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ABSTRACT BOOK

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Oxytocin receptor-expressing neurons in the medial preoptic area control social behavior in rats

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The neuropeptide oxytocin is released during social interactions, acts through oxytocin receptors (OTRs) to regulate social behavior. The medial preoptic area (MPOA) of the hypothalamus, exhibiting a high density of neurons expressing OTRs. While the role of the MPOA in reproductive behavior has been extensively studied, recent evidence suggests that the MPOA is also involved in the control of affiliative social behavior.

The objective of this study was to investigate the functional role of OTR-expressing neurons in the MPOA in social behavior. MPOA OTR+ neurons were selectively stimulated by chemogenetics in OTR-Cre female rats. Adeno-associated virus (AAV) expressing excitatory designer receptors (DREADDs) was injected into the MPOA in a Cre-dependent manner. The treatment day was compared to the previous and subsequent control days, during which the animals received only vehicle injections.

Following the stimulation of OTR+ neurons through the injection of the DREADD's ligand clozapine-N-oxide (CNO), a significant increase was observed in the number and duration of the following behavioral elements: allogrooming, body sniffing, mounting, and chasing. A significant reduction in the frequency and the duration of non-social behaviors was also observed. A control group of rats was also established, in which the subject animals were injected with AAV without the DREADDs. In this group, the behaviors were not affected by CNO treatment, they exhibited comparable behaviors to those observed in the rats in the excitatory group during the vehicle control days. Furthermore, the stimulation of the excitatory DREADDs did not alter the animals' sociability, social preference, depression-, and anxiety-like behavior. Using fiber photometry, we found that MPOA OTR+ neurons are activated during anogenital sniffing. Finally, the projections of MPOA OTR+ neurons were mapped by anterograde viral tract tracing demonstrating projections to multiple brain regions, including the periaqueductal grey matter (PAG) and the lateral septum (LS). Both regions are implicated in the control of social behavior. We also showed that OTR+ MPOA neurons are innervated by parathyroid hormone 2 containing terminals ascending from the thalamus, which are known to relay touch-related signals during direct social interactions. These observations suggest that MPOA OTR+ neurons may facilitate social interactions between adult female rats via projections to the PAG and the LS.

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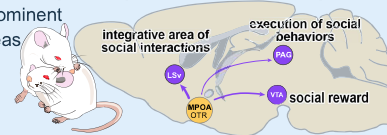


Introduction

Medial preoptic area which is the anterior region of the hypothalamus is known for its role in maternal behavior, however recent findings indicate its role in controlling affiliative social behavior, too. Our research group demonstrated that the MPOA promote social grooming between female conspecifics through its thalamic input. It is well established that the oxytocin system affects affiliative social behavior, however the role of these neurons in the MPOA in affiliative social behavior has not been studied yet. In this study our aim was to reveal the role of the OTR-expressing neurons in the MPOA in affiliative social behavior using chemogenetics and fiber photometry in transgenic (OTR-Cre) rats.

Results

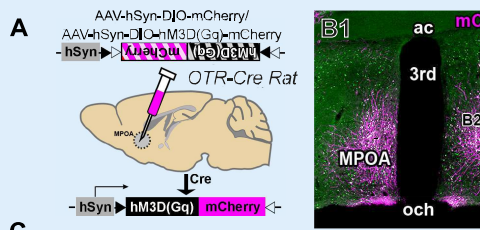
- Stimulation of OTR+ neurons in the MPOA led to increased social behavior between adult female rats.
- The stimulation did not affect the locomotor activity and the anxiety- and depression-like behavior of the rats.
- MPOA OTR+ neurons showed increased activity during anogenital sniffing which is followed by direct contact behaviors, such as mounting and allogrooming.
- MPOA OTR+ neurons send prominent projections to several brain areas involved in social behavior.



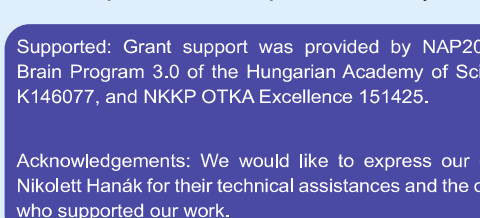
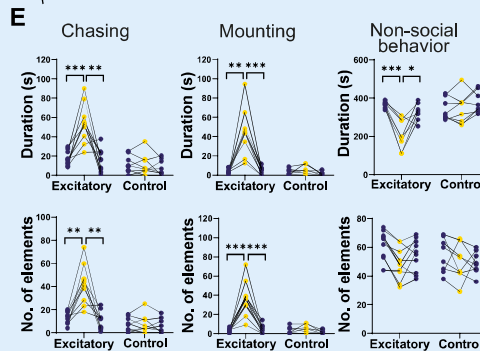
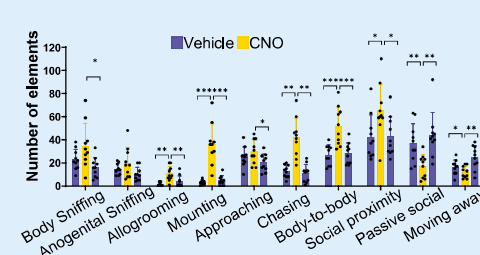
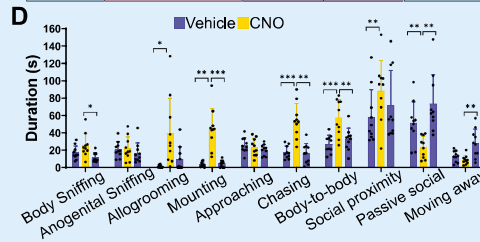
Conclusion

We identified OTR+ neurons and their inputs in the MPOA of female rats, implicating them in the regulation of affiliative social interactions. We also found that during anogenital sniffing MPOA OTR+ neurons are activated, and the stimulation of these neurons leads to increased chasing, and direct contact behaviors such as mounting. This suggests a potential function of MPOA OTR+ neurons in facilitating these direct contact behaviors following anogenital sniffing, which may be exerted by their major projections to the LSv, PAG and VTA.

The stimulation of oxytocin receptor-expressing neurons in the MPOA affects affiliative social behavior



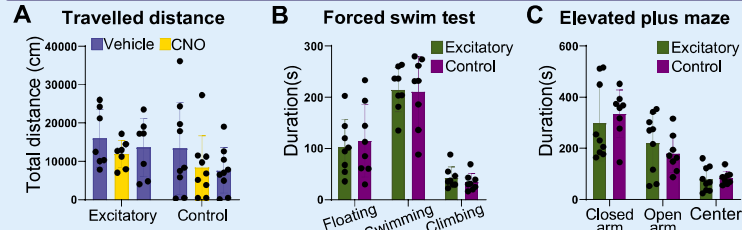
Day 1	Day 2	Day 3	Day 4	Day 5
Vehicle Social tests Open field test	CNO Social tests Open field test Elevated plus maze Forced swim test	Resting day	Resting day	Vehicle Social tests Open field test



(A) Injection of anterogradely spreading adeno-associated virus (AAV) to express excitatory designer receptors (hM3D(Gq)) and mCherry in a Cre-dependent manner in the MPOA of OTR-Cre rats. In the control group the animals lacked the receptors. (B1-2) Those cells that had taken up the virus and expressed designer receptors were activated after clozapine N-oxide (CNO) injection.

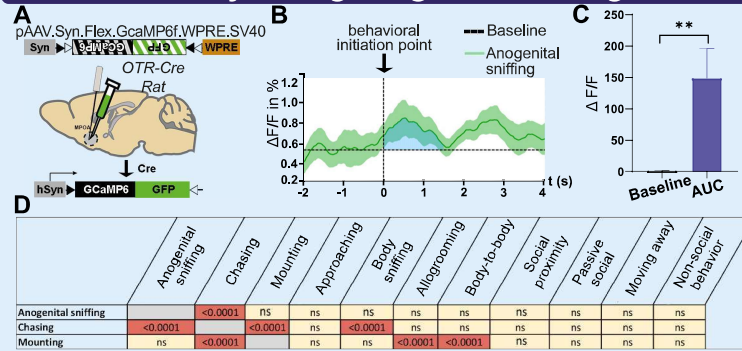
(C) Experimental method of behavioral tests. 'Social tests' refers to sociability, social recognition and direct social interaction tests. (D) The stimulation of OTR+ neurons in the MPOA resulted in significant increase in the duration and the number of several prosocial behavior elements meanwhile the antisocial behaviors were significantly decreased compared to the control vehicle days. (E) The graphs show the individual points and the changes in chasing, mounting and non-social behavior in the excitatory group after CNO administration. In contrast, CNO administration did not cause any changes in the behavior of the control group.

The stimulation of OTR+ neurons did not alter the locomotor activity and the anxiety- and depression-like behavior of the animals



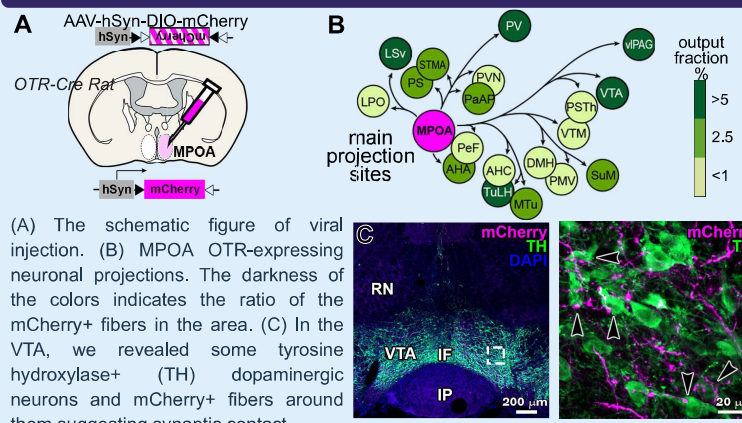
A) The stimulation of OTR-expressing neurons did not affect the locomotor activity. The travelled distance of the excitatory group was similar as the control group. B-C) Furthermore, both groups demonstrated comparable behavior in the forced swim test (B) and in the elevated plus maze (C).

The OTR-expressing neurons showed increased activity during anogenital sniffing



(A) Injection of anterogradely spreading AAV to express GCaMP, a calcium indicator and GFP. The cannula was placed into the MPOA as well. (B) Illustration of the analysis of the ΔF/F signal in case of anogenital sniffing. (C) Statistical analysis of the comparison of baseline and maximum ΔF/F value (area under curve value). (D) Anogenital sniffing is significantly followed by chasing, mounting and social proximity. It was also found that chasing is significantly followed by anogenital sniffing, mounting and body sniffing. The end point of the behavioral chain is the grooming behavior or body-to-body contact or remaining in social proximity as these behaviors follow mounting.

MPOA OTR+ neurons project to several brain regions involved social behavior



(A) The schematic figure of viral injection. (B) MPOA OTR-expressing neuronal projections. The darkness of the colors indicates the ratio of the mCherry+ fibers in the area. (C) In the VTA, we revealed some tyrosine hydroxylase+ (TH) dopaminergic neurons and mCherry+ fibers around them suggesting synaptic contact.

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