Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : May 23, 2023
Accepted : August 15, 2023
Published online : September 30, 2023
doi:10.24659/gsr.10.3_89

Review article

Life Events and Oxytocin -Recent Topics-

Yu Oshima, Yasuhiko Yamamoto

Department of Biochemistry and Molecular Vascular Biology,
Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Abstract

Oxytocin is a peptide hormone secreted into the blood from the posterior pituitary gland. Oxytocin's biosynthesis, receptors, and functions have been studied extensively, and in recent years, in addition to its typical roles in uterine contraction and ejaculation, its influence on social behaviors and anti-inflammatory effects have attracted attention. For oxytocin to influence social behaviors, oxytocin in the blood must cross the blood-brain barrier. The receptor for advanced glycation end-products (RAGE) has been found to act as a transporter to transfer it into the brain. Elucidation of the molecular mechanism of oxytocin's impact on social behaviors of affection and trust formation has the potential to help address recent problems, *i.e.*, child abandonment and maltreatment. Oxytocin can be a hormone that plays an important role in life events.

***KEY WORDS*:** oxytocin, social behaviors, inflammation, RAGE (receptor for advanced glycation end-products)

1. Oxytocin overview

In 1906, Henry H. Dale found that an extract of the posterior pituitary gland had uterine contraction effects, leading to the discovery of the peptide hormone oxytocin (hereafter OT)[1]. In 1953, Vincent de Vigneaud et al. in the U.S. discovered a peptide consisting of nine amino acids, where the first and sixth amino acids are cysteine (Cys) and form a cyclic structure by disulfide (S-S) bonding, and the seventh to ninth amino acids were found to be side-chained[2]. In 1954, he succeeded in the artificial synthesis of OT, for which Vincent de Vigneaud was awarded the Nobel Prize in Chemistry in 1955. The OT gene is located on human chromosome 20 (2 for mouse) and consists of three exons and two introns.

The arginine vasopressin (AVP) and OT genes are located at the same locus on the same chromosome, back-to-back across about 10 kb, and OT is first synthesized from the OT gene as an inactive precursor protein (prohormone containing neurophysin I, an OT carrier protein) (***Fig. 1***). It is then hydrolyzed stepwise via a series of enzymes to smaller fragments, one of which is neurophysin I; the final hydrolytic enzyme that forms the primary structure of OT is peptidylglycine α-amidating monooxygenase (PAM)[3]. PAM is a two-headed enzyme consisting of a PHM (peptidylglycine-hydroxylating monooxygenase) domain and a PAL (peptidylamidoglycolate lyase) domain. OT has the biological activity by amidation of the C-terminus of glycine, which enables it to bind to the OT receptor[4]. Besides OT, the C-terminal amide structures required for the active expression of about half of the biologically active peptides are generated by the catalytic action of the enzyme PAM.

After secretion, OT is known to be degraded by oxytocinase and leucyl/cystinyl aminopeptidase[5]. Morphological studies of peptides in the nervous system have a history of multi-stage progression.

In 1928, Ernst Scharrer discovered the presence of relatively large neurons at the base of the brain with long axonal projections to the neurohypophysis and contact with capillaries in fish, first suggesting that neurosecretory neurons located in the hypothalamus may play an endocrine role in cooperation with the pituitary gland[6].

Since then, numerous studies have put forth the concept of neurosecretion; OT is synthesized within the large neurosecretory neurons in the hypothalamic nucleus, mainly paraventricular hypothalamic nucleus (PVN) and supraoptic nucleus (SON), packaged as secretory granules in the endoplasmic reticulum, moving towards the axon terminal that projects to the posterior pituitary while being processed, and consequently released by exocytosis into the blood in an

Correspondence to: Yasuhiko Yamamoto, MD, PhD.
Department of Biochemistry and Molecular Vascular Biology,
Kanazawa University Graduate School of Medical Sciences
13-1 Takara-machi, Kanazawa 920-8640, Japan
TEL: +81-76-265-2181 FAX: +81-76-234-4217
e-mail: yasuyama@med.kanazawa-u.ac.jp
Co-author: Oshima Y, cantabile.6102@gmail.com

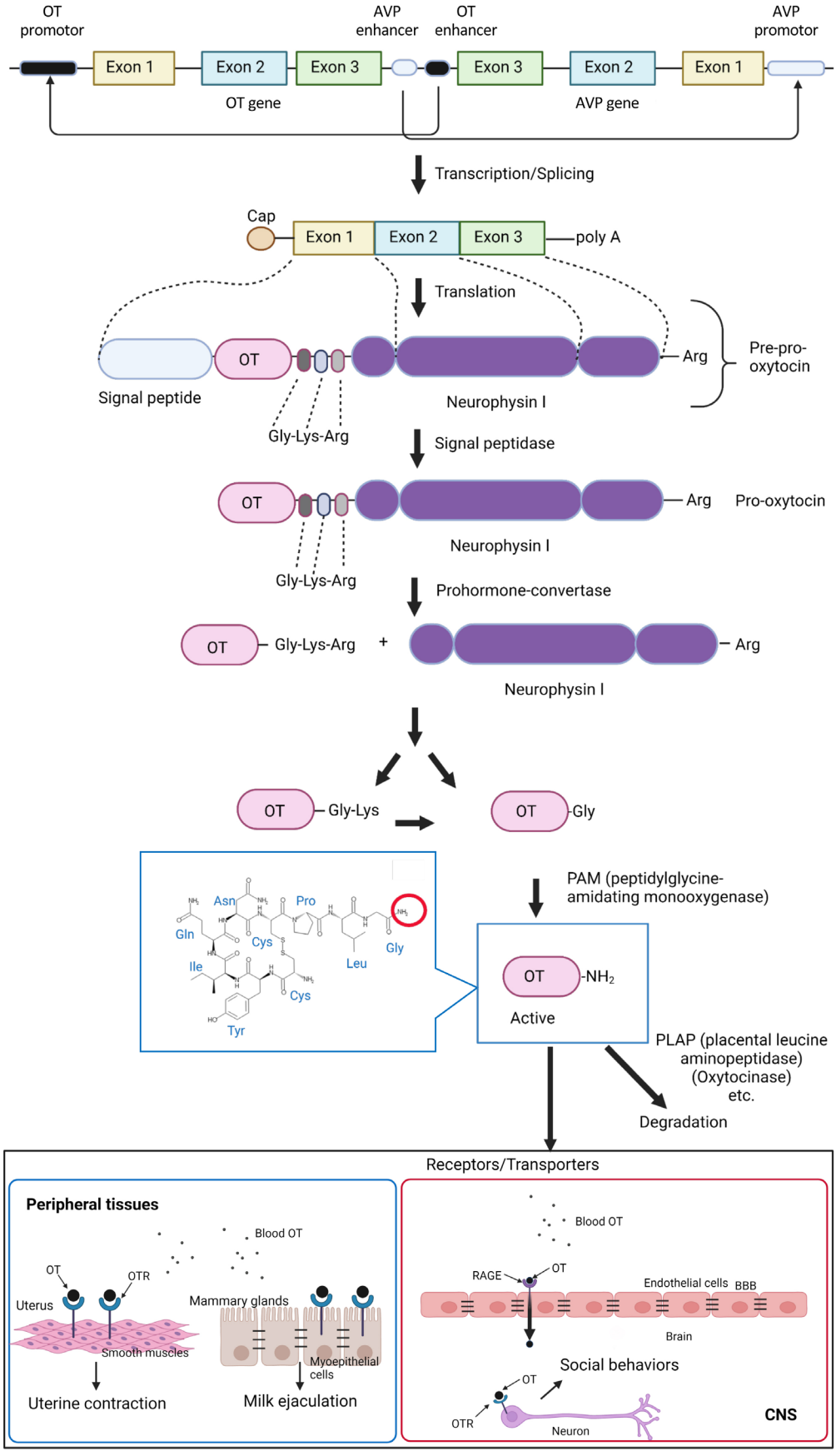

Fig. 1. **Schematic representation of the synthesis and actions of oxytocin.**

AVP, arginine vasopressin; BBB, blood-brain barrier; CNS, central nervous system; OT, oxytocin; OTR, oxytocin receptor; RAGE, receptor for advanced glycation end-products.

action potential-dependent manner. OT is also secreted into the brain from neuronal dendrites and neurosecretory cells.

The following items (1) to (5) are generally known for the functions of OT.

(1) In the last trimester, OT has a uterine contraction effect for delivery.
(2) OT has the promotion effect of lactation from mammary glands during breastfeeding (ejaculation).
(3) OT influences social behaviors, especially "all human interactions based on trust" through the "social brain" region including the amygdala, and is involved in the formation of affection and trust.

There is a known study in which 194 healthy male students at the Swiss Institute of Technology were divided into OT administration groups with nasal drops and placebo administration groups, and neuroeconomic experiments were conducted in both groups based on game theory [7-8]. In the game, when subjects were divided into investors who have money and trustees who manage money and receive refunds with different profit rates, it was examined if the OT-treated group would become attached to the other party and increase their trust and confidence. In the result, there was a tendency to deposit nearly the entire amount of money in investment in the OT-treated group. In addition, mothers who have experienced abuse were found to have lower blood OT concentrations than mothers who have not experienced abuse [9]. Moreover, in autistic patients, the blood OT concentration was also found to be low [10]. When a man diagnosed with autism was given OT nasal spray (16 IU a day), he stared at the examiner's face, occasionally smiled, and answered correctly to simple questions. A case is also reported to be able to answer multiple-choice questions [11].

(4) Possible effects of OT on sleep.

In clinical trials using OT, a certain level of effect was observed in patients with sleep apnea syndrome after nasal OT administration (40 IU) [12]. When the blood OT level was examined to be correlated with the quality of sleep, the OT level was found to have a certain correlation with the degree of sleep disturbance in patients with Human Immunodeficiency Virus (HIV) infection and cancer patients [13,14]. However, clinical application is still far away and further investigation is required.

(5) Anti-inflammatory action of OT.

Anti-inflammatory effects of OT have been reported in animal disease models and human patient studies, including cardiovascular, gastrointestinal, endocrine, genitourinary, and brain diseases. Examples are as follows.

OT receptors are reported to express on numerous types of immune cells, such as neutrophils, macrophages, and lymphocytes, and may play an important role in immunological surveillance, defense, and homeostasis [15]. OT was found to decrease IL-6 release, increase prostacyclin release, and inhibit platelet aggregation [16]. Additionally, by increasing nitric oxide synthase (eNOS) activity in platelets and endothelial cells, OT may inhibit sepsis-induced contact between neutrophils and endothelial cells and may play a role in maintaining microvascular patency in septic shock [17].

In macrophages, expression of the OT receptor gene increased during inflammation. This was mediated by the transcription factor nuclear factor-kappa B (NF-κB) [18,19]. OT prevented macrophages from transforming into active inflammatory cells by enhancing the expression of beta arrestin 2 (macrophage polarizing), a multifunctional scaffold that regulates G protein-coupled receptors (GPCRs).

OT also stimulated phosphorylation (or activation) of signal transducers and activator of transcription (STAT) 6 as well as suppression of NF-κB signaling in lipopolysaccharide (LPS)-stimulated macrophages [20]. As a result, the release of tumor necrosis factor (TNF)-α and other proinflammatory cytokines from macrophages was inhibited by the binding of OT to the OT receptor [21].

Furthermore, OT has been shown to upregulate the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), a potent transcription factor that suppresses inflammatory responses in macrophages [17,22]. This suggests that OT may act via PPAR-γ to modulate inflammation [21]. OT may also exert its anti-inflammatory effects by reducing the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and p38 mitogen-activated protein kinase (MAPK) [23,24]. In addition, OT was involved in self-tolerance by T cells; OT receptors were found on progenitor T cells in the thymus, and binding to OT regulated lymphocyte maturation, differentiation, and survival [25]. Once lymphocytes were exposed to antigen, OT stimulated lymphocyte proliferation by increasing the expression of IL-2R (CD25 chain) and the activation marker CD95 [26]. As described above, the anti-inflammatory action of OT has been understood thus far.

2. OT and RAGE (receptor for advanced glycation end-products)

It has been the prevailing belief that OT released into the blood does not cross the blood-brain barrier (BBB) due to its molecular size and hydrophilic characteristics. However, RAGE on the surface of cerebral vascular endothelial cells, which constitute the BBB, has been shown to allow OT to cross the BBB and be transported from the blood side to the brain side [27]. In other words, RAGE was found to function as a transporter of OT that unidirectionally transports OT from the blood to the brain side. However, this function does not require intracellular signaling of RAGE, and the binding of OT to RAGE does not affect the binding of various RAGE ligands to RAGE and their subsequent intracellular signaling (*Fig. 2*).

OT transferred into the brain in this way is thought to play an important role in maternal behavior, nurturing activities, and social behavior in the parent-child relationship [28-30]. OT is thus known as an affection hormone. In general, pregnant mice give birth to 6 to 10 offspring at a once, and the offspring grows up after drinking their mother's milk. However, when RAGE of the BBB in the mother was deficient, OT actions to the brain seemed to disappear, and only 10% of the babies survived [28]. Though no effects were observed in the mother's milk production, this phenomenon was caused by the dam's lack of concern in parenting. Vascular endothelial cells of the BBB consistently express RAGE, which mediates the transfer of OT into the brain. The binding site of OT on RAGE is different from that of other ligands including AGEs. OT bound to RAGE could pass through the BBB and enter the brain to exert "affection" [30].

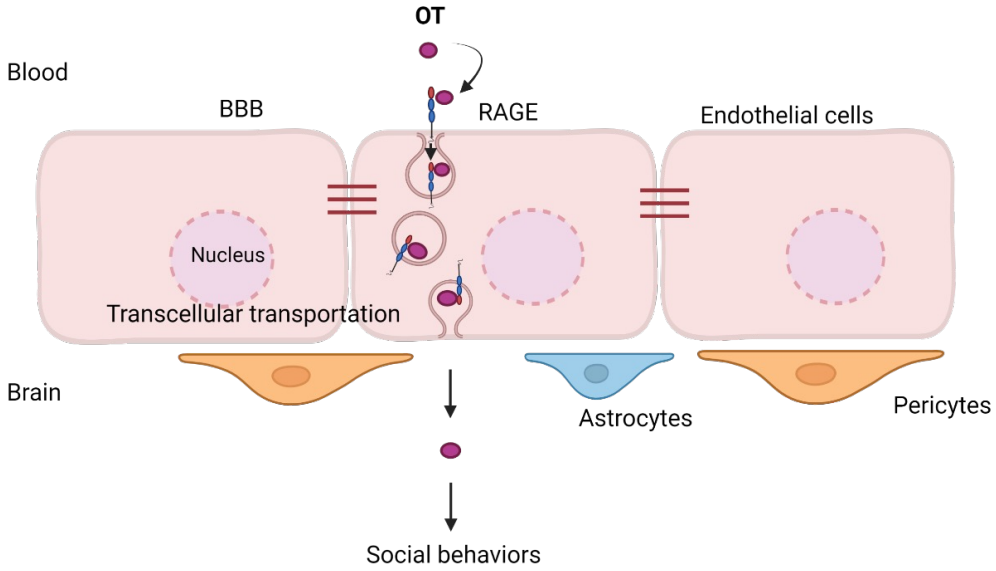

Fig. 2. **RAGE-dependent OT transport from the blood side to the brain side through BBB.**

The binding of OT to RAGE does not induce RAGE intracellular signal transductions. BBB, blood-brain barrier; OT, oxytocin; RAGE, receptor of advanced glycation end-products.

It is very fundamental and physiological function in mother-baby bonding. This may provide clues to solving social problems such as childcare abandonment and child abuse, which are becoming increasingly serious in this era of declining birthrates, and future developments are expected.

The following is a brief explanation of RAGE.

Glycosylation is a reaction that adds sugar chains to proteins or lipids and is an important post-translational modification. Glycosylation is known as an enzyme-controlled reaction. On the other hand, glycation, discovered by Maillard in 1912, is a complex reaction involving dehydration, condensation, cross-linking, etc., which eventually results in irreversible and heterogeneous products called advanced glycation end-products (AGEs). RAGE is a receptor for AGEs. RAGE belongs to the immunoglobulin superfamily of cell surface molecules and is composed of one V domain and two C domains [31].

RAGE is expressed on a variety of cells, including vascular endothelial cells, neutrophils, monocytes/macrophages, and neurons [32]. Numerous other ligands for RAGE are now known in addition to AGEs. RAGE is known to be involved in various pathological conditions such as inflammatory reactions in LPS-induced sepsis, the development of diabetic kidney disease and glomerulosclerosis, cerebral ischemic damages, Alzheimer's disease, and tumor progression [30].

On the other hand, RAGE has physiological roles in biological protection in addition to its function in parenting. Specifically, it has been reported that RAGE prevents the spread of pneumococcal infection, reduces adaptive immune responses in limb ischemia, ameliorates renal reperfusion injury by endogenous soluble RAGE, regenerates lung tissue through HMGB-1-dependent epithelial repair, and is involved in the recognition of phosphatidylserine by apoptotic cells during epherocytosis [30].

The fact that RAGE, which has such diverse roles in vivo, functions as a transporter for passage of OT is of great biological interest.

3. Current Topics and Future Possibilities

Our laboratory recently found that OT administration to mouse models of autoimmune diseases could improve their symptoms by inhibiting the pathogenesis of autoimmune diseases and inflammation. OT therapy may have clinical applications as a treatment for autoimmune diseases in the future.

Conflict of Interest Declaration

None applicable to this paper.

Research Funding

Grant-in-Aid for Scientific Research (KAKENHI) from JSPS (24590375, 25461335, 18K06889, 21H02695), Takeda Foundation for Advancement of Science, Life Science Research Grant, Kanazawa University Sakigake Project 2018 & 2020).

Reference

1) Dale HH. On some physiological actions of ergot. *J Physiol*. 1906; 34: 163-206.
2) Du Vigneaud V, Ressler C, Trippett S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. *J Biol Chem*. 1953; 205: 949-957.
3) Sheldrick EL, Flint AP. Post-translational processing of oxytocin-neurophysin prohormone in the ovine corpus luteum: Activity of peptidyl glycine alpha-amidating mono-oxygenase and concentrations of its cofactor, ascorbic acid. *J Endocrinol*. 1989; 122: 313-322.
4) Merkler DJ. C-terminal amidated peptides: Production by the in vitro enzymatic amidation of glycine-extended peptides and the importance of the amide to bioactivity. *Enzyme Microb Technol*. 1994; 16: 450-456.
5) Nomura S, Ito T, Yamamoto E, et al. Gene regulation and physiological function of placental leucine aminopeptidase/oxytocinase during pregnancy. *Biochim Biophys Acta*. 2005; 1751: 19-25.
6) Scharrer E. Die Lichtempfindlichkeit blinder Elritzen. I. Untersuchungen fiber das Zwischenhirn der Fische. *Z Vergl Physiol*. 1928; 7: 1-38. (in German)
7) Kosfeld M, Heinrichs M, Zak PJ, et al. Oxytocin increases trust in humans. *Nature*. 2005; 435: 673-676.
8) Zak PJ. The neurobiology of trust. *Sci Am*. 2008; 298: 88-92, 95.
9) Heim C, Young L J, Newport DJ, et al. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry*. 2009; 14: 954-958.
10) Modahl C, Green L, Fein D, et al. Plasma oxytocin levels in autistic children. *Biol Psychiatry*. 1998; 43: 270-277.
11) Munesue T, Yokoyama S, Nakamura K, et al. Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. *Neurosci Res*. 2010; 67: 181-191.
12) Raymond JS, Rehn S, Hoyos CM, et al. The influence of oxytocin-based interventions on sleep-wake and sleep-related behaviour and neurobiology: A systematic review of preclinical and clinical studies. *Neurosci Biobehav Rev*. 2021; 131: 1005-1026.
13) Fekete EM, Seay J, Antoni MH, et al. Oxytocin, social support, and sleep quality in low-income minority women living with HIV. *Behav Sleep Med*. 2014; 12: 207-221.
14) Lipschitz DL, Kuhn R, Kinney AY, et al. An exploratory study of the effects of mind-body interventions targeting sleep on salivary oxytocin levels in cancer survivors. *Integr Cancer Ther*. 2015; 14: 366-380.
15) Li T, Wang P, Wang SC, et al. Approaches mediating oxytocin regulation of the immune system. *Front Immunol*. 2017; 7: 693.
16) Wang SC, Wang YF. Cardiovascular protective properties of oxytocin against COVID-19. *Life Sci*. 2021; 270: 119130.
17) Khan R, Kirschenbaum LA, LaRow C, et al. Augmentation of platelet and endothelial cell eNOS activity decreases sepsis-related neutrophil-endothelial cell interactions. *Shock*. 2010; 33: 242-246.
18) Tang Y, Shi Y, Gao Y, et al. Oxytocin system alleviates intestinal inflammation by regulating macrophages polarization in experimental colitis. *Clin Sci* (*Lond*). 2019; 133: 1977-1992.
19) Albensi BC. What is Nuclear Factor Kappa B (NF-ϰb) doing in and to the mitochondrion? Front Cell Dev Biol. 2019; 7: 154.
20) Szeto A, Sun-Suslow N, Mendez AJ, et al. Regulation of the macrophage oxytocin receptor in response to inflammation. *Am J Physiol Endocrinol Metab*. 2017; 312: E183-E189.
21) Buemann B, Marazziti D, Uvnäs-Moberg K. Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? World J Biol Psychiatry. 2021: 22: 387-398.
22) Huang S, Zhu B, Cheon IS, et al. PPAR-g in Macrophages limits pulmonary inflammation and promotes host recovery following respiratory viral infection. *J Virol*. 2019; 93: e00030-19.
23) Rashed LA, Hashem RM, Soliman HM. Oxytocin inhibits NADPH oxidase and P38 MAPK in cisplatin-induced nephrotoxicity. *Biomed Pharmacother*. 2011; 65: 474-480.
24) Szeto A, Nation DA, Mendez AJ, et al. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. *Am J Physiol Endocrinol Metab*. 2008; 295: E1495-E1501.
25) Hansenne I, Rasier G, Péqueux C, et al. Ontogenesis and functional aspects of oxytocin and vasopressin gene expression in the thymus network. *J Neuroimmunol*. 2005; 158: 67-75.
26) Macciò A, Madeddu C, Chessa P, et al. Oxytocin both increases proliferative response of peripheral blood lymphomonocytes to phytohemagglutinin and reverses immunosuppressive estrogen activity. *In Vivo*. 2010; 24: 157-163.
27) Higashida H, Furuhara, K, Lopatina O, et al. Oxytocin dynamics in the body and brain regulated by the receptor for advanced glycation end-products, CD38, CD157, and nicotinamide riboside. *Front Neurosci*. 2022; 16: 858070.
28) Yamamoto Y, Liang M, Munesue S, et al. Vascular RAGE transports oxytocin into the brain to elicit its maternal bonding behaviour in mice. *Commun Biol*. 2019; 2: 76.
29) Yamamoto Y, Higashida H. RAGE regulates oxytocin transport into the brain. *Commun Biol*. 2020; 3: 70.
30) Oshima Y, Higashida H, Yamamoto Y, et al. Dual nature of RAGE in host reaction and nurturing the mother-infant bond. *Int J Mol Sci*. 2022; 23: 2086.
31) Neeper M, Schmidt AM, Brett J, et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J Biol Chem*. 1992; 267: 14998-15004.
32) Brett J, Schmidt AM, Yan SD, et al. Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *Am J Pathol*. 1993; 143: 1699-1712.