GRK 2174 Kolloquium

Speaker:

Dr. Jan Deussing

PhD

Max Planck Institute of Psychiatry

Department of Stress Neurobiology and Neurogenetics,

Munich

Time/Location:

21.06.2018 at 4 pm s.t.

New Biology Building / H52

invited by:

Prof. Dr. Inga Neumann

Title:

CRH-related circuits - shaping emotional behaviors

Abstract:

Dysregulated and/or hyperactive corticotropin-releasing hormone (CRH) circuits were shown to be involved in neuroendocrine and behavioral disturbances of stress-related disorders including anxiety and depression. While the role of CRH as an indispensable initiator of the neuroendocrine cascade of the hypothalamic-pituitary-adrenal axis is well defined, we are just starting to comprehend the function of extrahypothalamic CRH with regards to emotionality and behavioral stress responses. In this respect, we were able to provide a clearer understanding of the interaction of CRH and other neurotransmitter systems by unravelling that anxiety-related behavior is modulated by an imbalance between CRH receptor type 1 (CRHR1)-controlled anxiogenic glutamatergic and anxiolytic dopaminergic circuits (Refojo et al., 2011; Science 333,1903-7). However, the identity of CRH-releasing neurons and sites of CRH action that modulate anxiolytic behavioral responses have not been fully established yet. Using neurochemical and genetic tools we identified that cortical and limbic CRH is primarily expressed in GABAergic neurons, which exhibited distinct morphologies depending on the brain region. Anterograde tracing studies of

forebrain limbic CRH neurons revealed GABAergic long-range projecting axons, which innervated distant brain regions including the ventral tegmental area (VTA), which harbors the majority of CRHR1-expressing dopaminergic neurons. We found that deletion of CRH from these GABAergic long-range projection neurons enhanced anxiety and fear memory expression, implicating that this specific CRH circuit is required under physiological conditions to maintain a positive emotional state. Considering that deletion of CRHR1 from dopaminergic neurons produces similar effects and diminished dopamine release in the PFC (Refojo et al., 2011; Science 333,1903-7), we additionally assessed dopaminergic neurotransmission in mice lacking CRH in GABAergic projection neurons. Accordingly, these animals displayed reduced baseline dopamine release in the PFC, suggesting that a subset of CRH-expressing GABAergic projection neurons in the limbic forebrain target CRHR1 on dopaminergic neurons to modulate emotional behavior by regulating dopaminergic neurotransmission. In conclusion, our results reveal a previously unidentified anxiety-suppressing CRH circuit which regulates DA release to ultimately modulate emotional behavior. These results indicate that CRHR1 is balancing glutamatergic and dopaminergic circuits controlling anxiety-related behavior and suggests that a stress-associated dysfunction of a CRH/CRHR1-dependent control system might elicit an imbalance of these two neurotransmitter systems which could ultimately lead to emotional disorders.