Somato-axodendritic release of oxytocin into the brain due to calcium amplification is essential for social memory

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Abstract Oxytocin (OT) is released into the brain from the cell soma, axons, and dendrites of neurosecretory cells in the hypothalamus. Locally released OT can activate OT receptors, form inositol-1,4,5-trisphosphate and elevate intracellular free calcium (Ca²⁺) concentrations [(Ca²⁺)]i in self and neighboring neurons in the hypothalamus, resulting in further OT release: i.e., autocrine or paracrine systems of OT-induced OT release. CD38-dependent cyclic ADP-ribose (cADPR) is also involved in this autoregulation by elevating [Ca²⁺], via Ca²⁺ mobilization through ryanodine receptors on intracellular Ca²⁺ pools that are sensitive to both Ca²⁺ and cADPR. In addition, it has recently been reported that heat stimulation and hyperthermia enhance [Ca²⁺], increases by Ca²⁺ influx, probably through TRPM2 cation channels, suggesting that cADPR and TRPM2 molecules act as Ca²⁺ signal amplifiers. Thus, OT release is not simply due to depolarization–secretion coupling. Both of these molecules play critical roles not only during labor and milk ejection in reproductive females, but also during social behavior in daily life in both genders. This was clearly demonstrated in CD38 knockout mice in that social behavior was impaired by reduction of [Ca²⁺], elevation and subsequent OT secretion. Evidence for the associations of CD38 with social behavior and psychiatric disorder is discussed, especially in subjects with autism spectrum disorder.

Keywords Oxytocin · Hypothalamus · Social behavior · CD38 · TRPM2

Introduction

Oxytocin (OT) and arginine vasopressin (AVP) are nonapeptides that differ in two amino acid residues [1]. OT and AVP are synthesized mostly in distinct neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) in the hypothalamus [2, 3]. OT and AVP are secreted into the blood circulation and have physiological roles in peripheral organs, such as the uterus, mammary gland, and kidney. They induce contraction of uterine and mammary duct smooth muscle or diuretic action in the kidney as hormones [4–6].

OT, AVP, and their receptors are present in the brain not only in females during specific reproductive periods but also in non-reproductive females and males [6]. Accumulating evidence has established that, in addition to classical hormonal functions, both peptides play critical roles in social recognition and social behavior in mammals, including humans [7–20]. This review focuses mainly on OT. The main point is not a general functional role of OT in a comprehensive review, but the molecular mechanisms of OT secretion into the brain that is critical in the neuronal function of OT in social recognition and behavior [4, 11, 13, 21].

Another reason to focus on the release is that the mechanism contains a very important aspect in terms of physiological science, in that the proposed idea challenges the principal rule in physiology of depolarization–secretion...
coupling [22–24]. Furthermore, this mechanism seems to have a potential relationship to autism spectrum disorder (ASD), a serious developmental disorder, which is a rapidly advancing field in neuroscience and psychiatry and is a serious disorder in our society [25–28]. There have been many reviews regarding the relationship between ASD and OT [29–35]. However, there have been few regarding the molecular mechanism of OT release into the brain [4], which is the critical step for social recognition and social behavior [26–28].

**Somato-axodendritic release of oxytocin**

OT is secreted from the nerve terminals of axons of oxytocinergic neurons at the perivascular site in the posterior lobe of the pituitary into the circulation [4] (Fig. 1). Oxytocinergic neurons send their axons to the amygdala and some other limited brain regions and secrete OT from the nerve terminals [4, 12, 15]. It is known that adrenaline stimulates oxytocinergic neurons in the SON, which results in local release of OT in the brain [5, 36]. This release occurs from the cell soma, axons, and dendrites, i.e., somato-axodendritic release [37–39].

Locally released OT causes excitation of OT neurons by activating OT receptors expressed in neurons of both the PVN and SON [40–43]. OT stimulates OT receptors and facilitates OT release from the stimulated neurons. Released OT can stimulate OT receptors and elicits release from the same neurons (autocrine) or nearby neurons (paracrine) [44] (Fig. 2). This OT-induced OT release determines the basal brain concentrations and elevated concentrations of OT. The concept of autoregulation, OT-induced OT release, can be an extremely efficient way to achieve massive OT recruitment during uterine contraction in labor and milk ejection in lactation [5, 6, 45–47]. Autoregulation, however, is also an essential brain mechanism for social recognition in daily life in both genders, as proposed previously [25, 27, 28].

**Oxytocin receptors and cellular signaling**

OT receptors are seven-transmembrane proteins that couple with the Gq/11-type GTP-binding protein [48]. Stimulation of OT receptors leads to the production of inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) through the activation of phospholipase C (PLC) [48]. This results in activation of Ca2+ mobilization from IP3-sensitive Ca2+ pools [49].

On the other hand, another Ca2+ signal pathway of cyclic ADP-ribose (cADPR) [50, 51] was identified downstream of OT receptors [11]. cADPR mobilizes Ca2+ through cADPR-sensitive Ca2+ pools, in a mechanism referred to as Ca2+-induced Ca2+ release. In this process, cADPR plays an essential role in mobilizing Ca2+ through Ca2+ channels of ryanodine receptors [52–56] (Fig. 3). The recent review by Leng et al. did not mention this cADPR/CD38 hypothesis [4], probably because they described by their data based on their finding with thapsigargin [36].

It is known that intracellular cADPR concentrations are regulated in many different ways, including activation of ADP-ribosyl cyclase or CD38, via heterotrimeric GTP-binding proteins, or phosphorylation downstream of the G
A-kinase

Fig. 2 Scheme showing autocrine and paracrine release of oxytocin. OT is released from dendrites (dendritic release), from the cell soma (soma release), and from axons (axonal release) in the hypothalamus. Hypothalamic oxytocinergic neurons express OT receptors (OTR). Released OT binds to OTR. More OT (yellow circle) is released by CD38-mediated intracellular calcium amplification (not shown). The positive feedback of OT release occurs by OT released from self or nearby cells via autocrine and paracrine mechanisms, respectively.

Effects of oxytocin on ADP-ribosyl cyclase and intracellular \( \text{Ca}^{2+} \) concentrations

Application of OT stimulates ADP-ribosyl cyclase activity or CD38 in crude membrane fractions, when measured by cADPR formation from \( \beta\text{-NAD}^+ \) or by cyclic GDP-ribose (cGDPR) production from NGD\(^+\) [50, 68]. cADPR or cGDPR production increases in a concentration-dependent manner upon exposure to sub-nanomolar concentrations of OT [49].

Subsequently, in isolated hypothalamic neurons, application of 100 pM OT results in \([\text{Ca}^{2+}]_i\) increases: a rapid initial increase and a sustained elevation lasting for 5 min [69]. OT elicits an initial elevation of the maximum \([\text{Ca}^{2+}]_i\), and this phase is IP\(_3\)-dependent. Pretreatment with 8-bromo-cADPR, an antagonist of the cADPR-binding site of \( \text{Ca}^{2+} \) release channels of ryanodine, inhibits OT-mediated sustained \([\text{Ca}^{2+}]_i\) increases. ADPR and \( \beta\text{-NAD}^+ \) also induce elevation of \([\text{Ca}^{2+}]_i\); and replicate the second phase of sustained \([\text{Ca}^{2+}]_i\) increases [49, 69]. Under \( \text{Ca}^{2+}\)-free conditions, the OT-mediated increase of \([\text{Ca}^{2+}]_i\) shows little change in either phase, suggesting that the two phases of \([\text{Ca}^{2+}]_i\) elevation in hypothalamic neurons are due to \( \text{Ca}^{2+} \) mobilization from the intracellular \( \text{Ca}^{2+} \) pools [49].

Oxytocin release by extracellular application of cyclic ADP-ribose

High potassium-induced depolarization produces an increase of up to eightfold in OT secretion from isolated mouse hypothalamic neurons or their axon terminals in the posterior pituitary gland, respectively [21]. OT release is
enhanced by about fourfold by application of extracellular β-NAD⁺, a precursor of cADPR (refer to Fig. 4 in [21]). The increase is blocked completely by 8-bromo-cADPR. To further confirm the involvement of cADPR, we examined the effects of extracellular application of several β-NAD⁺ metabolites [49, 69]. Only cADPR showed a potentiation effect, indicating that OT release utilizes the cADPR/ryanodine calcium amplification system (Fig. 5).

**Involvement of TRPM2 channels**

Melastatin-related transient receptor potential channel 2 (TRPM2, previously named TRPC7 or LTRPC2) possesses ADPR hydrolase activity and is a Ca²⁺-permeable cation channel. β-NAD⁺, ADPR, and cADPR can activate TRPM2 channels [70]. TRPM2 activation by cADPR is promoted at body temperature (>35 °C) and is involved in insulin secretion in pancreatic β cells [71]. In addition, TRPM2 channels are related to receptor functions through cADPR formation [72].

Extracellularly applied cADPR can activate [Ca²⁺]ᵢ signaling via CD38 or TRPM2 channels downstream of OT receptors. [Ca²⁺]ᵢ increases in the model neuron, NG108-15 mouse neuroblastoma × rat glioma hybrid cells that possess CD38 [58, 73] but not OT receptors [74], as in the isolated whole hypothalamus after stimulation with extracellularly applied cADPR [69, 75]. Interestingly, the same tissues show significantly greater increases upon extracellular challenge with cADPR together by heating to 40 °C from 35 °C in the incubation medium (Fig. 6). Little or no cADPR-mediated [Ca²⁺]ᵢ elevation was observed at 40 °C in the absence of extracellular Ca²⁺ influx is expected, probably through non-selective cation TRPM2 channels, because elevation of [Ca²⁺]ᵢ is inhibited by the TRPM2 channel inhibitor, 2-aminoethoxydiphenyl borate (2-APB). Similarly, 8-bromo-cADPR inhibits responses to β-NAD⁺ and heat. These results suggest that cADPR contributes to both Ca²⁺ mobilization from internal Ca²⁺ pools and Ca²⁺ influx through TRPM2 Ca²⁺-permeable channels from the extracellular space. Such [Ca²⁺]ᵢ increases may result in OT release. However, there have been no previous reports regarding heat-induced OT release in the hypothalamus.

**Contribution of CD38**

In the central nervous system, ADP-ribosyl cyclase activity corresponding to CD38 is detected as early as embryonic day 15 in mouse development [76]. In the brain, expression levels of CD38 and ADP-ribosyl cyclase activity increase with further development [77]. The role of CD38 in
regulation of OT secretion through cADPR-mediated intracellular calcium signaling has been clearly demonstrated using CD38 knockout mice [11, 21, 78, 79]. The plasma and cerebrospinal fluid OT levels are reduced in CD38 knockout mice. Electron microscopic examination exhibited little to no release from the nerve endings of oxytocinergic neurons in the pituitary of CD38 knockout mice (Fig. 1). These phenotypes were rescued by simple subcutaneous injection of OT as well as brain local re-expression of human CD38, but not mutant CD38, by the lentivirus infection method in CD38 knockout mice [21].

Human social behavior and psychiatric disorders

As CD38 is recognized as being closely related to OT release and social memory in mice, we examined the association of single nucleotide polymorphisms (SNPs) in the human CD38 gene on ASD [80]. In a series of elegant studies in 323 mothers, fathers, and non-parents, Epstein and colleagues reported that risk alleles on CD38...
participants in the USA but not in Japan. These findings were shown to be linked with high-functioning ASD in

\[ CD38 \] examined, and the ASD \[ 84–87 \]. Ten SNPs and mutations of \[ CD38 \] genes are associated with less par-

Fig. 7 Scheme indicating \( \text{Ca}^{2+} \) influx through \( \text{Ca}^{2+} \) channels is not sufficient to trigger OT release. The \( \text{Ca}^{2+} \) signal must be amplified by \( \text{Ca}^{2+} \)-induced \( \text{Ca}^{2+} \) release through \( \text{Ca}^{2+} \) channels of ryanodine receptors type II or III by cADPR and some NAD metabolites in the hypothalamus (Fig. 7). In addition, \( \text{Ca}^{2+} \) influx through TRPM2 channels contribute more to increases in \( [\text{Ca}^{2+}]_i \). This hypothesis of depolarization-independent but heat-sensitive \( \text{Ca}^{2+} \) signaling for OT release is consistent with the previous suggestion of dendritic release of OT without depolarization \[ 4, 21, 39 \].

OT exerts an anxiolytic effect during stress, and stress sometimes induces hyperthermia. It is therefore interesting to examine how stress induces hyperthermia, which results in subsequent OT release. OT release seems to be important in damping the stress-induced disadvantage.

OT is an essential molecule for social memory and social behavior \[ 21, 29 \]. Deficiency in social behavior is the core symptom of ASD. Recently, Yamasue and his group reported that repetitive intranasal OT administration for 6 weeks improved symptoms of the social behavior domain \[ 88 \]. This result could be due to the delivery of OT to the brain by intranasal administration, but there is still little direct evidence regarding whether OT is recruited into the brain from the peripheral tissues or organs crossing the blood–brain barrier from the blood circulation. Several important questions regarding OT secretion into the brain and OT-induced \( \text{Ca}^{2+} \) signaling and OT transport from the blood to the brain remain to be resolved.

Acknowledgments This work was supported by a grant-in-aid from Integrated Research on Neuropsychiatric Disorders carried out under the Strategic Research Program for Brain Sciences.

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Fig. 7 Scheme indicating \( \text{Ca}^{2+} \) amplification with different ryanodine receptor subtypes. Skeletal muscle contraction and heart muscle contraction utilize type I and II ryanodine receptors, respectively. Oxytocin release uses type II or III ryanodine receptors

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