COMPLETE GENETIC ABLATION OF CREB IN THE BRAIN IMPAIRS CONDITIONED TASTE AVERSION BUT SPARES SPATIAL MEMORY AND CONTEXTUAL FEAR CONDITIONING

Hans-Peter Lipp[1], Peter Gass[2], Hans Welzl[1], Günther Schütz[3], Theo Mantamadiotis[3], and David P. Wolfer[1]

[1]Institute of Anatomy and Center for Neuroscience, University of Zürich, Switzerland; [3]Department of Molecular Biology of the Cell I, German Cancer Research Center, University of Heidelberg, and [2] Central Institute of Mental Health Mannheim, Germany

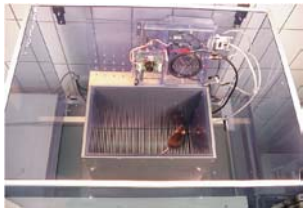
INTRODUCTION

Previous gene targeting studies addressing the role of the transcription factor CREB in mammalian long-term synaptic plasticity and memory were compromised by incomplete deletion of the ß-isoform of CREB. Therefore, we studied conditional knock-out lines with a deletion of all CREB-isoforms in the brain or specifically in the mature forebrain and compared them with earlier data obtained in hypomorphic CREB mutants.

METHODS

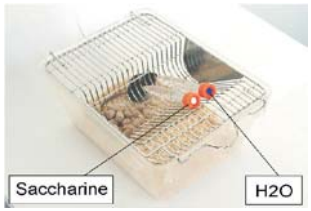
Animals
deletion of all CREB-isoforms .....
whole brain --> $CREB^{NesCre}$ mice
only mature forebrain --> $CREB^{CamKIICre7}$ mice

Apparatus
Hippocampus-dependent learning:
Water maze
Contextual fear conditioning (pictured)



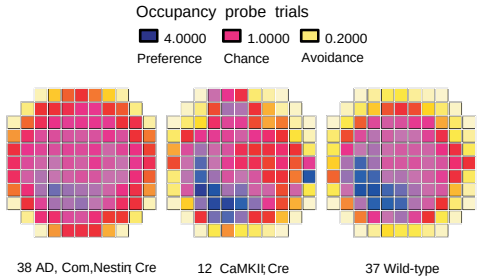
novel context (CS) + foot shock (UCS)

Hippocampus-independent learning:
Conditioned taste aversion (pictured)



novel taste (saccharin/CS) + malaise (LiCl/UCS)

RESULTS 'WATER MAZE'



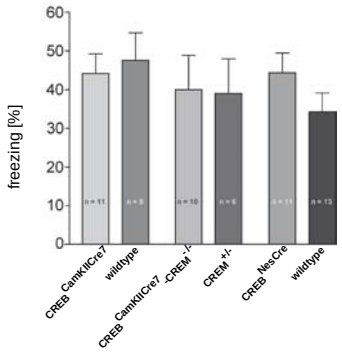
Mutants showed slightly reduced escape performance in the watermaze, reminiscent of the phenotype displayed earlier in the same paradigm by hypomorphic CREB mutants. However, the deficit in the watermaze was unrelated to spatial memory. Most strikingly, $CREB^{CamKIICre7}$ mice showed normal spatial preference during probe trials (see above).

Comparison of training and probetrial performance of CREB mutant mice in the water maze

		All animals N = 87 1-way ANOVA pooled wt, aD, comp, NesCre, CamKIICre	All mutants N = 49 1-way ANOVA aD, comp, NesCre, CamKIICre	1-way ANOVA	Mutans excl. CamKIICre N = 37 ANOVA aD, comp, NesCre	All animals N = 87 2-way ANOVA int. genotype x CamKIICre
training	escape latency (s)	p<.0019	ns		ns	ns
	path length (m)	p<.0016	ns		ns	ns
	search error (m*s)	p<.0015	ns		ns	ns
	wall hugging (%)	p<.0006	ns		ns	ns
probe trial 1	% time in trained quadrant	p<.0402	p<.0656		ns	p<.0234
	% time in trained zone	p<.0017	p<.0226		ns	p<.0121
	crossing preference (x/m)	p<.0263	p<.0149		ns	p<.0016
	proximity (m)	p<.0014	p<.0346		ns	p<.0364
	polar error (°)	p<.0343	p<.0368		ns	p<.0613
probe trial 2	% time in trained quadrant	p<.0512	p<.0628		ns	p<.0077
	% time in trained zone	p<.0173	p<.0502		ns	p<.0101
	crossing preference (x/m	ns	ns		ns	p<.0680
	proximity (m)	p<.0367	ns		ns	p<.0432
	polar error (°)	p<.0407	p<.0408		ns	p<.0197

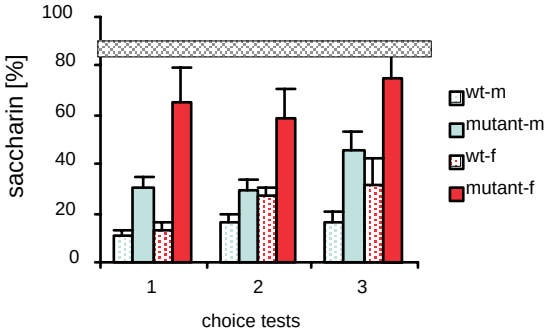
"Table cells indicate ANOVA p-values. Values > 0.1 are shown as ""ns"". wt = wild-type, definition of mutant lines: see text. Last column: factor genotype = pooled wt versus pooled CREB deficient , factor CamKIICre =CamKIICre mutation (exclusion of development, restriction to forebrain) versus ubation in which mutation is active during development (aD, comp, NesCre)."

RESULTS 'FEAR CONDITIONING'



Contextual fear conditioning was normal in both lines.

RESULTS 'TASTE AVERSION'



Conditioned taste aversion was impaired in male (blue) and even more so in female (red) $CREB^{NesCre}$ mice (solid columns) when compared to the respective wildtypes (dotted columns). In contrast, all mice displayed the same preference for the saccharin solution when consumption of it was not followed by malaise (gray bar).

CONCLUSIONS

These data of $CREB^{CamKIICre7}$ and $CREB^{NesCre}$ mutants imply that CREB .....
(i) is not essential for assumedly hippocampus-dependent learning and memory in the mouse;
(ii) might be of relevance in extrahippocampal regions, and
(iii) possibly undergoes partial functional compensation in the adult brain through upregulation of the associated transcription factor CREM or other mechanisms.

Further, ...
(iv) both CREBCamKIICre7 and CREBNesCre mutants also show normal hippocampal late-LTP and late-LTD (see Balschun et al., Soc. Neurosci. Abstr. 26, 2000), and
(v) the more severe deficits of the earlier hypomorphic mutants might have been caused by low prenatal levels of CREB.

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