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Specialty section:

This article was submitted to
Neuroendocrine Science,
a section of the journal
Frontiers in Neuroscience

Received: 19 January 2022

Accepted: 31 May 2022

Published: 07 July 2022

Citation:

Higashida H, Furuwara K,
Lopatina O, Gerasimenko M, Hori O,
Hattori T, Hayashi Y, Cherepanov SM,
Shabalova AA, Salmina AB,
Minami K, Yui T, Tsuji C, Fu P, Liu Z,
Luo S, Zhang A, Yokoyama S,
Shuto S, Watanabe M, Fujiwara K,
Munesue S-i, Harashima A and
Yamamoto Y (2022) Oxytocin
Dynamics in the Body and Brain
Regulated by the Receptor
for Advanced Glycation
End-Products, CD38, CD157,
and Nicotinamide Riboside.
Front. Neurosci. 16:858070.
doi: 10.3389/fnins.2022.858070

Oxytocin Dynamics in the Body and Brain Regulated by the Receptor for Advanced Glycation End-Products, CD38, CD157, and Nicotinamide Riboside

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Investigating the neurocircuit and synaptic sites of action of oxytocin (OT) in the brain is critical to the role of OT in social memory and behavior. To the same degree, it is important to understand how OT is transported to the brain from the peripheral circulation. To date, of these, many studies provide evidence that CD38, CD157, and receptor for advanced glycation end-products (RAGE) act as regulators of OT concentrations in the brain and blood. It has been shown that RAGE facilitates the uptake of OT in mother's milk from the digestive tract to the cell surface of intestinal epithelial cells to the body fluid and subsequently into circulation in male mice. RAGE has been shown to recruit circulatory OT into the brain from blood at the endothelial cell surface of neurovascular units. Therefore, it can be said that extracellular OT concentrations in the brain (hypothalamus) could be determined by the transport of OT by RAGE from the circulation and release of OT from oxytocinergic neurons by CD38 and CD157 in mice. In addition, it has recently been found that gavage application of a precursor of nicotinamide adenine dinucleotide, nicotinamide riboside, for 12 days can increase brain OT in mice. Here, we review the evaluation of the new concept that RAGE is involved in the regulation of OT dynamics at the interface between the brain, blood, and intestine in the living body, mainly by summarizing our recent results due to the limited number of publications on related topics. And we also review other possible routes of OT recruitment to the brain.

Keywords: oxytocin, RAGE, transport, endothelial cells, CD38

INTRODUCTION

It has been established that OT is not only secreted from the posterior pituitary into the circulation but is also released in the brain, where it has very diverse behavioral effects (Russell et al., 2003; Leng et al., 2015; Higashida, 2016; Russell, 2018). Hypothalamic neurons secrete oxytocin (OT) into the brain from dendrites and axons to function as an endogenous factor in species-specific social memory and behaviors, including emotion, interaction, and bonds (Baumgartner et al., 2008; Bridges, 2015; Huang et al., 2015; Numan and Young, 2016; Feldman, 2017; Higashida et al., 2018, 2019a,b; Jurek and Neumann, 2018; Borowiak and von Kriegstein, 2020; Carter et al., 2020; Quintana and Guastella, 2020; Tolomeo et al., 2020; Froemke and Young, 2021; Grinevich and Neumann, 2021; Yeomans et al., 2021; Zheng and Kendrick, 2021; Carter, 2022). CD38 and CD157 play an essential role in central OT release (Jin et al., 2007; Higashida et al., 2017b). The two molecules are related cell-surface antigens that produce cyclic ADP-ribose (cADPR), a calcium-mobilizing second messenger, from the substrate nicotinamide adenine dinucleotide (NAD; Lee and Zhao, 2019; Chini et al., 2020, 2021). cADPR functions as the potential intracellular second messenger that triggers Ca^{2+} mobilization from ryanodine receptor Ca^{2+} pools to produce cellular responses (Lee and Zhao, 2019; Avraham et al., 2021; Okamoto and Takasawa, 2021). In the hypothalamus, cADPR activates the elevation of intracellular free Ca^{2+} concentrations and subsequently elicits Ca^{2+} -dependent OT release from oxytocinergic neurons (Jin et al., 2007; Higashida et al., 2011). When this signaling pathway is prevented in CD38 knockout (CD38KO) mice, social memory and recognition or parental nurturing behavior are disrupted mainly owing to reduced OT release (Jin et al., 2007). Localized re-expression of human CD38 in the hypothalamus or simple subcutaneous administration of OT in CD38KO mice confirms the importance of CD38 and OT in social behavior (Chong et al., 2017). The phenotypes of CD157KO and CD38KO mice in social behavior are partly shared, but the significant differences are anxiety- and depression-like behaviors. In addition, CD157KO mice showed social avoidance as a substantial impairment.

A single nasal administration of OT, as an exogenous factor, in healthy humans showed increased social attention and interaction (Veening and Olivier, 2013; Quintana et al., 2018; Tanaka et al., 2018; Kurokawa et al., 2021, 2020) and in subjects with social behavioral deficits who suffer from autism spectrum disorders and schizophrenia (Munesue et al., 2016, 2010; Okamoto et al., 2016; Quintana et al., 2017; Higashida et al., 2019b; Huang et al., 2021). During this process, peripheral OT is assumed to reach the brain *via* the nasal-to-brain or blood-to-brain routes (Quintana et al., 2018, 2017; Lee and Jayant, 2019; Martins et al., 2020; Grinevich and Neumann, 2021; Yeomans et al., 2021). Plasma OT, however, is assumed to not cross the blood-brain barrier (BBB) because hydrophilic OT is larger than 1,000 Da in its molecular weight (Avraham et al., 2021). However, there was evidence that OT can pass through the BBB in rodent studies (Jin et al., 2007; Neumann et al., 2013), in that after subcutaneous and intraperitoneal injection of OT, OT concentrations in the cerebrospinal fluid (CSF) increase

(Jin et al., 2007; Yamamoto et al., 2019), as shown in **Figure 1**. In humans, along with the same analogy, it could be speculated that nasal OT permeates into the bloodstream through micro blood vessels, which are very well developed in the nasal mucosal membranes (Beju et al., 2004). OT can subsequently be taken up by the brain from the circulation.

To make the above estimation of brain recruitment of OT through the BBB, molecular mechanisms of entry were strongly expected for a decade. Higashida et al. (2017a) published the first evidence in 2017 that the receptor for advanced glycation end-products (RAGE) is a transporter of OT from the intestinal lumen to the body fluid at the intestinal barrier in male mice. Subsequently, the binding and transport properties of RAGE at the BBB have been shown in 2019 to 2021 by Yamamoto and Higashida (2020), and our other colleagues (Shimizu et al., 2020; Gerasimenko et al., 2021; Leerach et al., 2021; Munesue et al., 2021). Biochemically, the binding between OT and RAGE was demonstrated by the plasmon resonance method (Yamamoto et al., 2019). The transport of OT by RAGE after binding was demonstrated in the *in vitro* BBB system in two chambers, which represent the luminal (blood) and abluminal (brain) sides separated by cultured endothelial cells, astrocytes, and pericytes (Yamamoto et al., 2019). In such a system, RAGE functions as a transporter of OT primarily from the blood to the brain, with approximately 10-fold greater efficiency than in the reverse direction (Yamamoto et al., 2019; Zheng and Kendrick, 2021). Importantly, these data indicate that this transport is unidirectional from the blood to the brain chambers and is in saturation mode. In addition, we calculated the bioavailability of this transfer to be approximately 0.2% in mice. We compare these values with the values described by others (**Table 1**). This type of semi-unidirectional transport of OT was mostly disrupted by knockout (KO) of the mouse gene for RAGE, *Ager*, or knockdown of endothelial RAGE expression by siRNA (Yamamoto et al., 2019). The three forms of RAGE are known as follows: One is full-length RAGE, expressed in the membrane of vascular endothelial cells, membrane-bound RAGE (mRAGE; Mackic et al., 1998; Schmidt et al., 2000; Schmidt and Stern, 2001; Stern D. M. et al., 2002; Stern D. et al., 2002). Second, endogenous secretory RAGE, which is the product of an alternatively spliced mRNA that lacks a membrane-spanning domain and is found in the blood circulation (Yonekura et al., 2003; Harashima et al., 2006). Third, the third form is also soluble RAGE, which is an ectodomain-shedding form (Schmidt and Stern, 2001). It has recently been shown that these soluble forms act as a buffer for OT (Munesue et al., 2021). In addition, concerning intranasal administration of OT, although direct and specific routes have been proposed from the nasal cavity to the human brain (amygdala; Martins et al., 2020), when OT was applied to the nasal cavity in RAGE KO mice, no or little increase in OT was observed in the CSF. This may show that the direct nasal brain route, which has not yet been clearly identified, seems to be sensitive to mRAGE.

Originally, functional roles of advanced glycation end-products (AGEs) and their receptors (RAGE) have been reported in the pathological mechanism (secondary damages) underlying diabetic complications, such as diabetic cardiomyopathy, retinopathy, nephropathy, and intestinal hemorrhage

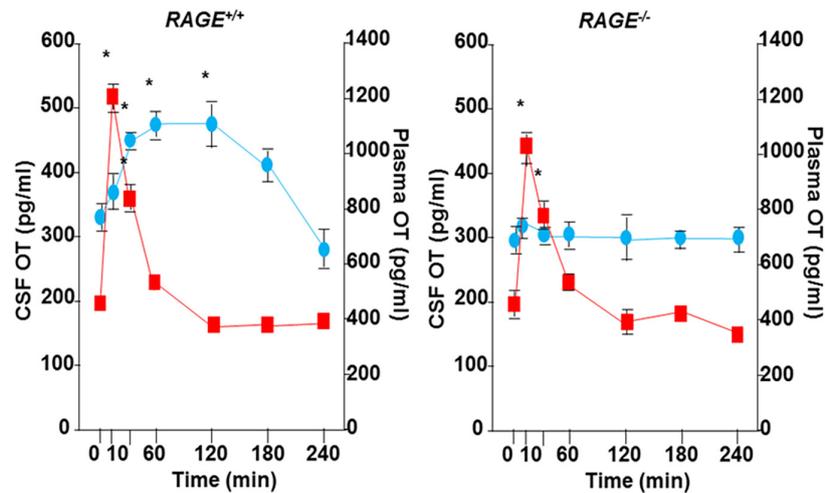


FIGURE 1 | Transportation of peripherally administrated oxytocin (OT) to the brain. Concentrations of OT in plasma (red) and cerebral spinal fluid (CSF) of the cisterna magna (blue) after subcutaneous injection of 30 ng OT (100 ng/mL × 0.3 mL) in wild-type (*RAGE*^{+/+}) or *RAGE* KO (*RAGE*^{-/-}) mice (*n* = 3–16/data point, **P* < 0.05 at time 0). The data shown are modified from Figure 4 of Yamamoto et al. (2019). OT was measured in un-extracted samples.

TABLE 1 | Estimated bioavailability of exogenous oxytocin into the brain.

	Sex	Drug	Dose	Injection	Min	%Availability	Extraction references/Method
Rat	Male	OT	5 μg	s.c.	10	0.02	+/RIA Neumann et al., 2013
Pig	Female	OT	50 μg	i.n.	10	0.001	-/ELISA Striepens et al., 2013
Rat	Male	OT	500 μg	i.n.	10	2	-/LC/MS Tanaka et al., 2018
Mouse	Male	OT	30 ng	i.p.	30	0.2	-/EIA Yamamoto et al., 2019
Mouse	Male	OT*	30 ng	i.p.	30	0.3	+/-LC/MS Yamamoto et al., 2019
Human	Male	OT	50 μg	i.n.	35	0.1	+/-RIA Rault, 2016
Monkey		OT	1 ng	Culture	30	1.2	-/EIA Yamamoto et al., 2019
Monkey		OT	10 ng	Culture	30	0.21	-/EIA Yamamoto et al., 2019

*Oxytocin isoleucine [¹³C, ¹⁵N] OT, as described in Higashida et al. (2017a).

RIA, radio immunoassay; ELISA, enzyme-linked immunosorbent assay; LC/MS, liquid chromatography mass spectroscopy; EIA, enzyme immunoassay; s.c., subcutaneous; i.n. intranasal; i.p., intraperitoneal; and i.v., intravenous.

(Yonekura et al., 2005, 2003; Raman et al., 2006; Yamamoto et al., 2007; Manigrasso et al., 2018). An example is that the expression of AGE and RAGE in the small intestine has been reported in healthy animals, and their expression levels are upregulated in diabetic rodents (Harashima et al., 2006; Hu et al., 2021). Increased expression of AGE and RAGE may contribute to diabetic tissue dysfunction. Therefore, based on the vast number of disease-related publications, it is challenging to speculate productively about the transport function of OT, a peptide hormone.

RAGE is typically involved in remodeling vascular endothelial cells of the retina and kidney as a secondary injury in diabetic pathological conditions (Yamamoto et al., 2001). AGEs are a broad heterogeneous group of compounds formed by non-enzymatic reactions. The accumulation of endogenous and exogenous AGEs has been implicated in the pathogenesis of numerous diseases in humans, such as diabetes (Schmidt et al., 2000; Stern D. M. et al., 2002, Stern D. et al., 2002). RAGE has been studied mainly related to lifestyle illnesses such as metabolic diseases, diabetes, hypertension, and secondary damage to

various organs, including blood vessels (Yonekura et al., 2005). In the neuronal degeneration processes of Alzheimer's disease, RAGE plays a pivotal role in the efflux of amyloid-beta protein from the brain (Mackic et al., 1998). In addition, RAGE has been shown to relate to psychiatric diseases. RAGE- or S100B-involvement in schizophrenia has been reported as a biomarker (Kouidrat et al., 2015). Therefore, not only the transport impairment of OT to the brain but also RAGE levels seem to be associated with ASD (Yamamoto and Higashida, 2020).

Our recent findings on RAGE suggest that RAGE has a new physiological role in the body, especially in the transport of OT, which has not been shown in the RAGE research field. Therefore, it is rational to review the new concept of RAGE- or nicotinamide riboside-dependent regulation of OT transport from the perspective of the dynamics of OT in the body. However, because one limitation is the limited number of articles intensively focused on this topic, to our knowledge, it is necessary to cite papers published by the laboratories of the current authors. Furthermore, we will discuss changes in brain OT concentrations after gavage supplementation of one of NAD precursors in mice,

nicotinamide riboside. This precursor is used in the synthesis of NAD in the salvage pathway.

NAD is synthesized by a salvage pathway of the vitamin precursors, including nicotinic acid, nicotinamide mononucleotide, and nicotinamide riboside, or from tryptophan in the *de novo* pathway (Nikiforov et al., 2015). Thus, the exogenous administration of nicotinamide riboside can increase the synthesis of NAD (Braidly et al., 2019). Concerning the elevation of mouse liver NAD, it is shown that nicotinamide riboside is more available orally than nicotinamide mononucleotide and nicotinic acid. This finding validates nicotinamide riboside's role as a favored NAD precursor (Trammell et al., 2016). Like nicotinic acid and nicotinamide mononucleotide, nicotinamide riboside is a natural product found in milk. It is incorporated into the intracellular NAD pool. Nicotinamide riboside could be used as a general supplement for people who have adverse reactions to nicotinic acid or nicotinamide mononucleotide (Trammell et al., 2016). In brain tissue activity, NAD synthetase is dramatically low, which makes nicotinic acid unsuitable as a supplement in this case (Mori et al., 2014). Nicotinamide riboside has already been used as a supplement or therapeutic agent to elevate or maintain cellular NAD contents (Ear et al., 2019). Recently, it has been shown that NAD is consumed more *via* an increase of CD38 in aged subjects. Thus, inhibition of CD38 or an increase in NAD may lead to a longer life span (Tarragó et al., 2018; Chini et al., 2021), which is another intriguing topic.

OXYTOCIN DYNAMICS IN THE INTESTINE

Oxytocin in Breast Milk

One of OT sources to babies is breastmilk (Takeda et al., 1986; Muranishi et al., 2016; Stevenson et al., 2020). The milk is produced from the mother's general circulation. In our preliminary study of breast milk, OT was approximately 70–120 pg/ml in three lactating human mothers [postpartum days (PPDs) 1–5; Yamamoto and Higashida, unpublished data]. Our values are higher than those of a previous study [approximately 10 pg/ml, (Takeda et al., 1986)], probably due to the different methods used.

The transfer of OT from circulation to milk is regulated by the so-called blood-milk barrier (Nielsen et al., 2020; Strasser et al., 2021; Wellnitz and Bruckmaier, 2021), which is rather leaky compared to the BBB but retains selectivity, especially in bacteria and immunological molecules in humans (Nielsen et al., 2020). The permeability of OT changes under different conditions in dairy cows (Strasser et al., 2021). It would be interesting to examine whether RAGE functions at this blood-milk barrier.

Absorption of Oxytocin in the Digestive System

In mouse infants, plasma OT originates from the secretion of the posterior lobe of the pituitary gland into the circulation and from the absorption of OT in the mother's milk into

the blood through intestinal permeability (Higashida et al., 2017a). The molecular mechanism underlying the absorption of orally administered OT across the intestinal epithelial barrier in infants revealed that RAGE mediates intestinal OT transmission (Higashida et al., 2017a).

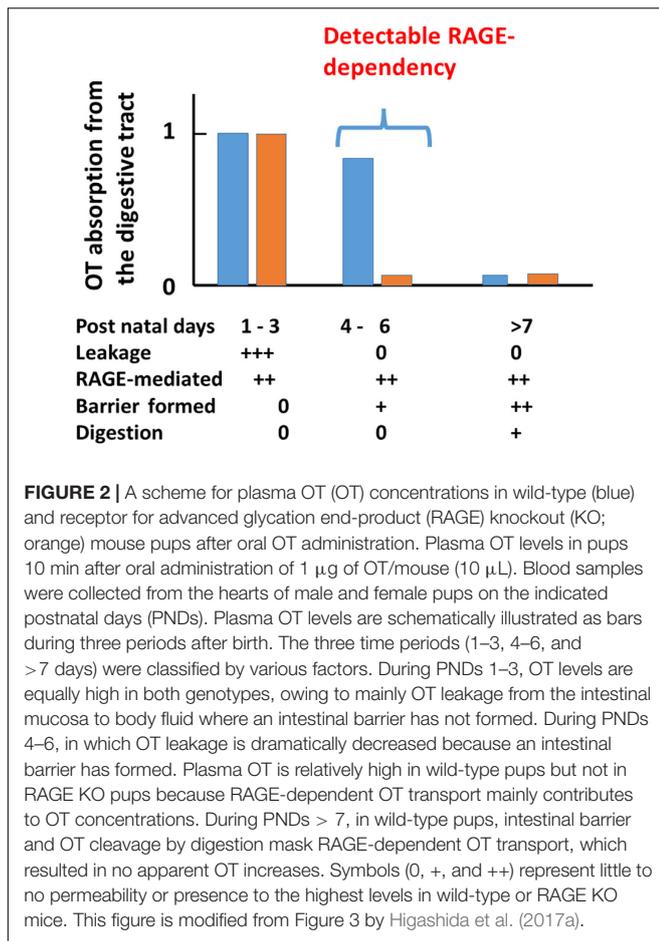
OT with nine amino acids is digested by intestinal peptidases but is relatively stable in gastric acid in humans (Takeda et al., 1986; Roca Rubio et al., 2021). OT in early life plays a role in the development of the social brain and in establishing social behavior in adults in humans and rodents (Higashida et al., 2011; Guastella et al., 2018; Carter et al., 2020). Therefore, breast milk not only feeds beneficial microbes and provides immunity but also appears to aid well-being by improving human communication (Lakkireddy et al., 2016; Krol and Grossmann, 2018; Chastant and Mila, 2019; Froemke and Young, 2021; Noel et al., 2021). OT in breast milk can be absorbed intact from the digestive tract into the blood of human neonates (Takeda et al., 1986). OT absorption is a RAGE-mediated process after the onset of gut closure in mice, as reported by Higashida et al. (2017a).

Plasma Oxytocin Levels After Oral Delivery in Young and Adult Mice

The possibility of transport can be examined with plasma OT levels at 10 min after oral delivery of 10 μ L synthetic OT solution (200 ng/pup) and compared with those after the same volume of saline to mouse pups after starvation for 30 min during the development period of suckling (from PND 1 to PND 15; Higashida et al., 2017a). Plasma OT concentrations were markedly higher in neonates to 5-old day pups (PND 1–5) and suddenly dropped at PND 6 in wild-type pups (**Figure 2**). This finding resembled the results of insulin-like growth factor 1 in suckling piglets (Xu and Wang, 1996). These increases are largely due to leakage from the intestine to body fluid before intestinal barrier formation during PND 1–3 in both genders (Camilleri, 2019). During PND 4–6 when leakage was suppressed by the formation of an intestinal barrier, OT increases are due to RAGE-dependent OT transport from the intestinal epithelium in the wild-type mice. In contrast, there is no increase in RAGE KO mice because of its absence. After PND 7, there was no transport, reflecting little or no transport by an increased barrier and shorter OT due to increased digestive activity (breakdown of OT) masking transport in both genders.

In the case of RAGE KO mice, after oral OT administration, plasma OT concentrations increased from PND 1 to 3. In contrast to the wild-type, increases in OT concentration were not observed after PND 4 (**Figure 2**). Similar elevated levels of OT on PND 1 to 3 in both genotypes suggest leakage, probably because no barrier was formed. No increase in RAGE KO mice indicates that this uptake between PND 4 and 5 in wild-type mice is RAGE-dependent. Only in this very narrow time window, during which the intestinal barrier seems to have not formed, was the dependency on RAGE revealed (**Figure 2**).

The effect of digestion was limited because, when higher doses of OT were applied in adult mice in which digestion appears to be fully active, plasma levels of OT were elevated (Higashida et al., 2017a). These data suggest that milk-born



OT can be transmitted across the digestive tract into the blood circulation, including the intestinal mucus and epithelial cells, and OT can cross the intestinal epithelial barrier (Figure 3; Higashida et al., 2017a; Manigrasso et al., 2018). This absorption from the intestine is not strain-specific because identical absorption was observed in the pups of the ICR and C57BL6 strains.

Since then, oral OT supplementation may be advantageous for OT drug development (Higashida et al., 2017a; Yamamoto and Higashida, 2020). A recent study demonstrated that OT administered orally can be transmitted into the blood if it is prevented from degradation in the stomach by pretreating mice with a proton pump inhibitor (Maejima et al., 2020), and using mass spectrometry to evaluate the non-radioactive isoform of OT, we confirmed that OT was absorbed in its intact form. RAGE is abundant in intestinal epithelial cells of villi in both suckling pups and adults in mice (Higashida et al., 2017a) and is an integral component of the intestinal tract.

Oxytocin Levels in the Hypothalamus After Oral Delivery in Mouse Neonates

One question remains whether orally administered OT in the digestive tract can immediately enter into the brain. Indeed, it is very easy to estimate that OT could be transported by

RAGE through two barriers in wild-type mice (Higashida et al., 2017a), RAGE in the intestine intakes OT from the digestive tract and then into the blood circulation, followed by the transport crossover of the BBB to the brain from the blood. Since direct evidence for this was missing, we present our preliminary results on this point. Since it is very difficult to obtain CSF from the small brains of mouse neonates, to assess this transportation, we measured OT levels in homogenates of the mouse hypothalamus after oral application of OT or saline at different PNDs. As shown in Figure 4, the OT levels in hypothalamic tissue were higher in pups treated with 100 μ L of OT (10 ng/mouse) than in saline control pups at PNDs 1, 3, and 4 (Lopatina et al., unpublished data). Concentrations reached the same levels as those of mice administered saline at PNDs 5–8. This result strongly suggests that milk-born OT can be absorbed from the digestive tract during suckling and can reach the brain in babies.

Plasma Oxytocin Levels After Administration of Lipo-oxytocin-1 in Adult Mice

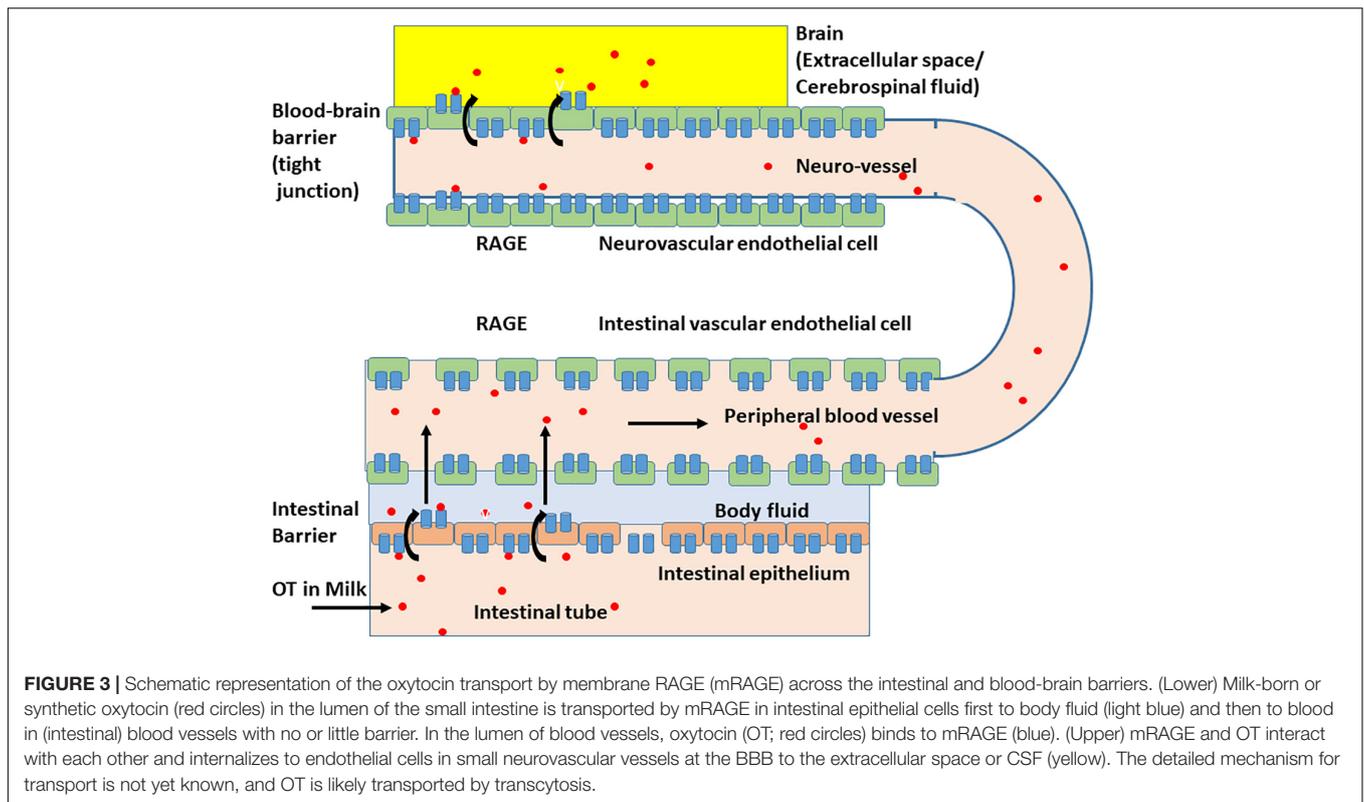
Highly homologous arginine vasopressin has been shown to bind to RAGE but is not transported efficiently and the nine amino acid peptide, bradykinin, does not completely bind to RAGE (Higashida et al., 2017a). These findings suggest that the RAGE-dependent transport system of OT possesses different efficacy compared with different peptides or the recognition ability of structural differences between OT and other peptides, indicating the specificity for OT.

The next question is whether RAGE can transport a lipidated OT analog, lipo-oxytocin-1 (LOT-1), which contains two palmitoyl acid chains [$-\text{CO}(\text{CH}_2)_{14}\text{CH}_3$] in cysteine and tyrosine residues (Mizuno et al., 2015; Cherepanov et al., 2017a,b, 2019). LOT-1 is one of our OT analog series and is composed of natural chemicals (Ichinose et al., 2019).

Bioactive peptide hormones have been used for clinical therapy (Davis et al., 2015). However, the therapeutic use of natural peptide hormones is substantially limited due to pharmacokinetic properties, such as poor absorption and brain transport, low metabolic stability, and rapid excretion from the kidney. On the other side, methods have been developed to mitigate the undesired pharmacokinetic properties of natural peptides (Egleton and Davis, 2005). One such methodology for this purpose, especially for the elongation of the lifetime in blood, is lipidation, which involves conjugating a peptide hormone with a long fatty acid (Eskandari et al., 2013).

Although the effect of lipidation of the parent molecule on BBB penetration is less documented, small-sized hydrophobic molecules can penetrate the BBB better than hydrophilic molecules (Eskandari et al., 2013). Thus, it is speculated that the lipidation strategy with increased hydrophobicity can extend its lifetime in the blood and improve its brain delivery capacity. An OT analog, LOT-1, was synthesized based on this hypothesis.

The effect of the new OT analog on social behavior defects was evaluated in CD157 KO mice. CD157 KO mice display psychiatric features of non-motor symptoms of Parkinson's disease, such as anxiety-related and depression-like behaviors,



fear, and social avoidance (Lopatina et al., 2014; Mizuno et al., 2015; Kasai et al., 2017). Furthermore, it has been shown that this social impairment in CD157 KO mice is readily recovered by single peripheral administration of OT (Lopatina et al., 2014; Higashida et al., 2017b), suggesting that these phenotypes may be

shared with other psychiatric impairments, for example, autism spectrum disorders and schizophrenia. LOT-1 has an advantage over native OT for long-lasting *in vivo* effects. In contrast, OT has better recovery effects than this analog on social impairment shortly after the treatment (Mizuno et al., 2015).

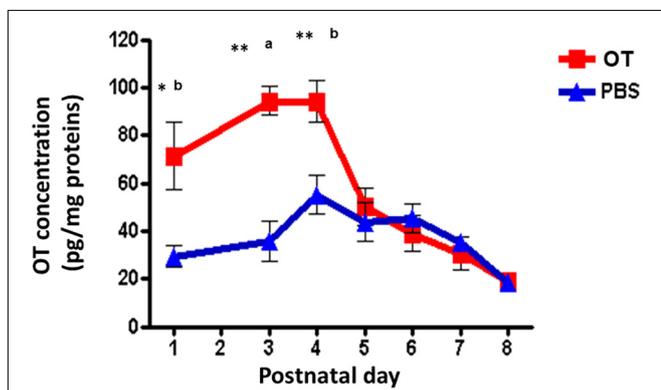
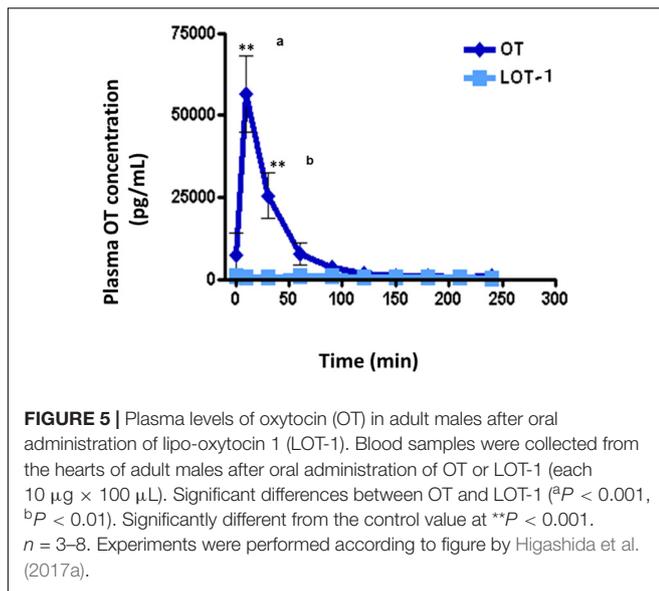


FIGURE 4 | Oxytocin (OT) levels in the hypothalamus of wild-type pups after oral administration of OT. Hypothalami are collected 10 min after oral administration of OT (1 µg in 10 µL) or the same volume of saline (PBS). The tissues were homogenized, and OT was measured by an enzyme immunoassay method. Significant differences between OT and saline at ^a $P < 0.001$, ^b $P < 0.01$. Significantly different from postnatal day (PND) 6 at ^{*} $P < 0.01$, ^{**} $P < 0.001$. OT levels are significantly higher on PND 1 ($P < 0.05$) and PND 4 ($P < 0.001$) from PND 5. Experiments were carried out essentially as described in Figure 3 by Higashida et al. (2017a).

We can also biologically examine whether LOT-1 can be cleaved into the OT and side chains in the digestive tract or blood within the measured time window for 240 min. This question is also important to estimate how long lappedated OT takes time for cleavage when we consider LOT-1 as a prodrug of OT as a pill in clinical application in the future.

No increase in plasma OT concentration was observed in wild-type adult male mice after oral administration of LOT-1 (10 µg/mouse) for 240 min, while in identical OT experiments, a substantial increase in plasma OT concentrations was observed after 10 min (Figure 5). OT levels returned after 60 min. As expected, after oral administration of LOT-1 (10 µg/mouse), plasma OT levels did not increase in RAGE KO mice (data not shown). These results suggest that LOT-1 did not cleave to OT within 240 min in the digestive tract or did not absorb LOT-1 due to structural selectivity in RAGE recognition in mice. Furthermore, if cleaved, the increase could be detected as an OT. Alternatively, even if RAGE can recognize LOT-1 and transport it, LOT-1 did not break down to OT in the blood in 240 min.

Unfortunately, this experiment was not sophisticated. The most significant limitation of this type of experiment is the lack of measurement of LOT-1 by mass spectroscopy. However, we wanted to know how and when OT breakdown occurred



during 4 h in the commonly used biological system; if so, this information allows us to consider LOT-1 as a prodrug (Cherepanov et al., 2017b). In addition, although indirect, RAGE's recognition capacity or sites should be evaluated in the near future.

RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS-DEPENDENT OXYTOCIN TRANSPORT TO THE BRAIN

Receptor for Advanced Glycation End-Products in Vascular Units in Mice

Immunohistochemically, RAGE in neurovascular patterns is limited to endothelial cells recognized by co-localization with CD31, a marker of vascular endothelial cells in the brain (Noguchi et al., 2020). RAGE is probably located in coated pits, showing an association with caveolin in the wild-type (Yamamoto et al., 2019). CD31 is located on the endothelial cells' luminal and abluminal plasma membranes. CD31 immunofluorescence intensity on the luminal surface is more abundant than on the abluminal surface (Mori et al., 2006). Usually, in doubly immunostained cryosections, anti-CAV-1 α antibodies are shown to be small and individual but punctate fluorescent structures (caveolae), primarily associated with the endothelial cell surface anti-CD31 antibody. Detecting their co-localization is a vital observation to investigate endocytosis of the RAGE-OT complex at the coated pit (Ramirez et al., 2002).

A preliminary study on Z-stack images confirmed RAGE and CD31 co-localization (**Supplementary Figure 1**), indicating that RAGE resides within mouse vascular endothelial cells and the RAGE action sites are on endothelial cells, alternatively on the BBB (Yamamoto et al., 2019).

Immunostaining of Human Vascular Units

Using a piece of brain tissue from adult human patients with glioma, we stained them with a RAGE antibody. Immune precipitation was observed on the endothelial cell surface of human brain tissue (**Supplementary Figure 2**). The presence of RAGE in the neurovascular unit of humans strongly supports the RAGE-dependent OT transport system in the human BBB (**Figure 3**).

Other Routes of the Brain Transport of Oxytocin

There find reports in which OT concentrations in the various brain regions and/or CSF are increased after peripheral administration in different mammals. In human studies, changes in images at given brain regions, such as amygdala, are monitored as central effects of OT in response to intranasal administration of OT, being detected by brain imaging devices. A part of such studies is listed in **Table 2**. However, none of reports deal with exact molecules involved in the OT transport, except for RAGE. Of course, it has been in part demonstrated and discussed the direct pathway to the brain from nasal cavity (the nose-brain route), intra-nerve transport, and the corpus callosum barrier at which the BBB is weaker. Anyhow, in such cases little or no molecular mechanisms have been reported.

FUNCTIONAL ASPECTS OF THE OXYTOCIN TRANSPORT OR INCREASES IN THE BRAIN

Maintenance of the Brain Supply of Oxytocin in Postpartum Dams Is Critical

Gerasimenko et al. (2021) reported that maternal behavior, such as pup retrieval, was impaired in RAGE KO mice, as after additional stress, impairment of pup care was observed in mother mice. This neglect leads to newborn death within 1–2 days. RAGE seems to play a critical role during the postpartum period and is important in the manifestation of normal parental behavior in dams. Therefore, it can be proposed that RAGE-dependent OT signaling can dampen the effect of additional exogenous stress on endogenous stress during pregnancy, delivery, and lactation (**Supplementary Figure 3**). From these results in mice (Gerasimenko et al., 2021), in the early postpartum period in human females, a potential role for RAGE in transporting OT to the brain is crucial in the jumble of emotions during the puerperium and postpartum periods as suggested (Monks and Palanisamy, 2021). Thus, in the future, it will be necessary to examine whether RAGE impairment is more closely related to postpartum depression and child neglect, which is seen in 10 and 20%, respectively, of new human mothers.

Nicotinamide Riboside

Finally, we discuss our recent results on a precursor of NAD (Chini et al., 2020, 2021). Similar to nicotinic acid and

TABLE 2 | Identified transport molecules and routes of oxytocin to the brain after peripheral administration.

Method	Route	Crossing	Molecule	Brain regions	Spices	References
(A) Animal studies						
i.p.	Blood	BBB	–	CSF	Mouse	Neumann et al., 2013
i.p.	Blood	BBB	RAGE	CSF	Mouse	Yamamoto et al., 2019
s.c.	Blood	BBB	RAGE	CSF	Mouse	Yamamoto et al., 2019
i.v.	Blood	BBB	RAGE	PVN	Mouse	Yamamoto et al., 2019
i.n.	Blood*	BBB	RAGE	Amygdala	Mouse	Yamamoto et al., 2019
i.n.	Blood*	BBB	RAGE	mPFC	Mouse	Munesue et al., 2021
i.n.	–	–	–	Amygdala	Mouse	Smith et al., 2019
s.c.	Blood	–	–	Hippocampus	Mouse	Bertoni et al., 2021
i.n.	–	–	–	Olfactory bulb	Rat	Ferris et al., 2015
i.n.	–	–	–	CSF	Pig	Mens et al., 1983
i.n.	Olfactory N	–	–	Hypothalamus	Macaque	Lee et al., 2020
i.n.	Trigeminal N	–	–	Hypothalamus	Macaque	Lee et al., 2020
i.n.	–	–	–	CSF	Monkey	Modi et al., 2014
(B) Human study						
Oral	Blood	–	–	Putamen	Male	Kou et al., 2021
i.n.	Blood*	–	–	Amygdala	Male	Martins et al., 2020
i.n.	–	–	–	Amygdala	Male	Spengler et al., 2017
i.n.	–	–	–	Amygdala	Female	Lieberz et al., 2020
i.n.	–	–	–	Amygdala	Female	Geng et al., 2018
i.n.	Nose-to brain	–	–	Amygdala	Male	Quintana et al., 2017
i.n.	–	–	–	Amygdala	Male	Kirsch et al., 2005
i.n.	–	–	–	Striatum	M/F	Kirsch et al., 2005
i.n.	–	–	–	Temporal lobe	M/F	Frijling et al., 2016
i.n.	–	–	–	CSF	Male	Striepens et al., 2013
i.n.	–	–	–	Mirror neuron	Male	Ono et al., 2021

Blood indicates that OT is taken up into blood circulation. Blood * indicates that OT is mainly included in blood circulation after i.n. administration. However, other routes cannot be excluded. Nose-to-brain indicates the authors' speculation that such routes exist. Blood routes are also possible but not specified or identified in each report. i.p., intraperitoneal; s.c., subcutaneous; i.v., intravenous; i.n., intranasal; BBB, blood-brain barrier; RAGE, receptors for advanced glycation end-products; CSF, cerebrospinal fluid; PVN, periventricular nucleus; mPFC, medial prefrontal cortex; N, nerve; and M/F, male and female.

nicotinamide, nicotinamide riboside is a natural product found in milk. It is incorporated into the intracellular NAD pool. Nicotinamide riboside could be used as a general supplement, potentially for people who have adverse reactions to nicotinamide or nicotinamide riboside (Trammell et al., 2016). In brain tissue, NAD synthetase activity is dramatically low, making nicotinic acid an unsuitable supplement, as in the case of mice (Mori et al., 2014). However, nicotinamide riboside has already been used as a supplement or therapeutic agent to elevate or maintain cellular NAD content in mice (Fletcher et al., 2017).

Recently, it has been shown that NAD is consumed more by an increase in CD38 in aged male mice and, thus, proposed that inhibition of CD38 or an increase in NAD may lead to a longer life span (Tarragó et al., 2018; Gerasimenko et al., 2020a,b). NAD metabolism also catalyzes the formation of cADPR (Lee and Zhao, 2019). It then participates in OT release in the hypothalamus (Jin et al., 2007). Although NR supplementation did not change CD38 expression (Gerasimenko et al., 2020b), *in vitro* studies have shown that NAD applied to the mouse hypothalamus leads to OT release (Gerasimenko et al., 2020a).

It has been shown that daily administration of nicotinamide riboside ameliorated the social and behavioral impairments observed in male CD157 KO mice (Gerasimenko et al., 2020a). In contrast, an identical improvement in social behavior was not

observed with saline gavage. Furthermore, nicotinamide riboside had essentially no effect on social behavior in wild-type mice. The increases in nicotinamide riboside treatment effects were only detected in CD157 KO mice. Therefore, these beneficial effects of nicotinamide riboside may be due to increased brain OT levels. No identical effect was observed with nicotinamide riboside in wild-type mice (Gerasimenko et al., 2020a).

CONCLUSION

It has long been argued that intranasally applied OT in humans can be transmitted to the brain from the viewpoint of medical and psychological therapies. Our article series answers this, explaining that OT can be transported into the mouse brain *via* circulation. At the same time, we must recognize that concentrated nasal OT is an artificial situation. Humans have not encountered these conditions since the species' origin several million years ago. Therefore, the recruitment of OT from the blood, in which the OT is present in the stream as a hormone that functions in remote places, to the brain is a more essential and natural condition for most mammals. This idea may be as important as the concept of OT release into the bloodstream of the pituitary. Harris and other researchers have reported this

finding as a fundamental step in neuroendocrinology over a century ago (Leng et al., 2015). Moreover, we know now that mRAGE plays a role in OT transport in endothelial cells in mouse neurovascular units.

Biologically, it is possible to understand that the RAGE-dependent transport system may be a minimally safe system for supplying OT to the brain to maintain social behavior. Furthermore, the OT supply system from the periphery may provide information to the brain. However, this point needs to be further studied in the future.

Additional data have been reported concerning RAGE. First, OT concentrations in the CSF increase directly after absorption of OT from the intestine of mouse neonates upon oral administration of OT during only a few postnatal days. Second, during the 40 min after oral administration of the OT analog, LOT-1, RAGE is not converted into OT. Thus, it is not transported in the digestive system. Third, the three-dimensional image provides the precise location of RAGE in the mouse neurovascular endothelial cells, and Fourth, RAGE is located in human vascular endothelial cells. Through these novel data, in the current review, we evaluated the new concept that RAGE is mainly involved in the regulation of OT dynamics and the interface between the brain, blood, and intestine in the living body.

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Finally, the RAGE-dependent OT transport hypothesis has been confirmed by measuring plasma OT concentrations by a simple extraction method called the PPT (acetonitrile protein precipitation) approach (Cherepanov et al., 2021). RAGE KO mice with less soluble forms of RAGE in the plasma displayed larger plasma OT concentration increases after intraperitoneal administration of OT. Furthermore, the changes were more extensive and lasted longer, proving that RAGE plays a role in OT dynamics in the blood.

AUTHOR CONTRIBUTIONS

HH, OH, YH, and YY wrote the manuscript. KfH, OL, MG, OH, YH, and HH draw figures. All authors performed experiments. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnins.2022.858070/full#supplementary-material>

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