Cocaine craving is accompanied by glutamate imbalance in the reward system

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Introduction

- → Chronic cocaine administration in rodents leads to decreased basal glutamate (Glu) levels in the nucleus accumbens (NAcc)[1]
- → Reinstatement of drug-seeking results in enhanced Glu transmission[1]
- → Limited knowledge about neurometabolism in human cocaine addiction
- → No approved pharmacotherapy for cocaine addiction

The glutamate homeostasis hypothesis of addiction

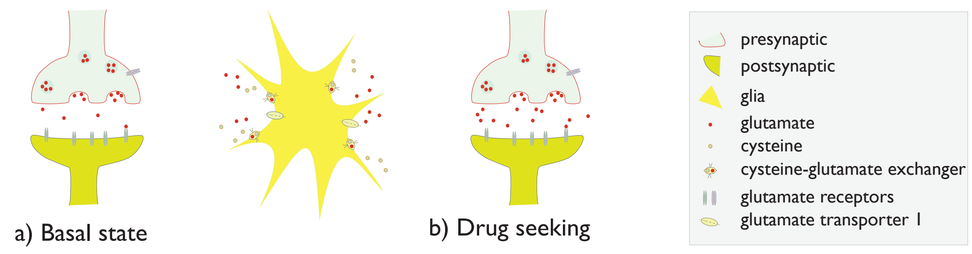

Fig. 1: Reduced glial regulation of glutamate in the nucleus accumbens core after chronic cocaine use. (a) Reduced level of extracellular glutamate during rest. (b) Overflow of synaptic glutamate after reinstatement of drug-seeking.[1]

Aim

Investigation of potential changes within Glu homeostasis in the NAcc of cocaine-addicted individulas during rest and cue-induced cocaine craving with a novel proton magnetic resonance spectroscopy (^{1}H-MRS) protocol for small voxels.

Methods

Participants

- 26 cocaine-addicted individuals with average use of 5.71grams/week (CAI)
- 30 matched healthy control individuals (HCI)

^{1}H-MRS

- Non-water suppressed PRESS with metabolite-cycling pulse and inner-volume saturation[2]
- Absolute quantification of metabolites[3]
- Metabolite quantification with LC Model[4]

Craving paradigm

- ^{1}H-MRS during two audio-visual stimuli:
  1. Baseline: presentation of a neutral film
  2. Craving: presentation of a cocaine film
- Craving rating on visual analogue scales

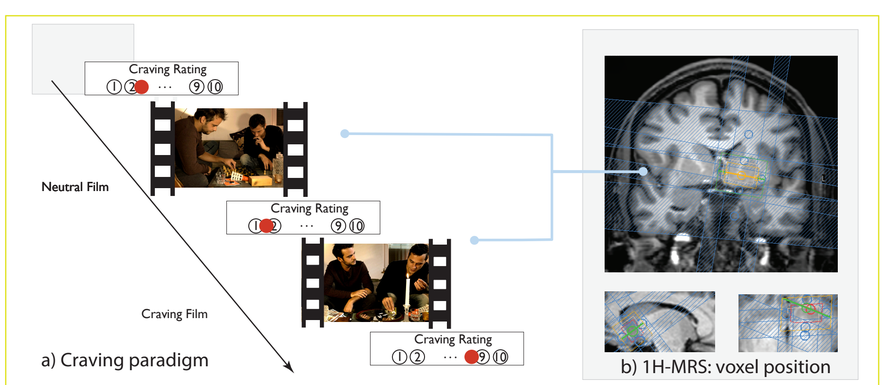

Fig. 2: a) Craving paradigm: All participants saw a neutral film, followed by a cocaine film. Before and after each film craving was rated on a visual analogue scale. During the film presentations glutamate concentration in the nucleus accumbens was measured with ^{1}H-MRS. b) Illustration of an exemplary voxel placement centred on the left nucleus accumbens as region of interest.

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Results

Reliable Glu detection in the human NAcc

Average SNR of 17.50, mean line width of 6.91 Hz indicate good spectral quality.

Glu hypo-concentration in cocaine dependence

During neutral state, Glu concentrations were significantly reduced in CAIs compared to HCIs, p = .008.

Craving-induced Glu increase

An opposing effect of cocaine film on Glu for the two groups was observed. Glu in CAIs increased from rest to craving, p = .017.

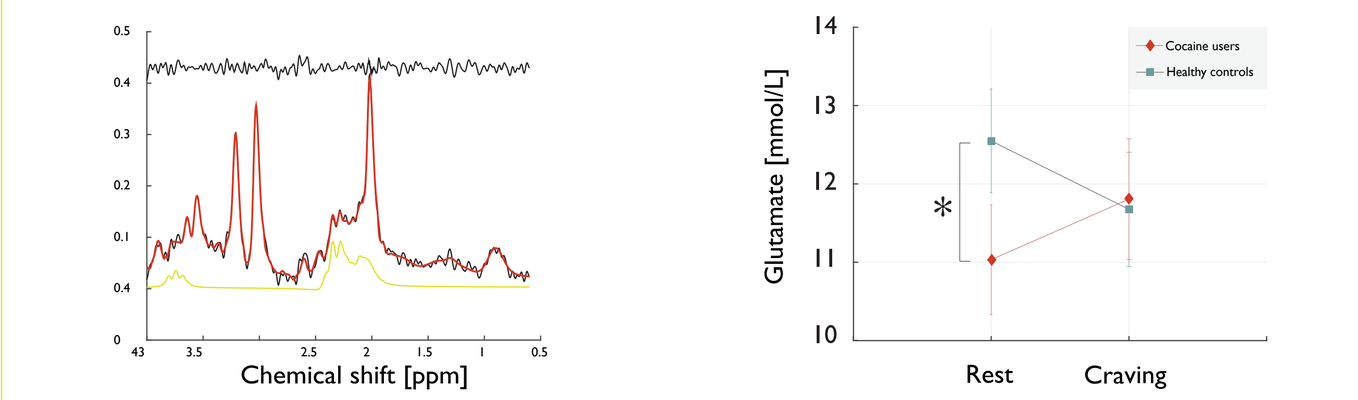

Fig. 4: Glutamate concentration in the nucleus accumbens. (a) Representative spectrum (red), LCModel fit (thereunder; black), fit-residuals (above; black) and glutamate combined with glutamine (yellow). No significant difference in data quality between groups. (b) Significant group difference in absolute basal concentrations of glutamate with lower levels in cocaine-dependent individuals compared to healthy controls. * p = .008.

Conclusion

- → Novel ^{1}H-MRS achieves high data quality in the human NAcc
- → First evidence for Glu changes in NAcc of cocaine-dependent humans
- → Cocaine induced Glu hypo-concentration and craving-induced Glu overflow in accordance with animal models of addiction
- → Decisive role of Glu system in maintenance of cocaine addiction
- → Glu system as a target for future pharmacotherapy approaches

Reference

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