Neuroendocrine
BRIEFING
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To bond or not to bond: Neuroendocrinology might have the answer

SUMMARY
Social animals seek social contacts as an essential part of life, ensuring their physical and mental well-being. Social bonds are formed and maintained by concerted neuroendocrine mechanisms, from ligand release to receptor binding and intracellular signalling involving oxytocin, vasopressin, dopamine and the corticotropin-releasing factor system, among others. Researchers have demonstrated how manipulating these neuroendocrine systems can break bonds, or augment them.

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During at least one phase of life, social animals form a bond, usually within the same species, e.g., between a mother (or parents in the case of biparental species) and her offspring, between siblings or between two sexual partners. Bonds are seen in mammals, birds, fish, reptiles and even invertebrates; and not forgetting one of the most common inter-species bonds - between a pet and their owner. The rather broad and simple definition of a bond is a mutual, selective relationship between two individuals for a certain time in life or even permanently. Both bonded partners benefit depending on the kind of bond, e.g., passing of parental genes, emotional, physical, and nutritional support, or pure survival. Interestingly, bond formation is thought to originate from the mother-infant bond - the first bond in life that shares overlapping neuropeptide systems and brain regions with other kind of bonds.

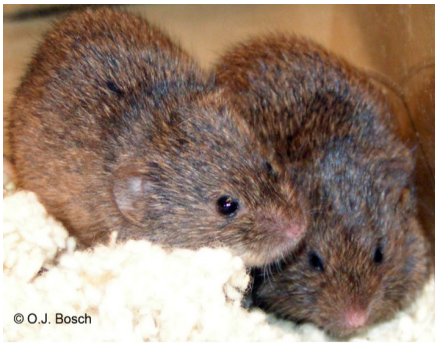
From sheep mothers to prairie vole couples

The underlying neuroendocrine basis is a fascinating topic that goes back to the 1980s when the maternal bond was studied between ewes and their lambs. Since then, our knowledge has increased significantly, especially due to maternal brain studies in rats and mice, which are easier to study than sheep. Likewise, studies using the monogamous, prairie vole (*Microtus ochrogaster*), where partners form a life-long pair bond with both parents caring for the offspring, in stark contrast to promiscuous montane (*Microtus montanus*) or meadow voles (*Microtus pennsylvanicus*), which don't show those specific bonds, have further advanced our understanding of bonding. Direct comparison of the brains of these species have revealed the neuroendocrine prerequisites necessary to establish a pair bond, to maintain it – but also what happens when the bond is dissolved (voluntarily or enforced).

Oxytocin does the trick - and vasopressin, too

For several years, the hypothalamic neuropeptide oxytocin was the focus of studies on social bonds - chiefly due to its role in mothers, i.e., induction of labour, milk let-down and for mother-offspring bonding. Oxytocin is colloquially referred to as the "love hormone" or "cuddle hormone", terms that imply a role in affiliation to another individual. Over time, attention shifted to the closely related neuropeptide, arginine vasopressin and its V1a receptor, especially in male pair bonding. Monogamous prairie voles have a much higher density of V1a receptors in the ventral pallidum compared to polygamous meadow voles. To attribute this difference to monogamy, scientists came up with a striking experiment - by blocking these receptors, prairie voles stopped showing a preference for their established partner. Even more fascinating, meadow voles became monogamous after increasing the expression of V1a receptors in the forebrain. The study attracted a lot of attention by

"…arginine vasopressin is not exclusive to bond formation in males - and neither is oxytocin for bonding in females"



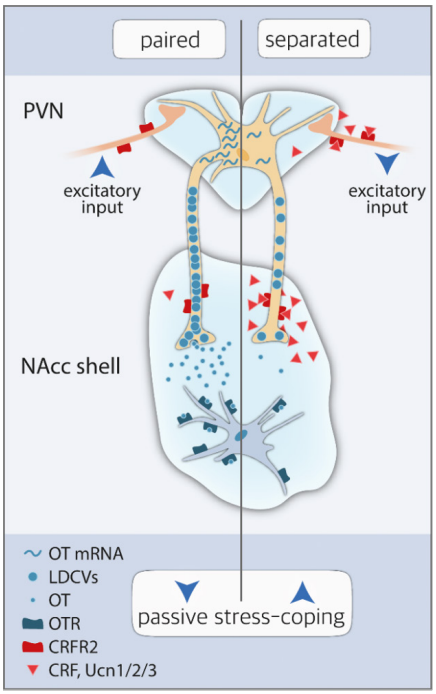


Image: Pair bond formation in monogamous prairie voles is mediated via oxytocin (OT) signalling from the paraventricular nucleus (PVN) to the nucleus accumbens (NAcc) shell, among others. After partner-loss, the OT signal is inhibited by chronic upregulation of corticotropin-releasing factor (CRF) system activity. Abbreviations: LDCV, large dense-core vesicle; Ucn, urocortin.

Figure: Reprinted from Int J Psychophysiol, 136, Pohl et al., Lost connections: Oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships, 54-63, 2019, with permission from Elsevier

the media, as in their words "the fidelity gene" or "key to faithfulness" had been discovered. However, arginine vasopressin is not exclusive to bond formation in males - and neither is oxytocin for bonding in females. Indeed, oxytocin is important for pair bonding in male prairie voles and arginine vasopressin is also important for the mother-offspring bond.

Reward and arousal having the same aim?

Equally important are the roles of the dopamine and corticotropin-releasing factor systems in bond formation. For the dopamine system, which is known for its key role in reward and motivation, this is not surprising. Positive interactions with others are perceived as rewarding, i.e., the dopamine system is activated even more in bonded relationships. However, it seems rather surprising that the corticotropin-releasing factor system, a key player in the stress response, can have somewhat positive effects on bond formation as demonstrated in prairie voles. In fact, acute activation of the corticotropin-releasing factor system leads to a degree of arousal or appetitive behaviour, which seems to be necessary for establishing a bond. On the other hand, bonds can be negatively influenced when activation of the corticotropin-releasing factor system becomes too great or lasts too long, i.e., following pharmacological interventions or persistent stressor exposure. In mothers, this can lead to neglecting the young. Moreover, the chronic stress associated with losing a pair-bonded partner, causes increased activity of the corticotropin-releasing factor system that, simultaneously suppresses oxytocin signalling – making a 'widowed' prairie vole suffer emotionally from the loss.

Where bonding research is heading

A variety of neurobiological tools have helped scientists study the neuroendocrine processes underlying bond formation or what happens when they are dissolved, from classic approaches such as immunohistochemistry, neuropharmacology, and electrophysiology to more modern techniques like optogenetics and chemogenetics. New emerging research is addressing other types of bonding, such as that between same-sex individuals or between different species. In the future, newly developed advanced imaging probes such as GRAB sensors will significantly advance our understanding of the neuroendocrine mechanisms and neurotransmitters behind bond formation, bond maintenance and even bond strength - potentially leading to the identification of targets for interventions in cases of neuroendocrine dysregulation, such as autism spectrum disorders or prolonged grief disorder.

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