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Lateral septum affects maternal adaptation via a parathyroid hormone 2 neuropeptide-containing pathway arising from the thalamus

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Introduction

Parental care is a special form of social behaviour, which increases the survival of the offspring. The neural network behind maternal behaviour is complex and includes different brain areas. Our research group previously described that neurons in the posterior intralaminar thalamic nucleus (PIL) express an excitatory neuropeptide, parathyroid hormone 2 (PTH2), whose expression is induced in mothers. We also showed that the medial preoptic area (MPOA), a well established, major site to control maternal behaviour, receives pup induced suckling information from the PIL via PTH2+ fibres. The lateral septum (LS), which was previously found to be involved in central maternal adaptation, also contains PTH2+ fibres. Therefore, we hypothesize that the LS takes part in maternal adaptation driven by the PTH2+ pathway originated from the PIL. To support our hypothesis, we addressed the following specific objectives:

- Determination whether PTH2+ fiber terminals closely appose LS neurons activated by pup exposure in mother rats
- Identification of the origin of PTH2+ fibers in the LS by anterograde and retrograde tract tracing
- Comparison of neuronal populations in the PIL projecting to the LS and the MPOA using double retrograde tracing

Results

- LS shows a significantly increased number of activated neurons in lactating females following pup exposure, which are closely apposed by PTH2+ fibres in rat dams
- The dense PTH2+ projection in the LS originates from the maternally activated and Cb+ neurons of the PIL
- Cb+ PIL neurons project to the MPOA neurons, too
- Some inputs received by both LS and MPOA originate from the same neurons of the PIL

Conclusion

Activation of LS neurons during pup exposure may be accomplished via the PTH2 mediated signalling pathway from the PIL. In turn, PIL neurons convey the stimulatory signal of pups to both the lateral septum and the MPOA thereby contributing to their roles in maternal behaviour.

2. PIL neurons activated following pup-exposure send PTH2+ projection to the lateral septum

A biotinylated dextran amine (BDA) **B** PIL **C** BDA PTH2

D LSv **E** LSv **F** LSv

G cholera toxin B (CTB) **H** CTB **I** CTB

J CTB **K** CTB

The lateral septum receives input from PTH2+ neurons of the posterior intralaminar thalamic nucleus. **A**: Illustration of the injection of the anterograde neuronal tracer, biotinylated dextran amine (BDA) into the posterior intralaminar thalamic nucleus (PIL). **B**: Injection site in the PIL followed by peroxidase-based immunoreaction. **C**: Confocal image shows that several BDA containing neurons express PTH2, as well. **D**: Representative image of the projection seen in the LS. **E**: BDA-containing terminals originated from the PIL show PTH2 immunopositivity, as well. **F**: c-Fos activated neurons in the lateral septum are surrounded by BDA containing fibres. **G**: Illustration of the injection of the retrograde tracer, cholera toxin B (CTB) into the LS of mother rat. **H-I**: Confocal images of the PIL show retrogradely labelled CTB+ (green) and pup-induced c-Fos+ (magenta) neurons. Black arrowheads sign the c-Fos+ LS-projecting neurons.

1. c-Fos activation in the lateral septum of mother rats

A 22 h 2 h **B** LSv

C 22 h 2 h **D** LSv

E **F** PTH2 c-Fos

G **H** CTB **I** CTB

J CTB **K** CTB

Lateral septum (LS) shows elevated number of c-Fos-activated neurons in its ventral part. In addition, PTH2+ axons originated from the PIL closely appose the c-Fos+ lateral septal neurons. **A**: Illustration of the experimental protocol of revealing neuronal activation in absence of pups in mother rats. **B**: Representative image of the LS of rat dams without pup interaction. **C**: Illustration of the experimental protocol of revealing neuronal activation in response to pups in mother rats. **D**: Representative image of the LS of rat dams following pup exposure. **E**: The number of c-Fos+ neurons in the examined area. ***: $p < 0.001$. **F**: PTH2+ axons closely appose c-Fos+ neurons located in the ventral part of LS.

3. Calbindin+ neurons of PIL project to the MPOA and the LS of rats

A cholera toxin B (CTB) **B** Calbindin CTB **C** Calbindin CTB

D retrogradely transported AAV-mCherry **E** Calbindin rAAV-mCherry **F** Calbindin rAAV-mCherry

G retrogradely transported AAV-mCherry **H** CTB rAAV-mCherry **I** CTB rAAV-mCherry

Calbindin+ (Cb+) neurons of the PIL project to the medial preoptic area (MPOA) and LS. Further, LS and MPOA receive input from the same neurons of the PIL. **A**: Illustration of the retrograde tracer, cholera toxin B (CTB) injection with a representative image of the injection site in the MPOA. **B, C**: CTB+ MPOA-projecting neurons of the PIL show Cb positivity (black arrowheads). **D**: Illustration of the retrogradely transported mCherry containing adeno-associated viral vector (rAAV) injection, and a confocal image of the injection site in the LS. **E, F**: Similarly to the MPOA, mCherry labelled LS-projecting neurons of the PIL show Cb positivity (black arrowheads). **G**: Illustration of the double retrograde tracing of the LS and the MPOA with representative images of the injection sites. **H**: Retrogradely labelled neurons are localized in the PIL. **I**: Higher magnification image demonstrates neurons projecting to the LS, to the MPOA and to both areas (black arrowheads).

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International Neuroscience Meeting, Budapest 2022

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Poster session - Topic 5
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P5.25 Lateral septum affects maternal adaptation via a parathyroid hormone 2 neuropeptide-containing pathway arising from the thalamus

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Parental care is a special form of social behaviour, which increases the survival of the offspring. Our research group previously described that neurons in the posterior intralaminar thalamic nucleus (PIL) express an excitatory neuropeptide, parathyroid hormone 2 (PTH2), whose expression is induced in mothers. Here, we demonstrate that PIL neurons expressing PTH2 send projection to the lateral septum (LS). Furthermore, we confirmed that lateral septal neurons show significantly elevated number of c-Fos-activated neurons in mother rats following pup exposure compared to control mothers without pup interaction. Nerve terminals of LS-projecting PTH2+ fibres arising from the PIL show the same distributional pattern within the LS as pup-activated c-Fos+ neurons. Therefore, we made further examinations and found that PTH2+ terminals closely appose c-Fos-activated septal neurons. Furthermore, PIL neurons projecting to the LS show c-Fos-activation in mother rats following interaction with the pups. Beside the LS, PTH2-expressing neurons of the PIL also send dense projection to the medial preoptic area (MPOA), therefore, we further examined this neuronal pathway. We determined that projections to LS and MPOA origin from the calbindin-positive neuron population of the PIL. By injecting different retrograde tracers into the LS and MPOA of the same rats, we demonstrated that PIL neurons projecting to the LS send axon collaterals to the MPOA, too.

We conclude that calbindin-positive PIL neurons project both to the lateral septal neurons and MPOA neurons. We investigated the septal projections where the terminals contain PTH2 neuropeptide, and innervate lateral septal neurons. Since pup exposure activates neurons in all 3 brain regions, our data suggest that PIL neurons convey the stimulatory signal of pups to both the lateral septum and the MPOA thereby contributing to their role in the maternal adaptation.

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