Hypocretins Drive Reward Seeking Through Activation of Stress Pathways in the Brain: an update since Swiss Addiction Day I on May 14th 2004

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Scientists are discovering the chemical secret to HOW WE GET ADDICTED ... and how we might get cured
Drug addiction

• Is a chronic relapsing disorder characterized by compulsive drug-seeking and drug-taking, with loss of control over intake despite evidence of harmful consequences such as disrupted interpersonal relationships and professional failures.

• The brain mechanisms responsible for drug craving and relapse are still not fully understood despite accumulating evidence delineating the cellular and molecular adaptations induced by chronic consumption of drugs of abuse.

• Identification of new neurobiological factors responsible for vulnerability to relapse is crucial for the development of promising therapeutic treatments for drug addiction.

Kreek et al., Nat Rev Drug Discov, 2002
Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior

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The Hcrt system and the brain reward function

Boutrel et al., 2005 in Hypocretins: Integrator of physiological functions, (de Lecea, Sutcliffe Eds) Springer, NY
ICV infusions of Hcrt-1 does not modulate cocaine intake

A  ShA (n=5)

B  LgA (n=5)

C  LgA (n=5)

Cocaine intake (mg/kg over 60 min)

1 hour

6 hours

- Saline
- Hypocretin-1 (1.5 nmol)
ICV infusions of Hcrt-1 reinstate previously extinguished reward seeking behaviors
ICV infusions of Hcrt-1 elevates ICSS thresholds

Boutrel et al., PNAS, 2005
ICV infusions of CRF elevate ICSS Reward Thresholds

Macey et al., Brain Res, 2000
Elevations in ICSS Reward Thresholds During Withdrawal

A. Amphetamine Withdrawal
   - Days Post Amphetamine
   - % of Baseline Threshold
   - [Patterson et al., Psychopharmacology 2002]

B. Ethanol Withdrawal
   - Hours Post Ethanol
   - % of Baseline Threshold
   - [Schulze et al., Proc Natl Acad Sci USA 1995]

C. Cocaine Withdrawal
   - Hours Post Cocaine
   - % of Baseline Threshold
   - [Markeu & Koob, Neuropsychopharmacology 1991]

D. Morphine Withdrawal
   - Naloxone Dose (mg/kg)
   - % of Baseline Threshold
   - [Schulze et al., J Pharmacol Exp Ther 1994]

E. Nicotine Withdrawal
   - Hours Post Nicotine
   - % of Baseline Threshold
   - [Epping-Jordan et al., Nature 1996]

F. THC Withdrawal
   - Frequency (Hz)
   - Percentage
   - [Gardner & Vorel, Neurobiol Dis 1999]
Hcrt-induced relapse for cocaine seeking depends on NA and CRF.
Suppression of footshock-induced reinstatement of cocaine seeking by systemic injection of a Hcrt-1 antagonist

Boutrel et al., PNAS, 2005
Conclusion

Does the hypocretin system contribute to the particularly vulnerable state of the brain that characterizes addiction?
- ICV infusions of Hcrt-1 lead to a dose-related reinstatement of previously extinguished cocaine seeking without altering cocaine intake.

- Antagonism of Hcrt-1 receptors blocks footshock-induced reinstatement of previously extinguished cocaine seeking.

- ICV infusion of Hcrt-1 significantly elevates ICSS thresholds reflecting a decrease in the activity of brain reward systems. This action is in sharp contrast to the well known cocaine-induced lowering of ICSS thresholds that is considered to reflect an increased reward sensitivity that underlies, or at least contributes to, the positive affective state associated with drug consumption.

- Overall, these present data identifies a new mechanism by which stress could influence relapse to drug-seeking. We provide here strong evidence suggesting that Hcrt-1 reinstates cocaine seeking by mechanisms different from increased dopamine release only; the blockade of Hcrt-1 induced reinstatement by CRF/Noradrenergic antagonism rather suggests that Hcrt and stress systems may closely interact to regulate cocaine seeking behaviors.

- Conclusion: Hcrt system may have a role in drug craving and vulnerability to relapse, possibly by driving drug seeking through coordination of stress pathways in the brain.


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