Social Behaviour and Oxytocin Secretion in the Brain
Regulated by CD38 in Human and Mice

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Abstract: - Oxytocin (OXT) in the hypothalamus is the biological basis of social recognition, trust, love and bonding. Previously, we showed that Cd38, a proliferation marker in leukaemia cells, plays an important role in the hypothalamus in the process of OXT release in adult mice. Disruption of Cd38 (Cd38-/−) elicited impairment of maternal behaviour and male social recognition in adult mice (Nature, 446, 41, 2007), similar to the behaviour observed in Oxt and OXT receptor (Oxtr) gene knockout (Oxt-/− and Oxtr-/−, respectively) mice. Impairment was also prominent in Cd38-/− newborn mice. However, these behaviours were much milder than those observed in Oxt-/− and Oxtr-/− mice. These phenotypes seemed to be caused by the high plasma OXT levels during development from neonates to 3-week-old juvenile mice. These results suggest that secretion of OXT into the brain in a Cd38-dependent manner plays an important role in the development of social behaviour. Based on these results in animal experiments, OXT treatment for autistic subjects as a restore method has been proposed, and its use has begun in several hospitals.

Key-words: - Oxytocin, Social recognition, Maternal behaviour, CD38, Autism

1 Introduction
Oxytocin (OXT), a nonapeptide involved in reproduction, is synthesised in the paraventricular nucleus and supraoptic nucleus of the hypothalamus, and travels down neuronal axons to the posterior pituitary. It is secreted into the general circulation from the nerve endings of the neurohypophysis and into the brain from dendrites. It is well known that OXT is linked to complex social behaviour [1-3]. In humans, intranasal OXT may promote
trust, gaze or face recognition and infusion of OXT can increase generosity [2-4]. In rodents, OXT is highly involved in social interaction, social recognition, pair bonding and maternal behaviour [1-3,5-8]. In addition, animal studies have shown that increased levels of OXT in the early postnatal period may affect behaviour and last into adulthood, and that subcutaneous administration of low doses of OXT facilitates social recognition [5]. Two types of mice with OXT (Oxt) or OXT receptor (Oxtr) gene knockout (Oxt-/- or Oxtr-/-) show profound social amnesia [5-8]. Social amnesia can be fully rescued by injection of OXT into the medial amygdale in Oxt-/- mice. Impairment of social behaviour is clearly observed even in pups. These observations suggest that OXT plays an important role in social behaviour by OXTR stimulation during brain development throughout the juvenile to adult stages [9].

Recently, we reported that adult mice with a null mutation in Cd38, a “niceness” protein with ADP-ribosyl cyclase activity, showed deficiency in social behaviour due to the abnormality of central and peripheral OXT secretion [9-11]. We also showed that decreased formation of cyclic ADP-ribose (cADPR) results in dysfunction of Ca2+-induced Ca2+-release for OXT secretion in hypothalamic OXT neurons (Fig. 1). Here, we report the relationship between social behaviour and OXT levels in Cd38 knockout mice, and compared the results among three different genotypes: Oxt-/-, Oxtr-/- and Cd38-/- . And we discuss on the usage of OXT on treatment for autism patients.

Fig. 1. A scheme showing that CD38-dependent cADPR- and NAADD-sensitive intracellular Ca2+ mobilization from ryanodine receptors in microsomes has a key role in oxytocin (OT) release. This system of OXT is important in social behaviour.

2 Critical time window of plasma OXT levels for adult from juvenile stages

The decrease in OXT concentration after weaning during development was observed only in Cd38-/- mice, suggesting an important critical period to distinguish different plasma OXT switching from the
juvenile stage to the adult stage [11]. As breast milk is the only food source in lactating pups, we speculated that OXT is inevitably taken in from the breast milk.

To confirm this, we performed quantitative analysis to determine whether OXT is present in the mammary glands of lactating dams and milk in pups. Milk curd was found in the stomachs of the offspring born to Cd38−/− females, Fig. 2. Plasma OXT levels in two genotypes during development.

which was quite different from that in those of Otx−/− and Oxtr−/− females. OXT was abundant in the mammary gland tissue and breast milk in lactating dams of both genotypes, with no significant difference between Cd38+/+ and Cd38−/− animals. In the three stages of growth and development, the plasma OXT seems to be controlled from different sources: Foetal stage, Infant stage (breastfeeding stage) and Adult stage (weaning stage). In wild-type mice, during all developmental stages, OXT levels are kept high (Fig. 2). In contrast, in Cd38 knockout mice OXT levels decreased significantly after weaning [10,11].

3 Implications for developmental disorders
A series of recent studies suggested that OXT is related to autism [13,14]. It has been reported that plasma OXT levels in autistic children are lower than those in age-matched normal controls, although the precise deviation is very small [15]. Infusion of OXT reduces repetitive behaviours in adults with autistic and Asperger’s disorders [16]. However, these studies have largely focused on autism in older children and adults. There have been only a few studies in infants during breastfeeding and the early postnatal period.

![Graph showing plasma OXT levels in two genotypes during development.](image)

Fig. 3. A scheme showing that nasal OXT infusion or local CD38 expression in the hypothalamus can rescue social impairment in autistic subjects.

Oxytocin Injection or Lentiviral CD38 expression

- Social Memory
- Nurturing Behavior
- Social Life

Treatment of Autistic behavior

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Although the exact mechanism is unclear [18], based on our data, we proposed that lack of adequate exogenous OXT during breastfeeding would affect the normal development of the brain in genetically susceptible infants, thereby increasing the risk of autism (Fig. 3). OXT treatment as a refill method has been proposed, and its use has begun in several hospitals, including Kanazawa and Krasnoyarsk University Hospitals [19]. In some cases, we observed improvement in social behaviour, as might be suggested from experimental data and as it has been reported previously [13,17].

4 Conclusion
We concluded that different sources of OXT seem to impact brain development at different stages of growth, and thus maintenance of high OXT level is secured for development and social behaviour. OXT treatment with a nasal spray has been proposed, and its use has begun in several hospitals.

Reference


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