Review

Biological Psychiatry

Oxytocin and Memory of Emotional Stimuli: Some Dance to Remember, Some Dance to Forget

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ABSTRACT

An ever-growing body of evidence suggests that the hypothalamic neuropeptide oxytocin plays a central role in the regulation of mammalian social behavior and relationships. Yet, mammalian social interactions are extremely complex, involving both approach and avoidance behaviors toward specific individuals. While in the past oxytocin was conceived merely as a prosocial molecule that nonselectively facilitated affiliative emotions and behavior, it is now recognized that oxytocin plays a role in a wide range of social relationships, some of which involve negative emotions such as fear, aggression, and envy and lead to avoidance behavior. However, the way by which a single molecule such as oxytocin contributes to contrasting emotions and opposite behaviors is yet to be discovered. Here, we discuss the role of oxytocin in the modulation of emotional memories in rodents, focusing on two paradigms: social recognition and fear conditioning, representing approach and avoidance behaviors, respectively. We review recent pioneering studies that address the complex effects of oxytocin in a mechanistic approach, using genetic animal models and brain region-specific manipulations of oxytocin activity. These studies suggest that the multiple roles of oxytocin in social and fear behavior are due to its local effects in various brain areas, most notably distinct regions of the amygdala. Finally, we propose a model explaining some of the contradictory effects of oxytocin as products of the balance between two networks in the amygdala that are controlled by the medial prefrontal cortex.

Keywords: Amygdala, Emotional memory, Fear conditioning, Medial prefrontal cortex, Oxytocin, Social recognition

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The central role played by the neuropeptide oxytocin in mammalian social behavior is now well documented (1). Yet, mammalian social interactions are extremely complex, involving both approach and avoidance behaviors toward specific individuals. Therefore, it seems surprising that a single molecule such as oxytocin may be involved in so many distinct types of social behavior, including pair bonding (2), aggression (3), social fear (4), parental relationships (5), intergroup relationships (6), and social trust (7). Furthermore, whereas oxytocin was initially conceived as a prosocial molecule that enhances social affiliation and trust (8), later studies showed that it facilitates a far wider range of social and emotional behaviors, including social fear, anger, and envy (9,10).

Recent research suggests that these diverse and contrasting effects of oxytocin may be attributed to the brain location of its activity. Here, we summarize several studies that employed genetic animal models and brain region-specific manipulations to explore the role of oxytocin in the acquisition and processing of emotional memories [see (11) for a comprehensive review of oxytocin and other types of memory]. Since the pattern of brain expression of the oxytocin receptor (OTR), thus the oxytocin effect in specific brain regions, was shown to be highly species-specific (12), we focus this review on the most common animal models—rats and mice. The research of oxytocin's influence on emotional memory makes use of two main paradigms: fear conditioning and social recognition memory, representing avoidance and approach responses, respectively. Accordingly, we divide this review into two parts discussing each of these paradigms.

SOCIAL MEMORY

Social Recognition Memory

The ability to recognize individual animals of the same species (conspecifics) and to distinguish them from other individuals is the basis for all mammalian social organizations and relationships (13). Social relationships may be divided into two classes. The first class includes those relationships involving a critical period associated with significant hormonal and physiological changes, such as infancy, motherhood, or mating. The type of memory associated with these relationships, in which the role of oxytocin has been reviewed in detail (14–17), seems to involve unique mechanisms resembling imprinting (18) or addiction (19). Notably, two recent works showed that oxytocin is involved in induction of maternal and sociosexual behaviors in female mice by modulating the activity of interneurons in distinct cortical areas (20,21).

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The second class includes relationships that are not associated with a unique period or event but rather based upon daily experience, such as the relationships that humans tend to develop with friends or colleagues.

Here, we will focus on the second type of social relationships, which are associated with social recognition memory (SRM) (22). Despite the intuitive conception that SRM should not be different from any other nonsocial recognition memory, a large body of evidence shows that SRM is mediated by a dedicated neuronal network. This network is regulated by molecules that act specifically to modulate this type of memory (23), the most studied of which is oxytocin (24).

Assessment of Social Recognition Memory

A behavioral paradigm for studying SRM was initially described by Thor and Holloway (25) more than three decades ago. Since then, several other paradigms, such as the social habituation-dishabituation (22,26) and social discrimination (27), were developed, each with its own advantages and limitations (28). The common denominator of all these paradigms is their use of the innate tendency of rats and mice to investigate novel social stimuli more persistently than familiar ones. For example, the social recognition paradigm initially proposed by Thor and Holloway (25) involves two short (2 to 5 minutes) unrestricted encounters of the subject with the same stimulus, separated by a certain time interval. Reduced investigation time in the second encounter compared with the first, presumably due to the decrease in stimulus novelty, is considered to reflect SRM.

All early studies using this paradigm reported that SRM could be observed only during a limited time period of 1 to 2 hours following the first encounter [reviewed in (29)]. Therefore, SRM was thought to be a form of short-term memory that for unknown reasons could not be consolidated into a long-term form (26). However, recent studies in mice (30) and rats (31) found that this is due to the fact that in most cases socially isolated animals were used as subjects, while the use of group-housed animals allows the formation of long-term SRM, lasting for at least a week. Thus, one unique feature of SRM is that rats and mice cannot form long-term SRM while held in social isolation.

The Neural Network Underlying Social Recognition Memory

In rodents, social memory was shown to be mediated mainly by chemical cues (semiochemicals) perceived via the main and accessory olfactory systems (23,32). Upon binding of semiochemicals to the receptors expressed by the sensory neurons of the main olfactory epithelium and the vomeronasal organ, sensory information is conveyed to the main olfactory bulb (MOB) and accessory olfactory bulb (AOB), respectively (33). Both bulbs project to the medial nucleus of the amygdala (MeA) either directly (34,35) or indirectly via the cortical amygdala (36). In turn, the MeA is thought to transfer the information to the lateral septum (LS) (37), which is strongly connected to various hippocampal and hypothalamic areas (38). Other brain regions that are associated with mammalian social behavior, such as the medial preoptic area (MPOA), bed nucleus of stria terminalis, entorhinal cortex, and medial prefrontal cortex (mPFC) (39–41) may also contribute to SRM.

A prerequisite for a neuromodulator to affect a brain region is the expression of its receptor in this area. Indeed, the oxytocin receptor is highly expressed in most brain regions associated with the main and accessory olfactory systems (Supplement 1). Moreover, most of these areas were found to be targeted by significant amounts of oxytocinergic fibers originating from magnocellular neurons in the hypothalamic paraventricular nuclei (PVN), accessory nuclei, and (for a minor extent) supraoptic nuclei (SON) (42).

Oxytocin and Short-Term Social Recognition Memory

During the last two decades of the 20th century, multiple studies investigated the effects of pharmacologic manipulations of oxytocin activity in the brain on short-term SRM (39,43–45). These studies mainly used the social recognition test with adult rats, and their conclusions were contradictory. Some studies showed an amnesic effect of oxytocin administration (44), while others, using a wider range of doses of intracerebroventricular (ICV)-administered OTR agonists and antagonists, came to a conclusion that at least in low doses oxytocin indeed improves short-term SRM (39,43,45,46). Yet, conclusive evidence for the role of oxytocin in SRM and the identification of brain areas involved in this activity were achieved only upon the use of genetic mouse models at the beginning of the 21st century.

In a seminal work, Ferguson *et al.* (47) used the social habituation-dishabituation paradigm to show that mice in which the oxytocin gene was knocked out (oxytocin knockout [OT-KO] mice) lacked short-term SRM. No differences were found between OT-KO mice and their wild-type (WT) littermates regarding their investigation of a novel social stimulus or in their performance in an olfactory-guided foraging task, suggesting no impairment in detection of novelty or olfactory stimuli. Moreover, OT-KO mice did not differ from their WT littermates in their habituation to olfactory or acoustic stimuli or in their performance in spatial memory tests. Finally, the researchers showed that ICV administration of oxytocin to OT-KO mice restored their SRM.

Similar results were obtained using mice in which the OTR gene was knocked out (48,49), as well as in CD38-KO mice in which oxytocin cannot be released from nerve terminals (50). Moreover, Crawley *et al.* (51) showed that in two distinct lines of OT-KO mice neither the social preference nor the novel social preference differed between OT null mice and their WT littermates, suggesting no impairment in social motivation or social novelty seeking. Altogether, these studies convincingly showed that oxytocin is important for short-term SRM but not for other types of nonsocial memory, signifying the involvement of unique, oxytocin-dependent mechanisms in SRM formation.

In a follow-up experiment, Ferguson *et al.* (52) located the site of action of oxytocin necessary for SRM. They showed that ICV-administered oxytocin rescues the short-term SRM deficit of OT-KO mice in a dose-dependent manner when given 10 minutes before, but not 10 minutes after, the first encounter with the social stimulus. This suggests that oxytocin is needed for SRM acquisition rather than retrieval of the