioni, C.; Gottero, C.; Prodam, F.; Destefanis, S.; Gauna, C.; van der Lely, A.J.; Deghenghi, R.; Bo, M.; Arvat, E.; Ghigo, E. The endocrine response to ghrelin as a function of gender in humans in young and elderly subjects. *J. Clin. Endocrinol. Metab.*, **2003**, *88*, 1537-1542.

[51] Messini, C.I.; Dafopoulos, K.; Chalvatzas, N.; Georgoulias, P.; Messinis, I.E. Growth hormone and prolactin response to ghrelin during the normal menstrual cycle. *Clin. Endocrinol. (Oxf).*, **2009**, *71*, 383-387.

[52] Tena-Sempere, M.; Aguilar, E.; Fernandez-Fernandez, R.; Pinilla, L. Ghrelin inhibits prolactin secretion in prepubertal rats. *Neuroendocrinology*, **2004**, *79*, 133-141.

[53] Tena-Sempere, M.; Barreiro, M.L.; González, L.C.; Gaytán, F.; Zhang, F.P.; Caminos, J.E.; Pinilla, L.; Casanueva, F.F.; Diéguez, C.; Aguilar, E. Novel expression and functional role of ghrelin in rat testis. *Endocrinology*, **2002**, *143*, 717-725.

[54] Caminos, J.E.; Tena-Sempere, M.; Gaytán, F.; Sanchez-Criado, J.E.; Barreiro, M.L.; Nogueiras, R.; Casanueva, F.F.; Aguilar, E.; Diéguez, C. Expression of ghrelin in the cyclic and pregnant rat ovary. *Endocrinology*, **2003**, *144*, 1594-1602.

[55] Gaytan, F.; Barreiro, M.L.; Chopin, L.K.; Herington, A.C.; Morales, C.; Pinilla, L.; Casanueva, F.F.; Aguilar, E.; Diéguez, C.; Tena-Sempere, M. Immunolocalization of ghrelin and its functional receptor, the type 1a growth hormone secretagogue receptor, in the cyclic human ovary. *J. Clin. Endocrinol. Metab.*, **2003**, *88*, 879-887.

[56] Gaytan, F.; Barreiro, M.L.; Caminos, J.E.; Chopin, L.K.; Herington, A.C.; Morales, C.; Pinilla, L.; Paniagua, R.; Nistal, M.; Casanueva, F.F.; Aguilar, E.; Diéguez, C.; Tena-Sempere, M. Expression of ghrelin and its functional receptor, the type 1a growth hormone secretagogue receptor, in normal human testis and testicular tumors. *J. Clin. Endocrinol. Metab.*, **2004**, *89*, 400-409.

[57] Furuta, M.; Funabashi, T.; Kimura, F. Intracerebroventricular administration of ghrelin rapidly suppresses pulsatile luteinizing hormone secretion in ovariectomized rats. *Biochem. Biophys. Res. Commun.*, **2001**, *288*, 780-785.

[58] Fernández-Fernández R, Tena-Sempere M, Aguilar E, Pinilla L . Ghrelin effects on gonadotropin secretion in male and female rats. *Neurosci. Lett.*, **2004**, *362*, 103-107.

[59] Ishizaki, S.; Murase, T.; Sugimura, Y.; Kakiya, S.; Yokoi, H.; Tachikawa, K.; Arima, H.; Miura, Y.; Oiso, Y. Role of ghrelin in the regulation of vasopressin release in conscious rats. *Endocrinology*, **2002**, *143*, 1589-1593.

[60] Korbonits, M.; Little, J.A.; Forsling, M.L.; Tringali, G.; Costa, A.; Navarra, P.; Trainer, P.J.; Grossman, A.B. The effect of growth hormone secretagogues and neuropeptide Y on hypothalamic hormone release from acute rat hypothalamic explants. *J. Neuroendocrinol.*, **1999**, *11*, 521-528.

[61] Yokoyama, T.; Saito, T.; Ohbuchi, T.; Suzuki, H.; Otsubo, H.; Okamoto, T.; Fujihara, H.; Nagatomo, T.; Ueta, Y. Ghrelin Potentiates Miniature Excitatory Postsynaptic Currents in Rat Supraoptic Magnocellular Neurones. *J. Neuroendocrinol.*, **2009**, *21*, 910-920

[62] Wuarin, J.P.; Dudek, F.E; Patch-clamp analysis of spontaneous synaptic currents in supraoptic neuroendocrine cells of the rat hypothalamus. *J. Neurosci.*, **1993**, *13*, 2323-2331.

[63] Meeker, R.B.; Swanson, D.J.; Greenwood, R.S.; Hayward, J.N. Quantitative mapping of glutamate presynaptic terminals in the supraoptic nucleus and surrounding hypothalamus. *Brain Res.*, **1993**, *600*, 112-122.

[64] Hosoda, H.; Kojima, M.; Matsuo, H.; Kangawa, K. Ghrelin and des-acyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue. *Biochem. Biophys. Res. Commun.*, **2000**, *279*, 909-913.

[65] Heijboer, A.C.; van den Hoek, A.M.; Parlevliet, E.T.; Havekes, L.M.; Romijn, J.A.; Pijl, H.; Corssmit, E.P. Ghrelin differentially affects hepatic and peripheral insulin sensitivity in mice. *Diabetologia*, **2006**, *49*, 732-738.

[66] Muccioli, G.; Baragli, A.; Granata, R.; Papotti, M.; Ghigo, E. Heterogeneity of ghrelin/growth hormone secretagogue receptors. Toward the understanding of the molecular identity of novel ghrelin/GHS receptors. *Neuroendocrinology*, **2007**, *86*, 147-164.

[67] Sharif Naeini, R.; Witty, M.F.; Seguela, P.; Bourque, C.W. An N-terminal variant of Trpv1 channel is required for osmosensory transduction. *Nat. Neurosci.*, **2006**, *9*, 93-98.

[68] Gimpl, G.; Fahrenholz, F. The oxytocin receptor system: structure, function, and regulation. *Physiol. Rev.*, **2001**, *81*, 629-683.

[69] Landgraf, R.; Neumann, I.D. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. *Front Neuroendocrinol.*, **2004**, *25*, 150-176.

[70] Olszewski, P.K.; Bomberg, E.M.; Martell, A.; Grace, M.K.; Levine, A.S. Intraventricular ghrelin activates oxytocin neurons: implications in feeding behavior. *Neuroreport*, **2007**, *18*, 499-503.

[71] de Castro, J.M. A microregulatory analysis of spontaneous fluid intake by humans: evidence that the amount of liquid ingested and its timing is mainly governed by feeding. *Physiol. Behav.*, **1988**, *43*, 705-714

[72] Morgan, C.A.; Emmans, G.C.; Tolkamp, B.J.; Kyriazakis, I. Analysis of the feeding behavior of pigs using different models. *Physiol. Behav.*, **2000**, *68*, 395-403.

[73] Kissileff, H.R. Food-associated drinking in the rat. *J. Comp. Physiol. Psychol.*, **1969**, *67*, 284-300.

[74] Tsushima, H.; Mori, M. Antidipsogenic effects of a TRPV4 agonist, 4alpha-phorbol 12,13-didecanoate, injected into the cerebroventricle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2006**, *290*, R1736-R1741. 22.

[75] Toshinai, K.; Yamaguchi, H.; Sun, Y.; Smith, R.G.; Yamanaka, A.; Sakurai, T.; Date, Y.; Mondal, M.S.; Shimbara, T.; Kawagoe, T.; Murakami, N.; Miyazato, M.; Kangawa, K.; Nakazato, M. Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. *Endocrinology*, **2006**, *147*, 2306-2314.

[76] Asakawa, A.; Inui, A.; Fujimiya, M.; Sakamaki, R.; Shinfuku, N.; Ueta, Y.; Meguid, M.M.; Kasuga, M. Stomach regulates energy balance via acylated ghrelin and desacyl ghrelin. *Gut*, **2005**, *54*, 18-24.

[77] Matsuda, K.; Miura, T.; Kaiya, H.; Maruyama, K.; Shimakura, S.; Uchiyama, M.; Kangawa, K.; Shioda, S. Regulation of food intake by acyl and des-acyl ghrelins in the goldfish. *Peptides*, **2006**, *27*, 2321-2325.

[78] Stricker, E.M.; Verbalis, J.G. Interaction of osmotic and volume stimuli in regulation of neurohypophyseal secretion in rats. *Am. J. Physiol.*, **1986**, *250*, R267-R275.

[79] Johnson, A.K. The sensory psychobiology of thirst and salt appetite. *Med. Sci. Sports Exerc.*, **2007**, *39*, 1388-1400.

[80] McKinley, M.J.; Walker, L.L.; Alexiou, T.; Allen, A.M.; Campbell, D.J.; Di Nicolantonio, R.; Oldfield, B.J.; Denton, D.A. Osmoregulatory fluid intake but not hypovolemic thirst is intact in mice lacking angiotensin. Am J Physiol Regul Integr Comp. Physiol., **2008**, *294*, R1533-1543.

[81] Kozaka, T.; Fujii, Y.; Ando, M. Central effects of various ligands on drinking behavior in eels acclimated to seawater. *J. Exp. Biol.*, **2003**, *206*, 687-692.

[82] Tachibana, T.; Kaiya, H.; Denbow, D.M.; Kangawa, K.; Furuse, M. Central ghrelin acts as an anti-dipsogenic peptide in chicks. *Neurosci. Lett.*, **2006**, *405*, 241-245.

Received: March 24, 2011 Revised: March 24, 2011 Accepted: April 02, 2011

ELSEVIER

Pathophysiology 19 (2012) 283–298

ISP
PATHOPHYSIOLOGY

www.elsevier.com/locate/pathophys

Review

Pathophysiological function of oxytocin secreted by neuropeptides: A mini review

Hirofumi Hashimoto [a], Yasuhito Uezono [b], Yoichi Ueta [a,*]

[a] *Department of Physiology, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan*

[b] *Devision of Cancer Pathophysiology, Group for Translational Research, National Cancer Centre Research Institute, Tokyo, Japan*

Received 11 February 2012; received in revised form 4 July 2012; accepted 11 July 2012

Abstract

Oxytocin (OXT) is well known for its ability to stimulate milk ejection and uterine contraction. OXT is also involved in several physiological and pathological functions such as antinociception, anxiety, feeding, social recognition and stress responses. Previous studies showed that neuropeptides such as cholecystokinin (CCK) activate OXT-secreting magnocellular neuron in the supraoptic (SON) and the paraventricular nuclei (PVN) of the hypothalamus and cause OXT release from the axon terminal in the posterior pituitary into the systemic circulation. Our recent studies showed that central administration of adrenomedullin (AM) family (AM, AM2 (identical to intermedin) and AM5) induced the expression of the c-*fos* gene in the SON and the PVN and elicited the marked increase of plasma OXT levels in conscious rats. Here, we review pathophysiological properties of OXT in whole body and effects of novel peptides such as AM family as well as other peptides on OXT release.

Keywords: Adrenomedullin family; Cholecystokinin; Hypothalamus; Neuropeptides; Paraventricular nucleus; Supraoptic nucleus

Contents

Abbreviations: AM, adrenomedullin; α-MSH, α-melanocyte stimulating hormone; AP, area postrema; AVP, arginine vasopressin; AVPV, the anteroventral periventricular nucleus; BNST, the bed nucleus of the stria terminalis; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CeA, the central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; CNS, central nervous system; LHA, the lateral hypothalamic area; NAcc, the nucleus accumbens; NTS, the nucleus of the solitary tract; OLETF, Otsuka Long-Evans Tokushima Fatty rat; OTR, oxytocin receptor; OXT, oxytocin; POMC, proopiomelanocortin; PrRP, prolactin-releasing peptide; PVN, the paraventricular nucleus; RFRP, RFamide-related peptides; SON, the supraoptic nucleus; VLM, the ventrolateral medulla; VMH, the ventromedial nucleus of hypothalamus.

* Corresponding author. Tel.: +81 93 691 7420; fax: +81 93 692 1711.
E-mail address: yoichi@med.uoeh-u.ac.jp (Y. Ueta).

0928-4680/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pathophys.2012.07.005

1. Introduction

Oxytocin (OXT), a nine amino acid neuropeptide, was discovered in 1906 as the extracts with uterus-contracting effects from pituitary [1]. OXT was the first peptide hormone to be sequenced and synthesized in 1953 [2–4]. OXT and Arginine vasopression (AVP) are closely related peptides synthesized primarily in magnocellular neurons of the hypothalamus localized in the supraoptic (SON) and the paraventricular nuclei (PVN), which project their axon terminals into the posterior pituitary where it is released into the systemic circulation [5,6].

OXT is well known for its roles in reproduction, especially during and after childbirth. A large amount of OXT is released after distension of the cervix and uterus during labor to help birth, and after stimulation of the nipples to milk ejection. Previous many studies showed that OXT is involved in several of physiological and pathological functions such as antinociception, anxiety, feeding, social recognition and stress responses [7–12] (Fig. 1).

In this review, we focus on (1) synthesis and distribution of OXT, (2) physiological functions of OXT, and (3) novel peptides, which stimulate OXT release (Table 1).

2. Synthesis and distribution of OXT

2.1. Regulation of synthesis and release of OXT

OXT is produced in the magnocellular neurosecretary cells of the SON and the PVN of the hypothalamus and is released into the systemic circulation from axon terminals in the neurohypophysis, particularly during parturition, lactation and in response to osmotic challenge [13]. The parvocellular OXT cells in the PVN, project their axon terminals to the brainstem and the spinal cord where OXT regulates autonomic functions [14]. Additional parvocellular OXT cells are found in the preoptic area and the lateral hypothalamus, whereas accessory magnocellular OXT cells are found scattered across the hypothalamus.

OXT is well known for its roles in reproduction, especially during and after childbirth. The pulsatile OXT release into the circulation is stimulated by vaginocervical stimulation associated with labor and suckling stimulus on the nipple. The uterine muscle increases its OXT receptor (OTR) and sensitivity to OXT during the latter few months of pregnancy. That level of OXT release from the neurohypophysis is considerably increased at the time of labor. In lactation, OXT causes milk to be expressed from the alveoli into the ducts of the breast that the baby can obtain it by suckling. The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the OXT-secreting magnocellular neurons in the SON and the PVN. OXT in plasma is carried to the breast, where it causes contraction of myoepithelial cells that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after baby's suckling, milk begins to flow.

OXT is also recognized as having endocrine and paracrine roles in male reproduction. OXT is synthesized within the mammalian testis, epididymis and prostate and OTRs in the reproductive tract supports a local action for OXT [15–23]. In ejaculation, a burst of OXT is released from the neurohypophysis into the systemic circulation and stimulates contractions of the reproductive tract for sperm release [24–26]. OXT has a paracrine role in stimulating contractility of the seminiferous tubules, epididymis and the prostate gland.

Interestingly, OXT is also released from soma and dendrites during parturition and lactation [27]. Although OXT released from soma and dendrites of magnocellular neurons in the SON and the PVN may act in a paracrine to activate distant receptors [27], OXT-like immunoreactivity (LI) fibers can be found throughout the brain, including the nucleus accumbens (NAcc), lateral septum, amygdala, and some areas in the hindbrain, brainstem, and spinal cord

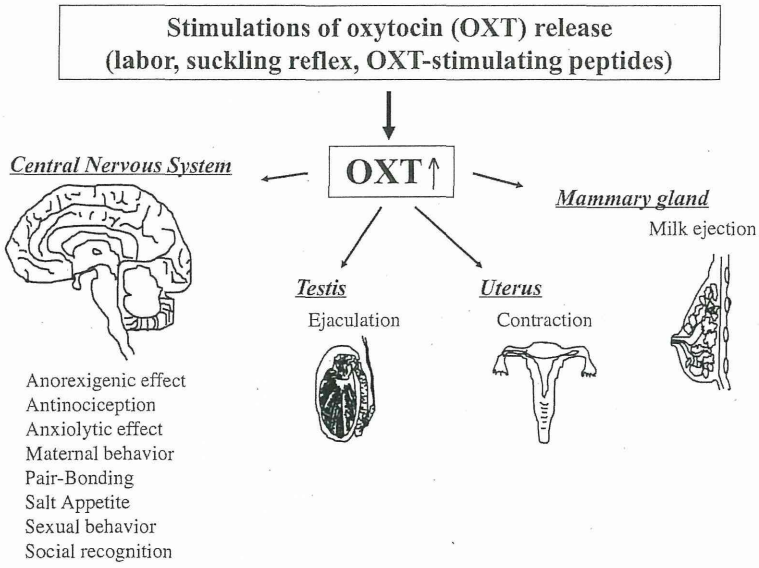

Fig. 1. Physiological function of OXT.

[14,28]. A notable reduction was observed in OXT-LI fibers throughout the brain by the lesioning the PVN [29]. Although little is known about the regulation of OXT release from these forebrain projections, they maybe contribute significantly to the regulation of behavior.

2.2. The OXT gene expression

The OXT gene expression is stimulated during pregnancy and lactation [30,31]. Interestingly, estrogen or progesterone alone does not increase OXT synthesis, however, the OXT gene expression in the SON and the PVN was increased by the administration of prolonged estrogen and progesterone, followed by progesterone withdrawal [32]. By contrast, the OXT gene expression in the uterine was highly stimulated by combined estrogen and progesterone application [33].

2.3. Distribution of OTR

The central effects of OXT are mediated by OTRs distributed widely in the brain. OTR mRNAs are distributed in the ventromedial nucleus of hypothalamus (VMH) and PVN which is involved in steroid-sensitive reproductive behaviors, in the PVN substantia nigra and ventral tegmental area which is involved in maternal behaviors, in the hippocampus which is involved in learning and memory and in

Table 1
Novel peptides which activate oxytocin (OXT) neurons and stimulate OXT release.

Peptides	Activation of oxytocin (OXT) neuron or OXT release		References
	OXT neuron	OXT release	
Adrenomedullin (AM)	Activate (icv)	Increase (icv)	[111,112]
Adrenomedullin 2 (AM2)/intermedin	Activate (icv)	Increase (icv)	[113,118]
Adrenomedullin 5 (AM5)	Activate (icv)	Increase (icv)	[120]
Apelin	Inhibite (icv)	Not determined (ND)	[136]
Cholecystokinin (CCK)	Activate (iv, ip)	Increase (iv, ip)	[138–141,145]
Cocaine- and amphetamine-regulated transcript (CART)	Activate (icv)	Increase	[76]
Corticotropin-released factor (CRF)	Not determined (ND)	Increase (icv, iv)	[220]
Kisspeptin	Activate (iv)	Increase (iv)	[173,175]
Glucagon-like Peptide-1 (GLP-1)	Activate (icv)	Increase (iv, high dose icv) Decrease (low dose icv)	[221–223]
α-melanocyte-stimulating hormone (αMSH)	Activate (icv)	Decrease (icv)	[224,225]
Nesfatin-1	Activate (icv)	Not determined (ND)	[181,182]
Neuromedin U (NMU)	Activate (icv)	Increase (icv)	[226]
Opioids (naloxone-induced OXT release)	Inhibite (icv)	Decrease (icv)	[227,228]
Prolactin-releasing peptide (PrRP)	Activate (icv)	Increase (icv)	[197,200]
Secretin	Activate (icv)	Increase (icv)	[215]
Thyrotropin-releasing hormone (TRH)	Not determined (ND)	Increase (iv)	[229]
Vasoactive intestinal polypeptide (VIP)	Not determined (ND)	Increase (icv)	[230]

the substantia nigra, ventral tegmental area, lateral septum, caudate putamen, amygdaloid nuclei, olfactory tubercle and cingulate, perirhinal, and frontal cortices which are involved in reinforcement [34].

2.4. The OTR gene expression

Gonadal steroids play an important role in mediating the regulation of the OTR expression. Most peripheral OXT-binding sites, including pituitary, renal, and uterine, are upregulated by estrogens [35–37]. The upregulation is accompanied by OTR mRNA expression. These results suggested that the upregulation is a consequence of a genomic estrogen effect on the OTR gene transcription [38,39]. In the behavioral studies clearly showed that a necessary potential of OXT to elicit maternal or sexual behavior is priming with estrogen alone or with both estrogen and progesterone [40,41]. This evidence suggests that OTR are under the control of gonadal steroids in the central nervous system (CNS).

The OTR gene expression increased during pregnancy and/or at parturition in olfactory bulb, medial preoptic area, bed nucleus of the stria terminalis (BNST), the SON, and the medial amygdala in rat [42,43]. OTRs-binding sites increased in the medial preoptic area, the BNST, VMH, and the ventral tegmental area on postpartum day 1 [42,44,45]. These changes suggest that OXT and OTR likely play a role in both lactation and the regulation of maternal behavior.

3. Pathophysiological function of OXT

3.1. Antinociception

OXT neurons in the PVN project not only to the posterior pituitary gland, but also to other brain areas and the spinal cord and OXT-LI fibers could be found in the dorsal horn of the spinal cord [46–48]. Several studies showed that OXT modulates nociception in the CNS. In the behavioral studies, intrathecally administered OXT enhanced antinociceptive effects in a dose-dependent manner in rats [47,49,50]. The antinociceptive effect, relief of low back pain, of intrathecally administered OXT was also reported in humans [51]. The antinociceptive effects of OXT were also shown in a model of experimental neuropathy developed following a spinal nerve ligation in rats [52]. The antinociceptive effects of intraperitoneally administered OXT were reversed by an OXT antagonist, not by naloxone [53]. After the administration of OXT into the periaquaductal gray, nucleus rapha magnus, and the NAcc, nociceptive response reduced in rats. These effects were blocked by OTRs antagonist [50,54]. As infusion of on opioid receptor antagonist dose-dependently attenuated the antinociceptive effects of OXT in the NAcc, the antinociceptive effects of OXT may involve an interaction with the opioid system [54]. Interestingly, recent study showed that OXT-induced analgesia was blocked in AVP receptor knockout mice [55]. The central and peripheral effects of OXT are thought to be mediated by its binding to a single isoform of the OTR [56], which activates the phospholipase Cβ (PLCβ) signal transduction pathway [57–59]. Centrally effects of AVP are mainly through the AVP-1A receptor (V1AR), which is also coupled to the PLCβ pathway [60–62]. Both OXT and AVP, as well as the OTR and V1AR, display a high degree of sequence homology, and both peptides can therefore activate both receptors [63]. OXT and AVP would have the functional interactions via their receptor system in antinociception.

3.2. Anxiety

Many studies reported that OXT had anxiolytic effects in rats, mice, and humans. In rats, intracerebroventricular (icv) administration of OXT suppressed the increase in plasma corticosterone level following 10 min of noise stress [64]. When rats placed in a novel environment, icv administration of OXT display decreased anxiety-like behavior in female rats in the elevated plus maze [65]. Moreover, OXT knockout mice display increasing anxiety-related behavior in the elevated plus maze, and enhanced corticosterone levels following a psychogenic stressor [66]. The effects of OXT on the stress response and on anxiety-like behavior are thought to partially mediate the anxiolytic effects observed during lactation. A steroid regimen that mimics changes in estradiol and progesterone during pregnancy, that is, estradiol and progesterone treatment followed by progesterone withdrawal, results in a decrease in anxiety-like behavior in the elevated plus maze and an attenuation of corticosterone secretion following noise stress in female rats. The effects of steroid treatment were blocked by OTR antagonist [67]. The treatment of estrogen has also been found to enhance the anxiolytic effects of OXT in mice [68]. The anxiolytic effects of estrogen may be mediated, at least in part, via OTR in the central nucleus of the amygdala. After the administration of OXT in the central nucleus of the amygdala (CeA), the anxiety-like behavior increase, while the administration of OTR antagonist into the CeA decreased anxiety-like behavior [69]. In human, intranasal OXT infusion enhanced the effects of social support in the suppression of cortisol secretion and subjective responses to psychosocial stress [70]. Moreover, functional magnetic resonance imaging study demonstrated that a similar intranasal OXT decreases activation at amygdala following the viewing of fear-inducing visual stimuli [71].

3.3. Feeding

OXT has an anorexic effect that is thought to play a role in signaling satiety. Icv administration of OXT inhibits feeding in hungry rats, while this inhibition of feeding was prevented by co-administration of OTR antagonist [72,73]. These studies were confirmed in the observations

that OXT knockout mice consume larger quantities of sweet and nonsweet carbohydrates than wild-type mice [74]. In the Prader–Willi syndrome, characterized by extreme hyperphagia leading to morbid obesity in human, the number of OXT-containing neurons is decreased in the PVN [75].

Some studies showed that nerve fibers containing the feeding-inhibitory peptides, such as cocaine- and amphetamine-regulated transcript (CART) [76] and prolactin-releasing peptide (PrRP) [77], have synaptic contact with hypothalamic OXT neurons. OXT neurons are activated by the administration of CART or PrRP [78]. It has also been suggested that α-melanocyte stimulating hormone (α-MSH), a feeding inhibition factor released by proopiomelanocortin (POMC) neurons, activates OXT neurons [79]. It is therefore possible that OXT contributes to feeding inhibition by CART, PrRP and α-MSH.

OXT has a short-term feeding-inhibitory effect. However, when OXT is administered for a long period, it has been reported that food intake becomes increased after an initial decrease in feeding [80]. In addition, OTR antagonists also do not block feeding inhibition by α_1 receptor agonists [81].

The site of OXT action upon the feeding inhibition is not completely understood. OXT neurons in the PVN project to the medullary dorsal nucleus of the vagus nerve, and microinjection of OXT into the dorsal nucleus of the vagus nerve inhibits gastric motility, suggesting that OXT neurons of the PVN projecting to the medulla oblongata may act to inhibit feeding [82]. OXT neurons in the PVN also project to sympathetic preganglionic neurons of intermediolateral nuclei in the spinal columns. OXT has been suggested to excite these sympathetic preganglionic neurons. Consequently, it is possible that activation of the sympathetic nervous system may cause inhibition of feeding. OXT reduces binding affinity in the hypothalamus of α_2NA receptor agonists that have a feeding promotion effect [81]. Thus, modification of NA receptors may also contribute to feeding inhibition by OXT. In addition to feeding inhibition, OXT released in the CNS after various stress stimuli has been proposed to modify neuroendocrine stress responses, such as ACTH secretion, and to affect anxiety behaviors [83]. More recently, Maejima et al. showed that peripheral OXT treatment reduced food intake and visceral fat mass, and ameliorates obesity, fatty liver and glucose intolerance [84]. Peripheral OXT treatment provides a new therapeutic avenue for treating obesity and hyperphagia.

In human, the overnight secretion of OXT in women with anorexia nervosa is decreased compared with healthy women [85]. In underweight anorexia nervosa patients, estrogen- or insulin-induced hypoglycemia results in an impaired response in plasma OXT level [86]. In recovered anorexia nervosa patients, cerebrospinal fluid OXT level was normal [87]. Although it is still unclear the pathophysiological mechanism of OXT in anorexic nervosa, OXT maybe have an important role in hypopahagia, including anorexia nervosa and cachexia.

3.4. Salt appetite

OXT appears to play an important role in salt appetite. Icv administration of OXT inhibited hypovolemia-induced salt appetite but had little effect on water intake [88]. Icv administration of OXT also inhibited angiotensin-induced salt appetite [89]. The salt intake was increased in the OXT knockout mice [90]. Moreover, hypovolemia-induced saline intake was increased in rats where OTR bearing neurons were selectively ablated by the application of OXT conjugated to the A chain of ricin [91]. In the OXT knockout mice, the hypovolemia- and dehydrated-induced sodium intake was increased [92,93]. By contrast, sodium intake did not decrease in OXT knockout mice [94]. These studies suggested that OXT pathways are not the only regulator of salt intake, OXT may be more critical in controlling salt intake over brief intervals when an animal is quickly compensating for a dehydrating stimulus [94].

3.5. Social recognition

Social recognition is necessary for the development of all social relationships and requires the appropriate processing of social cues and the activation of processes related to learning and memory. OXT plays an important role in the neural processing of social information and in social recognition. Low doses of central administration of OXT facilitate social recognition in rats, however, higher doses of OXT can be amnestic [95]. Both male and female OXT knockout mice had a profound disruption of social recognition [96,97]. OXT facilitated social recognition through its actions on OTR in the medial amygdala during memory formation. The administration of OXT into the medial amygdala, prior to but not after the initial social exposure to a stimulus female, completely rescues social recognition in OXT knockout mice [98]. In female wild-type mice, infusion of OTR antisense DNA into the medial amygdala decreases OTR protein and blocks social recognition [99].

4. Peptides to stimulate oxytocin release

4.1. Adrenomedullin family

Adrenomedullin (AM) is a 52-amino acid neuropeptide that was originally isolated from tissue extracts of human pheochromocytoma and later found to be widely distributed in peripheral organs and the CNS [100] (Fig. 2). A similar 47-amino acid neuropeptide, adrenomedullin 2 (AM2), identical to intermedin, was first isolated from pufferfish [101,102] and later from mammals [102,103] by the search in the genomic databases [101,102] (Fig. 2). AM2 is identical to intermedin, which was discovered by Roh et al. [102]. AM, AM2/intermedin, and amylin belong to the calcitonin gene-related peptide (CGRP). Each member of AM family has an N-terminal ring structure and an amidated carboxyl

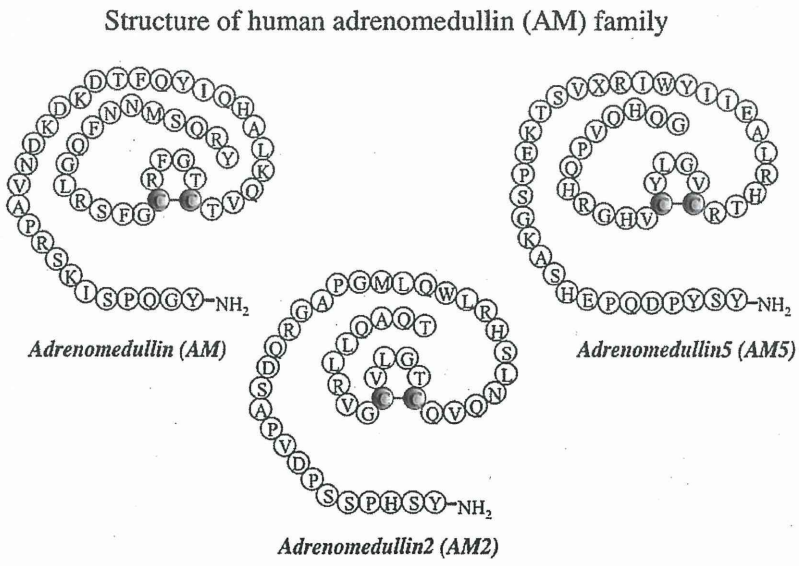

Fig. 2. Structure of adrenomedullin (AM) family. Each member of AM family has an N-terminal ring structure and an amidated carboxyl terminus.

terminus (Fig. 2). Both of these structures are critical for receptor binding and subsequent signaling [104,105].

AM and AM2 are both considered potent vasodilators because peripheral administration of either peptide decreases arterial blood pressure, inhibits urine flow, decreases food intake, and suppresses gastric activity [102,103,106–109]. By all accounts, the effects of the two peptides are qualitatively and quantitatively similar [102,103,106,107]. The actions of AM or AM2 given centrally are quite different from their actions when given peripherally. Central administration of AM2 inhibits food intake and drinking in rats in much the same manner as it does when given peripherally, but centrally administered AM2 elevates arterial blood pressure and heart rate [110]. Icv administration of either AM2 or AM caused hypertension and tachycardia [103,108,110]. We showed that central administration of AM activated OXT neurons [111,112] and caused an elevation of plasma OXT levels in rats [111]. We also showed similar activation of OXT neurons and circulating OXT levels after central administration of AM2 [113] (Fig. 3). These effects of AM2 are similar to those of AM [108,109,111,114–117] and may be mediated by both AM and CGRP receptors [110]. Moreover, we showed that centrally effects of AM2 were stronger than those of AM in the expression of the c-*fos* gene in the SON and PVN, plasma OXT level, and blood pressure in rats [118]. Interestingly, combined AM and CGRP receptor blockade was incomplete for central effects of AM2 [118]. These results suggested that the more potent central effects of AM2 and only partial blockade by AM/CGRP receptor antagonists may result from its action on an additional, as yet unidentified, specific receptor in the CNS.

More recently, in teleost fish, AM peptides were identified as five AMs (AM1–5), and they form an independent subfamily [101]. Takei et al. searched the orthologs of the AMs in the genome and established sequence tag databases and identified AM2 and AM5 genes in mammals [103,119] (Fig. 2). Since AM and AM2 have many effects on the CNS in mammals, AM5, which is a newly discovered 50-amino acid peptide identical to fish AM5, may also have similar actions on the CNS through the CLR/CTR–RAMPs complexes. We showed that centrally administered AM5 induced the expression of c-*fos* gene in the SON and the PVN, and this induction was significantly reduced, incomplete, by pretreatment with both the CGRP and AM receptor antagonists [120]. Therefore, we presume that central AM5 activates OXT-secreting neurons in the SON and the PVN partly through the CGRP and/or AM receptor. Further study is required to explore the possibility that unknown specific receptors for AM5 and/or AM2 may exist in the CNS.

What is the relationship between AM family and OXT? We showed that coexistence of AM- and OXT-LI was identified in the SON and PVN in rats [121]. Although we don't know whether other AMs would be co-existed with OXT, we suggested that AM family might play a role as autocrine/paracrine functions. Further study is required to explore the relationship between AM family and OXT functions.

4.2. Apelin

Apelin, a 36-amino acid peptide, originally has been isolated from bovine stomach tissue extracts as the endogenous ligand of the human orphan G protein-coupled receptor APJ [122,123]. APJ is now therefore commonly referred to as the apelin receptor [124]. Apelin and its receptor are widely distributed throughout the rat nervous system [125–132] and are particularly strongly expressed in the SON and PVN [126–129]. Both AVP and OXT neurons produce apelin

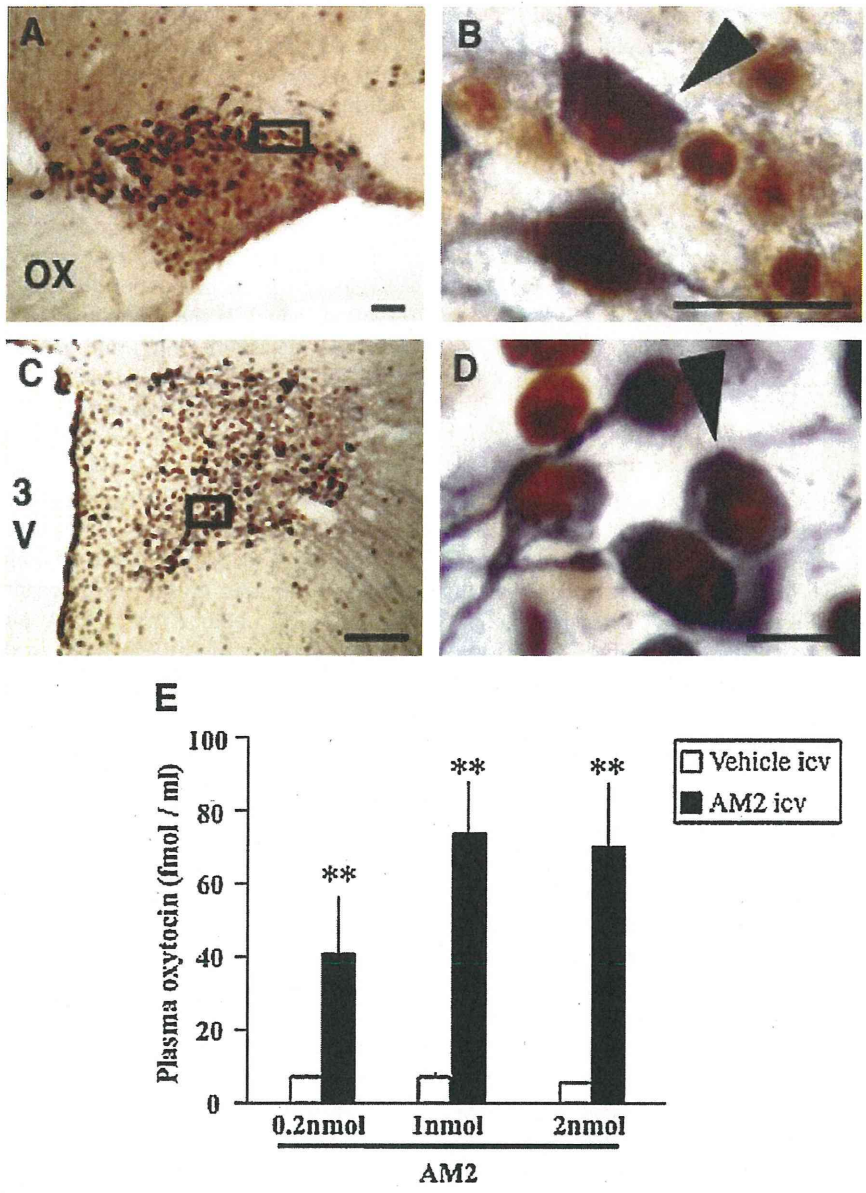

Fig. 3. Central effects of adrenomedullin 2 (AM2) in the OXT release.A–D: Coexistence of Fos-like immunoreactivity (LI) and OXT-LI in the supraoptic nucleus (SON; A and B) and the paraventricular nucleus (PVN; C and D) of rats 90 min after icv administration of AM2 (2 nmol/rat). A and C: Coexistence of Fos-LI (brown, in round structures) and OXT-LI (violet, in spindle-shaped structures). B and D: Enlargements from the boxed areas in A and C. Black arrowheads indicate coexistence of nuclear Fos-LI and OXT-LI. White arrowheads indicate OXT-LI without Fos-LI. 3V, third ventricle; OX, optic chiasma. Bars indicate 50 μm. E: Effects of icv administration of AM2 (0.2, 1, and 2 nmol/rat) or saline (vehicle) on plasma concentrations of oxytocin in conscious rats. All rats were decapitated 30 min after icv administration of the AM2 (0.2, 1, and 2 nmol/rat) or vehicle. Data for plasma concentrations of OXT are expressed as means ± SE ($n = 6$ rats). $^{**}P < 0.01$ compared with vehicle-administered rats. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
Modified with permission from Figs. 1 and 2 in ref. [110].

receptor mRNA in the SON in rats [127,133]. In immunohistochemistry study, OXT neurons contain apelin in the SON and PVN in male and virgin female rats [134]. APJ immunoreactivity cell were also seen in the somata, dendrites, axon fibers, the ventral glial lamina, and axon terminals of magnocellular OXT and AVP neurons [135]. Apelin-13 increased the firing rates of AVP cells but had no effect on the firing rate of OXT neurons in extracellular electrophysiological recordings from the transpharyngeally exposed SON of urethane-anaesthetized rats [135].

Recently, Bodineau et al. showed that apelin modulated the activity of magnocellular and parvocellular OXT neurons in the lactating rat [136]. They revealed that the colocalization of apelin with OXT in about 20% of the hypothalamic

OXT neurons by double immunofluorescence study. They also showed that icv administered apelin inhibited the activity of magnocellular and parvocellular OXT neurons by immunohistochemistry for c-*fos* and electrophysiological study. These central effects of apelin were correlated with a decrease in the amount of milk ejected. Thus, apelin may inhibit the activity of OXT neurons through a direct action on apelin receptors expressed by these neurons in an autocrine and paracrine manner. They suggested that the inhibitory role of apelin as an autocrine/paracrine peptide acting on OXT neurons during breastfeeding [136].

4.3. Cholecystokinin (CCK)

CCK is regarded as an important physiological satiety signal [137]. The pathway from CCK to OXT release has been well investigated. Previous studies have shown that peripheral administration of CCK-8 stimulated secretion of OXT but not AVP and inhibited feeding [138–141]. Otsuka Long-Evans Tokushima Fatty (OLETF) rats have been established as an animal model of non-insulin dependent diabetes mellitus and obesity [142,143], has a congenital defect in the expression of the CCK-A receptor gene [144]. We showed that peripheral administration of CCK-8 does not activate hypothalamic OXT neurons and the brainstem neurons in the nucleus of the solitary tract (NTS) and the area postrema (AP) in OLETF rats [145]. We suggested that systemic administration of CCK-8 might selectively activate the hypothalamic OXT neurons and brainstem neurons through CCK-A receptor in rats. OXT release induced by peripheral administration of CCK-8 was abolished by subdiaphragmatic vagotomy and chemical destruction of vagal afferents [146,147], and also by administration of the selective CCK-A receptor antagonist, but not by the CCK-B receptor antagonist [148]. Moreover, systemic administration of CCK stimulates gastric vagal afferents via CCK-A receptor and activates noradrenergic neurons in the NTS [149]. It is postulated that these noradrenergic inputs activate magnocellular OXT neurons in the SON and the PVN and cause secretion of OXT into the systemic circulation in rats [150,151]. In addition, selective gastric vagotomy eliminates the OXT response to CCK, and lesions of the NTS abolish the behavioral effects of CCK-8 on food intake [148,152]. Therefore, CCK-A receptors in the stomach are stimulated, the abdominal vagus nerve is activated, NA neurons in the A2 region of the NTS are excited, and NA is released in the hypothalamus, which activates magnocellular OXT neurons [153–155].

In addition to the A2 NA neurons [156], NA neurons in the medullary ventrolateral A1 region also play an important role in OXT secretion after stressful stimuli such as noxious stimuli [157]. It is unlikely that OXT in the peripheral blood controls feeding directly. At the time when OXT release from the posterior pituitary is promoted, OXT release within the hypothalamus was increased, and OXT in the CNS induced to inhibit feeding [82]. Icv administration of an OXT receptor antagonist attenuates feeding reduction in response to LiCl or CCK [158,159] and blocked feeding reduction in response to CRH [160]. These studies suggest that intrinsic OXT may play an important physiological role in inhibition of feeding during satiety and stress.

4.4. Kisspeptin

Kisspeptin, a placental polypeptide secreted throughout pregnancy, is suggested to play a role at parturition. Kisspeptin is the product of the *kiss1* gene and its receptor, GPR54, which is the product of *kiss1r*. Kisspeptin stimulate the release of GnRH and gonadotrophin and advance vaginal opening in rodents, sheep and primates [161–166]. Kisspeptin is found in both the periphery and the CNS. In the periphery, kisspeptin has been identified in the testis, ovary, anterior pituitary gonadotrophs, pancreas and small intestine [167–169]. However, peripheral expression of kisspeptin is highest in the placenta with maternal plasma levels of kisspeptin in the third trimester of pregnancy rising to 7000-fold greater than in the non-pregnant state [167,170,171]. In the CNS, both *Kiss1* mRNA and kisspeptin protein are particularly highly expressed in the Arc, anteroventral periventricular nucleus (AVPV) and periventricular nucleus [162] in the mice. In primates including humans, hypothalamic *KISS1* mRNA is predominantly found within the infundibular nucleus, which is the equivalent of the Arc in this order of mammals [172].

Previous studies showed that intravenous (iv) administered kisspeptine-10 increased plasma OXT level in female rats [173], whereas icv administered kisspeptin-10 increased plasma AVP level in male rats [174]. Recently, in vivo extracellular single unit recording, peripheral administered kisspeptin increased plasma OXT level and icv administered kisspeptin-10 increases AVP levels [175]. Iv administered kisspeptin-10 significantly increased the firing rate of OXT neurons from 3.7 ± 0.8 to 4.7 ± 0.8 spikes/s, but only a quarter of AVP neurons responded to iv administered kisspeptin-10, showing a short (<3 s) high-frequency (>15 spikes/s) burst of firing. By contrast, icv administered kisspeptin-10 (2 and 40 μg) did not alter OXT or AVP neuron firing rate. This effect of peripheral administered kisspeptin-10 in OXT neurons on firing rate blocked by pretreatment of capsaicin which desensitize vagal afferents. Kisspeptin may activate on magnocellular neuron via the vagus, and presumably NTS during pregnancy and lactation, when circulating kisspeptin levels are increased.

4.5. Nesfatin-1

Nesfatin-1 is a recently discovered, 82-amino acid protein derived from the cleavage of a precursor, NEFA/nucleobindin2 (NUCB2) [176]. Nesfatin-1 is produced in several hypothalamic nuclei, such as the SON, PVN, arcuate nucleus (Arc), and lateral hypothalamic area (LHA) [176], and in extra-hypothalamic areas as well, including the raphe pallidus, the Edinger–Westphal nucleus, and the NTS