Psychoneuroendocrinology (2012) xxx, xxx—xxx

Available online at www.sciencedirect.com

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Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: Male juvenile versus female adult conspecifics

Michael Lukas [1], Iulia Toth [1], Alexa H. Veenema [2], Inga D. Neumann *

Department of Behavioral and Molecular Neurobiology, University of Regensburg, 93053 Regensburg, Germany

Received 6 March 2012; received in revised form 24 September 2012; accepted 25 September 2012

KEYWORDS
Social memory;
Mice;
Microdialysis;
Rats;
Retrieval;
Social discrimination

Summary Brain oxytocin (OXT) plays an important role in short-term social memory in laboratory rodents. Here we monitored local release of OXT and its functional involvement in the maintenance and retrieval of social memory during the social discrimination test. We further assessed, if the local effects of OXT within the medial amygdala (MeA) and lateral septum (LS) on social discrimination abilities were dependent on the biological relevance of the social stimulus, thus comparing male juvenile versus adult female conspecifics.

OXT release was increased in the LS of male rats during the retrieval, but not during the acquisition or maintenance, of social memory for male juvenile stimuli. Blockade of OXT activity by intracerebroventricular (ICV) administration of a specific OXT receptor antagonist (OXTR-A, rats: 0.75 μg/5 μl, mice: 2 μg/2 μl) immediately after acquisition of social memory impaired the maintenance of social memory, and consequently discrimination abilities during retrieval of social memory. In contrast, ICV OXTR-A was without effect when administered 20 min prior to retrieval of social memory in both species. Non-social memory measured in the object discrimination test was not affected by ICV OXTR-A in male mice, indicating that brain OXT is mainly required for memory formation in a social context.

The biological relevance of the social stimulus seems to importantly determine social memory abilities, as male rats recognized a previously encountered female adult stimulus for at least 2 h (versus 60 min for male juveniles), with a region-dependent contribution of endogenous OXT; while bilateral administration of OXTR-A into the MeA (0.1 μg/1 μl) impaired social memory for adult females only, administration of OXTR-A into the LS via retrodialysis (10 μg/ml, 1.0 μl/min) impaired social memory for both male juveniles and female adults. Overall, these results indicate

* Corresponding author at: Behavioral and Molecular Neurobiology, Institute of Zoology, University of Regensburg, 93053 Regensburg, Germany. Tel.: +49 941 943 3053; fax: +49 941 943 3052.
E-mail address: inga.neumann@ur.de (I.D. Neumann).
[1] These authors contributed equally to the manuscript.
[2] Present address: Department of Psychology, Boston College, 140 Commonwealth Avenue, McGuinn 522, Chestnut Hill, MA 02467, USA.

0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2012.09.018

Please cite this article in press as: Lukas, M., et al., Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: Male juvenile versus female adult conspecifics. Psychoneuroendocrinology (2012), http://dx.doi.org/10.1016/j.psyneuen.2012.09.018

that brain OXT is a critical mediator of social memory in male rodents and that, depending on the biological relevance of the social stimulus, distinct brain regions are recruited to mediate its effects.

1. Introduction

Recognition of and discrimination between conspecifics are essential behavioral components in the repertoire of social animals, such as humans and rodents, to enable appropriate social interactions that allow group living. In most non-primate mammals, social recognition is mediated via olfactory, mainly pheromonal signals (Carr et al., 1976). In laboratory rodents, short-term social memory can be measured using either the social recognition test or the social discrimination test. The former is performed by exposing animals to a conspecific during the acquisition period and then, after a defined inter-exposure interval (IEI), re-exposing the experimental rodent to the same conspecific stimulus during the retrieval period (Thor et al., 1982). In the social discrimination test, the acquisition is performed similarly, but the retrieval comprises of exposing the experimental rodents to the same conspecific along with a novel one (Engelmann et al., 1995). In these tests, short-term social memory is indicated by a decline in the investigation of the same conspecific during the retrieval period. Male juveniles or ovariectomized (OVX) adult females are typically used as social stimuli to prevent potential aggressive and/or sexual behavior from interfering with the main readout (e.g. social memory). Interestingly, memory duration can depend on the species and housing conditions. For example, individually housed male rats and mice typically maintain social memory for male juveniles for up to 60 min (Ferguson et al., 2000; Lukas et al., 2011a) reflecting a short-term memory, whereas group-housed male mice seem to maintain social memory for male juveniles for 24 h (Richter et al., 2005; Noack et al., 2010) up to 7 days (Kogan et al., 2000) reflecting a long-term social memory. However, the biological relevance of the social stimulus on social memory abilities has never been directly assessed in rats or mice, for example comparing social memory duration of male rodents for male juvenile, adult male or adult female conspecifics.

The neuropeptide oxytocin (OXT) has been recognized as an important modulator of various aspects of social behavior (Donaldson and Young, 2008; Neumann, 2009). Studies employing acute manipulation of the brain OXT system, and both OXT and OXT receptor (OXTR) knockout mice revealed its importance in short-term social memory (hereafter referred to as ''social memory'') in both male and female rats and mice (Dantzer et al., 1987; Bluthe and Dantzer, 1990; Popik et al., 1992a; Engelmann et al., 1998; Ferguson et al., 2000; Choleris et al., 2003; Takayanagi et al., 2005). In more detail, peripheral or central administration of OXT immediately after the acquisition period alter recognition of male juveniles, with low doses facilitating and high doses impairing recognition of juvenile conspecifics (Dantzer et al., 1987; Popik and Vetulani, 1991; Popik et al., 1992a; Benelli et al., 1995). These effects of OXT were blocked by pre-treatment with a selective OXTR antagonist (OXTR-A) revealing their specificity (Dantzer et al., 1987; Popik and Vetulani, 1991; Benelli et al., 1995), as the closely related neuropeptide arginine vasopressin also plays a role in social memory (see Bielsky and Young, 2004). Although intracerebroventricular (ICV) OXT had no effect on recognition of juvenile conspecifics in female rats, the OXTR-A impaired social memory, when administered immediately after the acquisition period (Engelmann et al., 1998) revealing the importance of the OXT system in social memory in both sexes. Furthermore, OXT and OXT-R knockout mice show sex-independent social memory deficits, which in male OXT knockout mice could be reversed by ICV administration of OXT before, but not after, the acquisition period (Ferguson et al., 2000; Choleris et al., 2003; Takayanagi et al., 2005), thereby complementing the earlier studies in rats.

Regional administration of OXTR ligands have further aided in the localization of OXT effects on social memory, thus increasing our understanding of the social brain network. While OXTR-A infusion into the olfactory bulbs, medial preoptic area or the lateral septum (LS) at the same timepoint did not affect juvenile recognition, OXT infusion into these regions facilitated social memory (Popik and van Ree, 1991; Popik et al., 1992b; Dluzen et al., 1998).

In this context, the most consistent data regarding OXT and social memory come from a series of studies focusing on the medial amygdala (MeA). Administration of OXTR-A or OXTR antisense oligonucleotide into the MeA of male and female mice, respectively, prior to the acquisition period impaired recognition of adult female conspecifics (Ferguson et al., 2001; Choleris et al., 2007). Further, the deficit in social memory observed in male OXT knockout mice could be rescued via intra-MeA OXT infusion. A functional role of these brain regions in the processing of social information is further indicated by the finding that contact with male juvenile or adult female social stimuli in male rats and mice was found to induce neuronal activation within the MeA and LS, respectively, as assessed using the immediate early gene cFos (Ferguson et al., 2001; Richter et al., 2005; Arakawa et al., 2010).

Although the involvement of OXT in social memory has been repeatedly demonstrated, OXT release patterns within relevant brain regions during the different stages of social memory have never been studied. Therefore, in the first part of the present study, we monitored OXT release by means of intracerebral microdialysis within the LS of male rats during acquisition, maintenance (the term maintenance is used instead of consolidation, as the latter refers to long-term memory), and retrieval of social memory for male juveniles. Next, we aimed to reveal whether the endogenous OXT system is involved in the maintenance versus retrieval of social memory in rats and/or mice. Finally, we tested the hypotheses that the duration of social memory is dependent on the biological relevance of the social stimulus, with prolonged maintenance of social memory for an OVX adult female, thought to be of higher biological valence, versus a

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