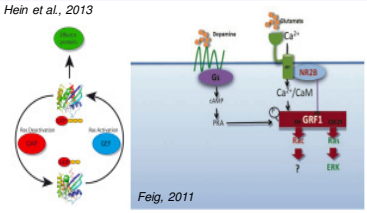
The Role of Ras-GRF1 in Cocaine Self-Administration

Anastasia Olevska[1], Rick E. Bernardi[1], Riccardo Brambilla[2], Rainer Spanagel[1]

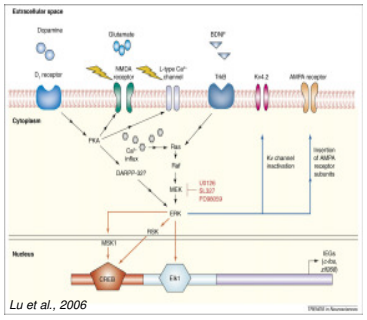
[1] Central Institute of Mental Health, Mannheim, Germany
[2] Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy

SFB 636

Background



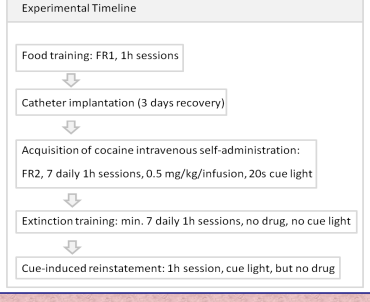
- Ras acts as molecular switch and is part of ERK signaling.
- Ras - Guanine Nucleotide Releasing Factor 1 (Ras-GRF1) catalyzes binding of GTP by Ras.
- Ras-GRF1 integrates both glutamate and dopamine signals in the striatum *(Fasano et al., 2009)*, a brain region associated with the development, progression and persistence of drug addiction.
- Both cocaine locomotor sensitization and conditioned place preference are attenuated in Ras-GRF1–deficient mice and facilitated in Ras-GRF1–overexpressing animals *(Fasano et al., 2009)*.



Methods

Figure 1. Operant conditioning chamber.

Subjects: Male *ras-grf1* knockout (KO) and overexpressing (OE) mice and their wild-type conspecifics.



Results

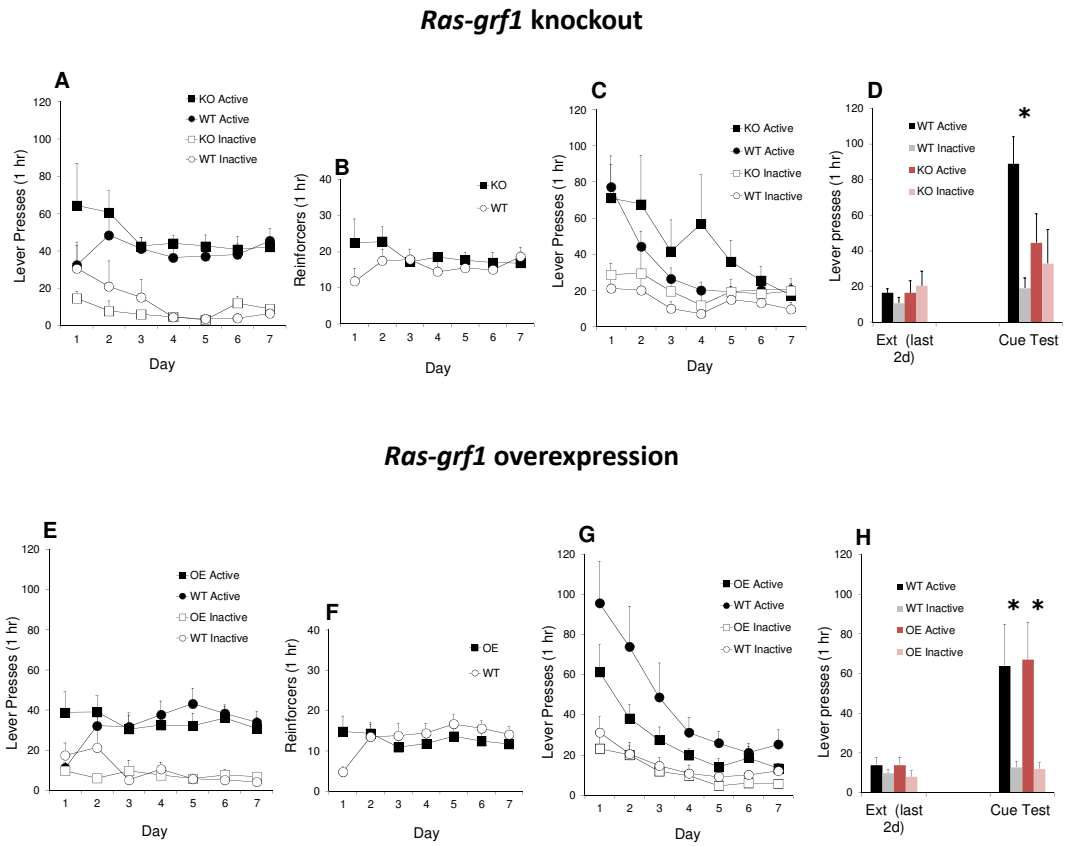


Figure 2. Role of Ras-GRF1 in cocaine-associated cue-induced reinstatement in *ras-grf1* KO (A-D, N=6/group) and *ras-grf1* OE (E-H, N=10/group) mice.

(A,B,E,F) Mice were trained to lever press for intravenous cocaine (0.5 mg/kg per infusion) paired with a cue light (20s) located above the levers on an FR2 schedule of reinforcement for 7 consecutive days. No differences were detected in the acquisition of cocaine self-administration between groups. **(C,G)** Following acquisition, animals underwent minimum 7 days of extinction. Responses on the active lever no longer resulted in the delivery of a cocaine injection or cue light. No significant differences between the groups were seen. **(D,H)** After reaching the extinction criteria, animals underwent cue-induced reinstatement. Presses on the active lever resulted in the presentation of the light cue but no cocaine was delivered. Here, although both *ras-grf1* KO and wild-type mice reinstated responding relative to extinction levels [three-factor (lever, test, group) ANOVA; main effect of test: $F_{(1,10)}=20.61$, $p<.01$], the *ras-grf1* KO animals failed to reinstate the selectivity between the reinforced and the non-reinforced levers as assessed using paired *t*-test analysis of active and inactive levers in each group [*ras-grf1* KO: t(5)=.92, $p=.40$ vs. wild-type: t(5)=2.79, $p=.04$]. No differences were seen in the *ras-grf1* OE animals compared to wild-types. Total numbers of active and inactive lever presses (A,C,D,E,G,H; mean+SEM) or obtained reinforcers (B,F; mean+SEM) per session are shown.

Conclusions

a) Loss of Ras activator Ras-GRF1 resulted in an impaired cue-induced reinstatement of previously established cocaine self-administration behavior.

b) Consistent with findings using the CPP paradigm (*Fasano et al., 2009*), Ras-GRF1 appears to mediate the secondary, but not primary, reinforcing properties of cocaine.

c) In the case of *ras-grf1* overexpression, another experimental setting may be more sensitive to detect genotype effects.

References:

Fasano S *et al.*, 2009. *Biol Psychiatry 66 (8):* 758-768.
Feig LA, 2011. *Genes Cancer 2(3)*: 306-319.
Hein C *et al.*, 2013. *eLife 2*:e01159.
Lu L *et al.*, 2006. *Trends in Neurosciences 29(12):* 695-703.

Supported by the DFG, SFB 636/B1