

Summary

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“Mechanisms of contextual fear memory generalization”

Three models were applied to identify molecular factors involved in emotional relevant behavior. Combination of behavioral paradigms and gene expression analysis via laser capture microdissection and quantitative real time PCR highlighted the contribution of different hippocampal subregions to these processes.

Firstly, using classical fear conditioning to auditory cues and contextual stimuli, a pivotal role of neuropeptide Y (NPY) signaling in the dentate gyrus in determining contextual salience during auditory cued fear conditioning was revealed. Activation of NPY-positive interneurons in the hilus via immunohistochemically detected transcription factor P-CREB was found after cued but not contextual fear conditioning. Selective inhibition of CREB activation via conditional viral vectors in these interneurons resulted in increased contextual fear responses. Such contextual generalization was also observed when NPY signaling itself was pharmacologically blocked prior to cued fear conditioning.

Secondly, GABAergic factors like GAD65 and GABA A receptor subunits contributed to adaptive processes in response to juvenile stress in the ventral CA1 region in a model for posttraumatic stress disorder. Combined adult and juvenile stress omitted the correlation between marker genes for GABAergic and glutamatergic functioning, suggesting changes in the inhibitory/excitatory balance in the ventral CA1. These changes might also contribute to generalization towards the background context in auditory cued fear conditioning observed after juvenile stress in mice.

Fear memory reactivation applied as the third model induced such contextual generalization as well by retuning of the system after initial fear conditioning and exerted anxiolytic effects via corticosterone action in the ventral CA3 area.

All three models modulate anxiety and fear-related emotional behavior dependent on amygdalo-hippocampal interaction. Inhibitory signaling in different hippocampal subregions thereby regulates the balance between cue and contextual response in fear conditioning and contributes to contextual generalization. These findings are highly relevant for understanding (mal-) adaptation to fear-eliciting situations in anxiety disorders like posttraumatic stress disorder.