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Special Issue on: “Oxytocin in Development and Plasticity”

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Oxytocin is a nine amino acid neuropeptide and hormone, secreted by the paraventricular, accessory, and supraoptic nuclei of the hypothalamus. It was first identified for its functions in regulating uterine contractions during labor and milk ejection during nursing. In the late 1970s, oxytocin received much attention for its role in regulating social behavior, with research in rats and sheep demonstrating its ability to promote the mother–infant bonds (Pedersen and Prange, 1979; Kendrick et al., 1997; Rilling and Young, 2014; Numan and Young, 2016), and work in the monogamous prairie vole revealing its central role in the formation of pair bonds between mates (Young and Wang, 2004). In 2005, a study in humans, demonstrating that intranasal oxytocin administration increased trust (Kosfeld et al., 2005), led to a surge of human intranasal oxytocin studies. The results suggested positive roles of oxytocin in prosocial behaviors including trust, altruism, affiliation and empathy. Various clinical trials also began to test the potential role of oxytocin in the treatment of different psychiatric conditions, including schizophrenia and autism. The recent flurry of attention on oxytocin, in addition to promoting interest in oxytocin research, also revealed the complexity of its effects, urging the scientific community to reexamine its effects from multiple perspectives.

The contributions to this Special Issue of Developmental Neurobiology review current knowledge about the functions of oxytocin, mainly through developmental and evolutionary perspectives. Although the functions of oxytocin were first identified in mammals, it is an evolutionarily highly conserved neuropeptide, with its homologue nematocin, for example, shown to modulate male mating behavior and gustatory learning in the nematode C. elegans. The review by Lockard, Ebert and Bargmann (2017) traces the evolution of oxytocin through invertebrate lineages and describes its functions in regulating invertebrate behaviors, including reproductive behavior, learning and memory, food arousal, and predator/prey relationships. Characterization of the simple and well-defined neural circuits in invertebrates may reveal new insights and principles that add new dimensions to the more complex effects of oxytocin in vertebrates. An interesting example is the duplication of the peptide and its receptors in cephalopods, an event that only appears again in vertebrates. In both cases, the duplications have been correlated with the evolution of cognitive abilities, although the causal relationship remains to be shown. Another instance is the surprising absence of oxytocin in insects, such as the eusocial honeybees and various species of Drosophila, which suggests that these species

may have developed a parallel system with similar and/or overlapping functions. The question thereby arises as to whether a second system might also have evolved in vertebrates.

Following this review of the phylogeny of oxytocin in adult invertebrates, the two reviews by Vaidyanathan and Hammock (2017) and by Sannino, Chini and Grinevich (2017) highlight the ontogeny of oxytocin signaling in mammals. Grinevich and colleagues point out that oxytocin production in the fetal paraventricular, accessory and supraoptic nuclei of the hypothalamus may be triggered by the crossing of maternal oxytocin through the placenta during delivery. In contrast, its receptor appears already in the developing embryo (Saunders et al., 2012), and oxytocin signaling may thus play an important role in the long-term effects of early life experiences, as noted by Vidyanathan and Hammock. Mother–infant interaction may play an important role in this context, but to what extent their effects on later behavior may target or be mediated by changes in oxytocin signaling remains to be determined. Grinevich and colleagues point to the striking parallel expression profiles of oxytocin receptor and potassium-chloride cotransporter 2 (KCC2) during development, suggesting an important role for oxytocin in regulating the developmental switch of GABA from excitation to inhibition. They also point out that transient changes in receptor level during adolescence may play important roles in the development of social behaviors and of self control (drug dependence, aggression, etc.). Vidyanathan and Hammock further complement this point by describing how gonadal hormones may affect oxytocin signaling and how these transient changes may differ between species such as mouse, rat, prairie vole, and montane vole. Both reviews also point out that few developmental studies have been performed in humans and other primates, partly caused by a lack of appropriate ligands for the receptor. They further point to the lack of studies that have examined the role of oxytoxin in the ageing brain, directions that merit future attention.

The importance of oxytocin in the modulation of sensory processing is explored in the review by Marlin and Froemke (2017), which focuses on the olfactory and auditory systems. For the latter system, it highlights the sexual dimorphism and the importance of oxytocin in the development of maternal responses such as retrieval of vocalizing pups. In considering emotional processing of sensory information, Marlin and Froemke note the modulation of pain and fear processing by oxytocin as it happens in the amygdala, and its effects on reward processing in the nucleus accumbens. As a potential mechanism for these effects, this review considers the effect of oxytocin on inhibitory feedforward processing and its implications for signal to noise filtering, as recently shown in the hippocampus (Owen et al., 2013).

An important approach to studying gene function is through loss-of-function studies. To these end, multiple knockouts of oxytocin and the oxytocin receptor have been generated in mice. Caldwell et al. (2017) systematically reviewed the results of behavioral studies of these knockout mice, which have contributed toward our understanding of oxytocin function with regard to social recognition memory, maternal behavior and aggression, as well as other social behaviors. Differences in the phenotypes of oxytocin and oxytocin receptor knockout mice suggest potential contributions of compensatory mechanisms following congenital loss-of-function and/ or crosstalk with the vasopressin signaling system. The dependence of progeny aggressive phenotype on whether the dams (rather than the offspring) were homozygous or heterozygous knockouts highlights the importance of the oxytocin system during development on neural circuit wiring and adult behavior.

The discussion of the developmental contributions of oxytocin signaling to behavior brings us to the topic of autism spectrum disorder (ASD). Polymorphisms in OXTR (oxytocin receptor) and CD38 (Cluster of differentiation 38), a transmembrane protein that regulates oxytocin release, have been detected in patients with ASD. Consistently, some beneficial effects of intranasal oxytocin administrations in ASD patients have been reported although many of the studies were relatively small, and larger, well-controlled clinical trials are much needed (Walum et al., 2016). The review by Penagarikano (2017) examines alterations in oxytocin and/or oxytocin receptor expression in mouse models of ASD. Most interestingly, in two models directly related to human syndromes, notably the Magel2 and Cntnap2 mouse mutants, a deficit in oxytocin in the hypothalamus can be permanently rescued by a single acute dose of oxytocin during early postnatal life. In the valproic acid treated mice and in the Fmr1 mice, phenotypic changes are correlated with altered GABA switching and could be rescued by oxytocin treatment. While the link between oxytocin signaling and ASD is still mostly correlative at present, mouse models of ASD provide a valuable tool for investigating potential underlying mechanisms.

Our interests in oxytocin and in its potential therapeutic role in treating ASD and other neuropsychiatric disorders arise from its role in regulating social behavior. In the final review, Kenkel, Perkeybile, and Carter examine the neurological basis of alloparenting (Kenkel et al., 2017), the caring of the young by individuals other than their biological parents. Alloparenting is a social behavior universal among humans, and its dysfunction can have serious consequences for vulnerable infants and children. Yet we know relatively little about its underlying mechanism. The authors draw on existing data from the few animal models available for studying alloparenting, including meerkats, primates, and especially voles. Their original findings, that intraperitoneal administration of the oxytocin receptor antagonist L-368,899 significantly reduced alloparental behavior in male prairie voles, is discussed in light of other findings, such as the observation that 20–30 minutes of exposure to pups can result in changes in hypothalamic oxytocin expression in the alloparent and can exert anxiolytic effects. Intriguingly, increased heart rate of the alloparent was also observed, an effect possibly necessary to meet the thermoregulatory needs of the pups. From a developmental perspective, a basis for adult alloparental behavior seems to be formed early in life and to be accompanied by changes in oxytocin receptor levels in the bed nucleus of the stria terminalis (BNST) and nucleus accumbens. Manipulations of oxytocin signaling early in life seem to correlate with corresponding changes in alloparental behavior in adult life, arguing for a positive role of oxytocin signaling.

In summary, this special issue on “Oxytocin in Development and Plasticity” reviews how oxytocin signaling contributes to the regulation of behavior, especially social behavior, from a developmental and evolutionary perspective. By reviewing existing knowledge and highlighting open questions from different angles, we hope to provoke thought and generate insight in the field.

REFERENCES

Caldwell HK, Aulino EA, Freeman AR, Miller TV, Witchey SK. 2017. Oxytocin and behavior: Lessons from knockout mice. Dev Neurobiol. doi: 10.1002/ dneu.22431

Kendrick KM, Da Costa AP, Broad KD, Ohkura S, Guevara R, Levy F, Keverne EB. 1997. Neural control of maternal behaviour and olfactory recognition of offspring. Brain Res Bull 44:383–395.

Kenkel WM, Perkeybile AM, Carter CS. 2017. The neurobiological causes and effects of alloparenting. Dev Neurobiol. doi: 10.1002/dneu.22465

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. 2005. Oxytocin increases trust in humans. Nature 435: 673–676.

Lockard MA, Ebert MS, Bargmann CI. 2017. Oxytocin mediated behavior in invertebrates: An evolutionary perspective. Dev Neurobiol. doi: 10.1002/dneu.22466

Marlin BJ, Froemke RC. 2017. Oxytocin modulation of neural circuits for social behavior. Dev Neurobiol. doi: 10.1002/dneu.22452

Numan M, Young LJ. 2016. Neural mechanisms of motherinfant bonding and pair bonding: Similarities, differences, and broader implications. Horm Behav 77:98–112.

Owen SF, Tuncdemir SN, Bader PL, Tirko NN, Fishell G, Tsien RW. 2013. Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. Nature 500:458–462 . Pedersen CA, Prange AJ. Jr. 1979. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. Proc Natl Acad Sci U S A 76: 6661–6665.

Penagarikano O. 2017. Oxytocin in animal models of autism spectrum disorder. Dev Neurobiol. doi: 10.1002/ dneu.22450

Rilling JK, Young LJ. 2014. The biology of mammalian parenting and its effect on offspring social development. Science 345:771–776.

Sannino S, Chini B, Grinevich V. 2017. Lifespan oxytocin signaling: Maturation, flexibility and stability in newborn, adolescent and aged brain. Dev Neurobiol. doi: 10.1002/ dneu.22449

Saunders NR, Liddelow SA, Dziegielewska KM. 2012. Barrier mechanisms in the developing brain. Front Pharmacol 3:46.

Vaidyanathan R, Hammock EA. 2017. Oxytocin receptor dynamics in the brain across development and species. Dev Neurobiol. doi: 10.1002/dneu.22403

Walum H, Waldman ID, Young LJ. 2016. Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. Biol Psychiatry 79:251–257.

Young LJ, Wang Z. 2004. The neurobiology of pair bonding. Nat Neurosci 7:1048–1054.