Chemogenetic activation of the locus coeruleus increases noradrenaline levels in the hippocampus and modulates its hippocampal excitability

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Purpose: The brainstem locus coeruleus (LC) is the sole source of noradrenaline in the neocortex, hippocampus and cerebellum. Noradrenaline is an endogenous neuromodulator involved in the regulation of excitability and plasticity of large-scale brain networks. Previous pharmacological studies have indicated that noradrenaline is able to potentiate dentate gyrus excitability and increases the population spike of perforant-path evoked potentials. These studies hold several limitations, since pharmacological interventions are likely to induce unintended off target effects. Recent development of tools for precision modulation of the LC, including Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) allow the study of LC physiology with unprecedented detail. In this study, we assessed the influence of chemogenetically activating the LC on noradrenergic signaling and excitability in the hippocampus.

Methods: Male Sprague Dawley rats (n=5) were stereotactically injected with the viral vectors CAV2-PRSx8-hM3Dq-HA hSyn-mCherry in the LC and AAV9-hSyn-NE2m-mRuby3 in the hippocampus to induce expression of hM3Dq in noradrenergic LC neurons and the $GRAB_{NE2m}$ noradrenaline biosensor in hippocampal neurons. Two weeks after vector injection rats were anesthetized and implanted with a stimulation electrode in the perforant path (PP) and a recording optrode in the dentate gyrus. Rats were injected with deschloroclozapine (DCZ, 0.1 mg/kg, s.c) to chemogenetically activate the LC and the effects on noradrenaline signaling and dentate gyrus electrophysiology were assessed by comparing $GRAB_{NE2m}$ fluorescence, EEG and evoked potentials before and after DCZ injection.

Results: Injection of DCZ resulted in a pronounced increase in $GRAB_{NE2m}$ fluorescence (z-score range: 5 - 15), a decrease in EEG power and an increase in the amplitude of the population spike of the dentate gyrus evoked potential (a marker for postsynaptic activation of DG neurons). No significant change in the slope of the evoked potential (a marker of synaptic strength) was found. In individual animals, changes in the population spike amplitude and EEG power were significantly correlated to the observed changes in $GRAB_{NE2m}$ fluorescence.

Conclusions: This study is the first to assess the effect of chemogenetic activation of the LC on noradrenaline signaling in the hippocampus with GRAB-sensor technology, providing unprecedented temporal resolution. By means of cell-type specific modulation of LC neurons, we were able to confirm previous findings of pharmacological studies with superior precision and specificity.

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