

Stress, Arousal and Addiction:

The hypocretin connection

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Human narcolepsy-cataplexy



- Excessive daytime sleepiness
- **Cataplexy**
- Sleep paralysis
- Hypnagogic hallucinations
- Disturbed nocturnal sleep

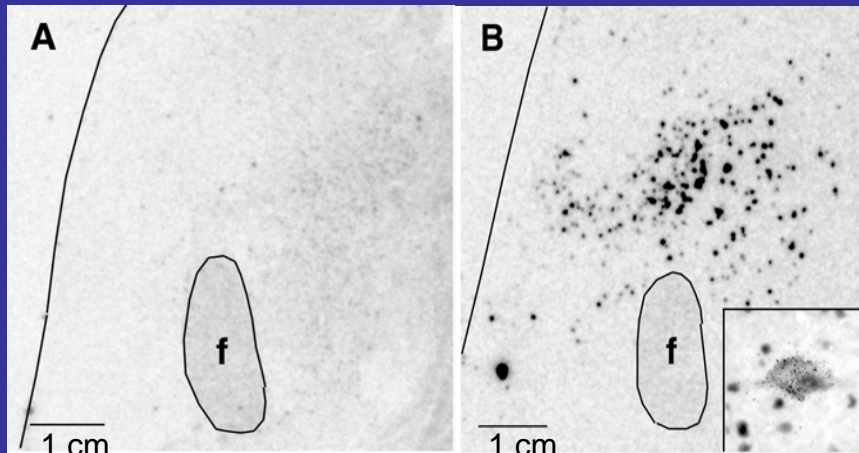
Courtesy of Dr. Zuberi

Prevalence: 1/2000, onset during adolescence
Treatment: Psychostimulants (EDS) and
Antidepressants (Cataplexy)

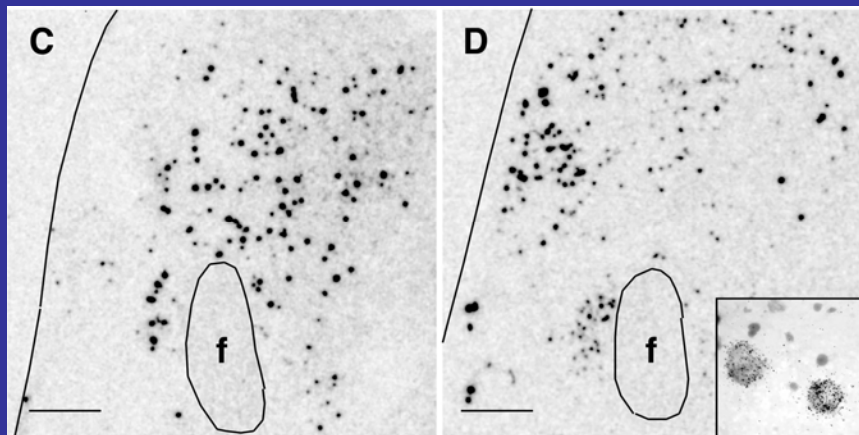
Narcolepsy is a disease of the hypocretinergic system

mRNA in situ Hybridization

Hypocretin



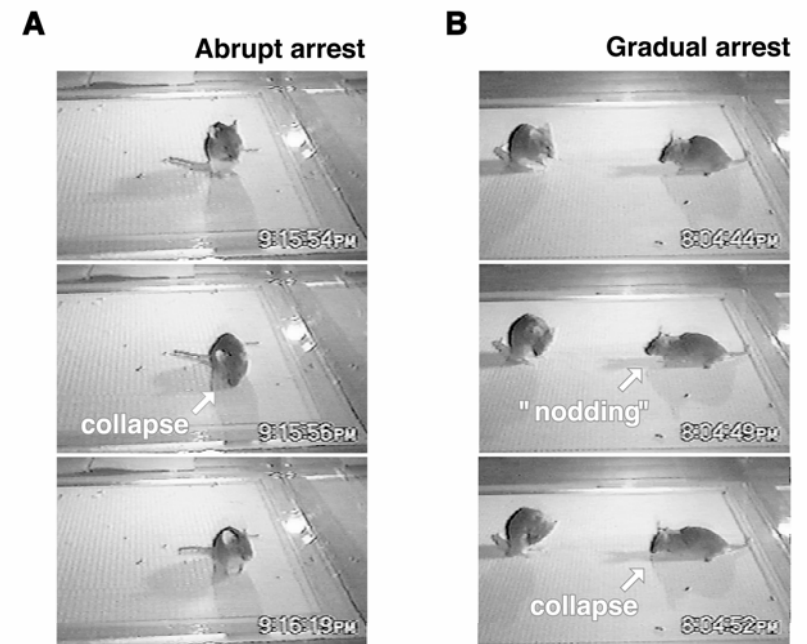
MCH



Narcoleptic

Control Peyron *et al.*, 2000

Hcrt ko are narcoleptic



Chemelli *et al.*, 1999

Two new members of the incretin neuropeptide family

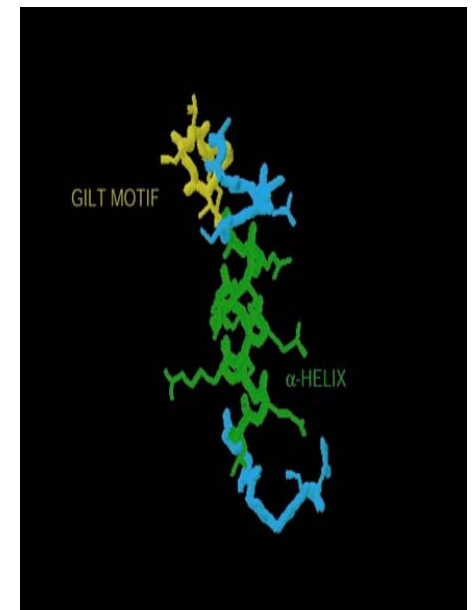
A

	KR	RR	R(R)
Signal	Hcrt1	Hcrt2	
	34-mer	28-mer	

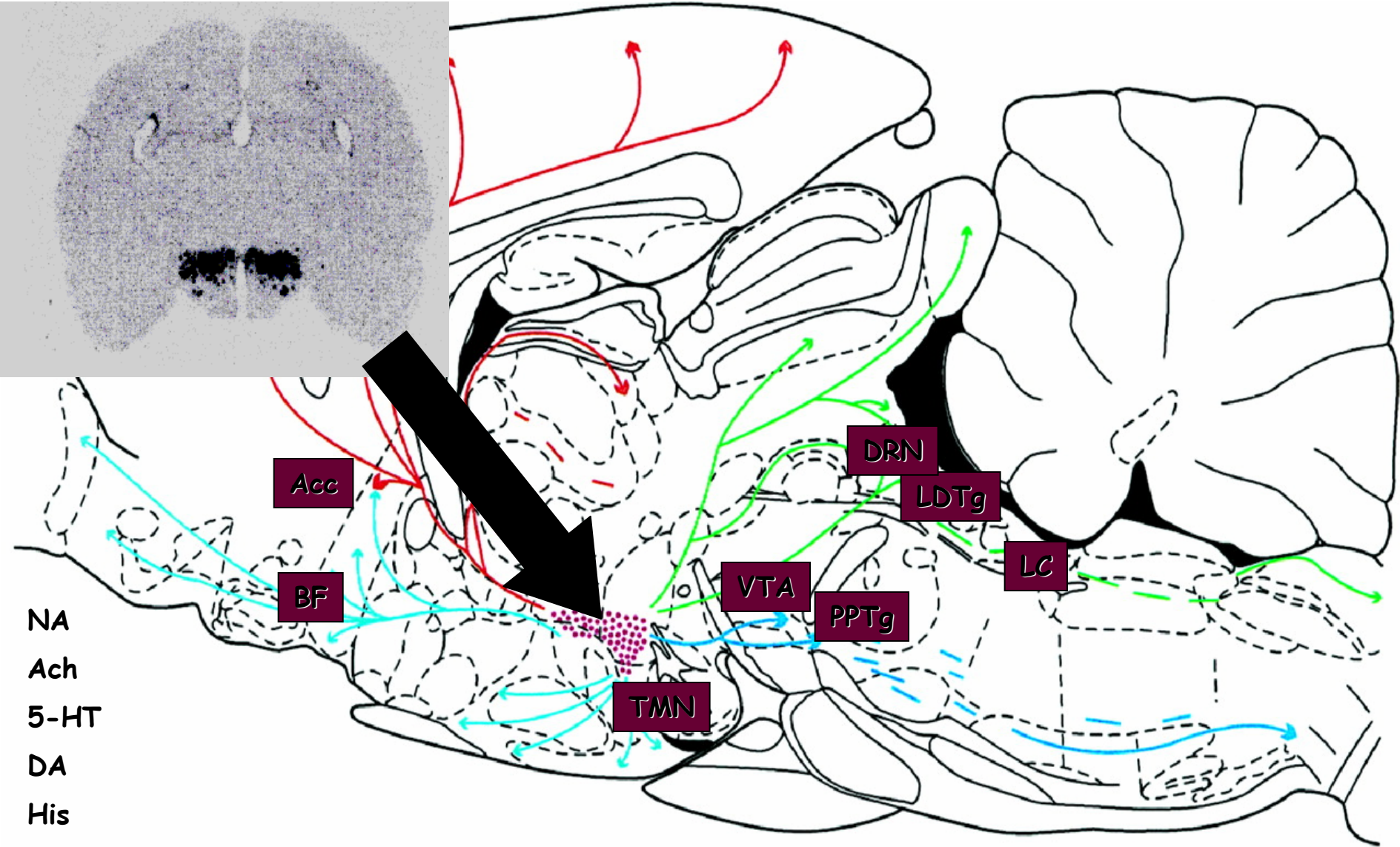
B

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Hcrt1:      QPLPDCCRQKTCSCRLYE1*LLHGAGNHAAGILTLG
Hcrt2:      PGPPGLQGR1*LQRLLQANGNHAAGILTMG
Secretin    HSDGTFTSKLSRLRDSARLQRLLOGLV HSDGTFTSK
VIP         HSDAVFTDNYTRLRKQMAVKKYLNSILN
PACAP27     HSDGIFTDSYSRYRKQMAVKKYLAAVLG
PACAP38     HSDGIFTDSYSRYRKQMAVKKYLAAVLGKRYKQRVKNKG
Glucagon    HSQGTFTSDYSKYLDSRRAQDFVQWLMNT
GLP-1       HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
Hcrt1-----HAAGILT
    
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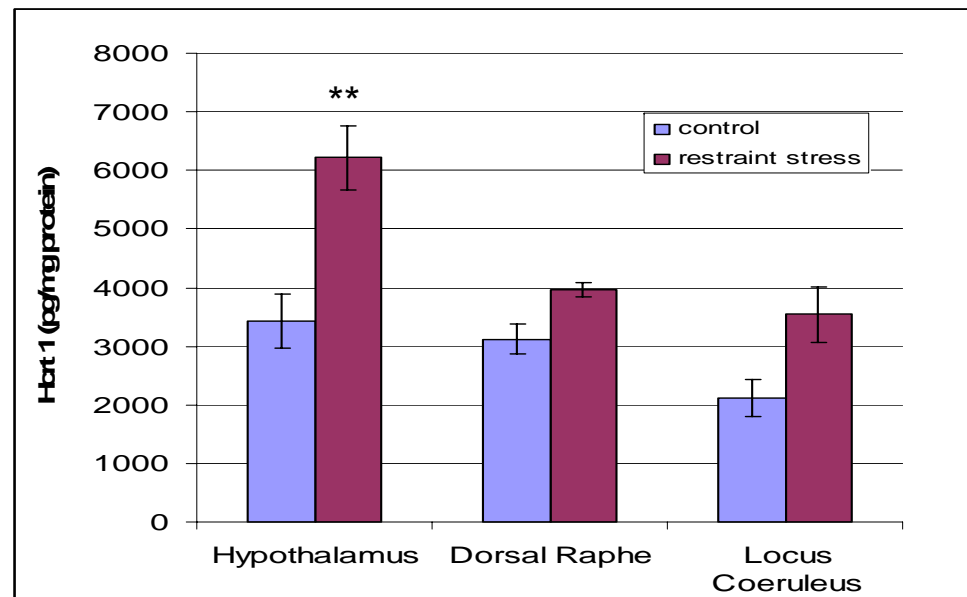
Anatomy of the hypocretinergetic system



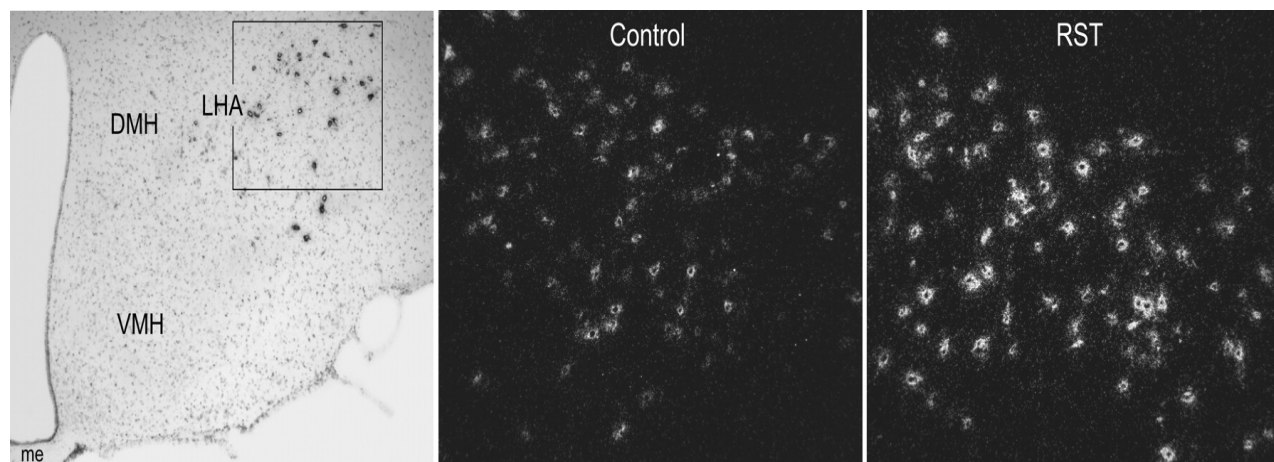
(de Lecea et al., 1998; Peyron et al., 1998)

The hypocretins in hyperarousal

Hcrt and hyperarousal: acute stress

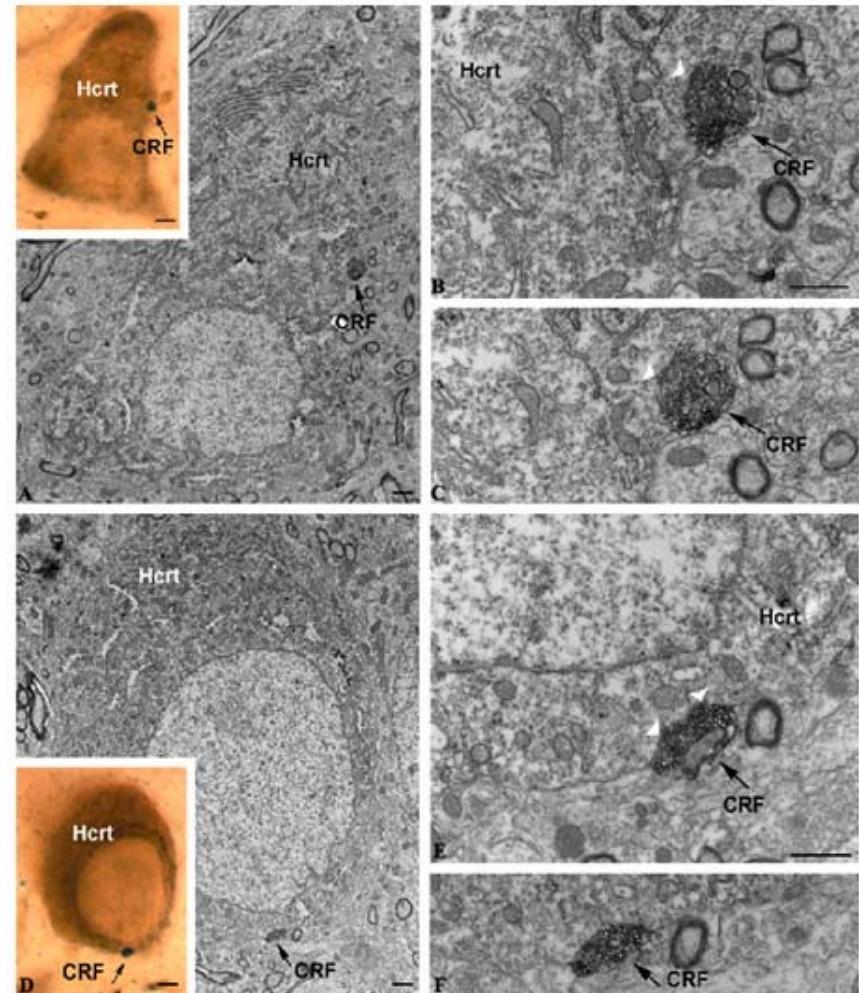
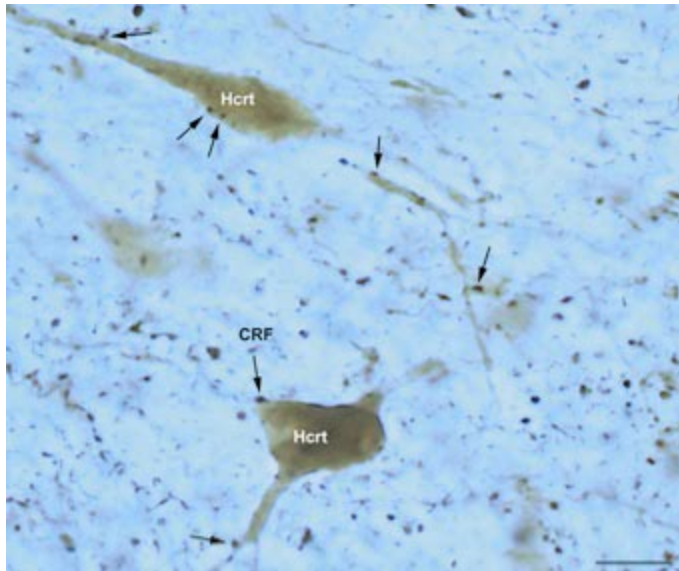


Fabre et al.,



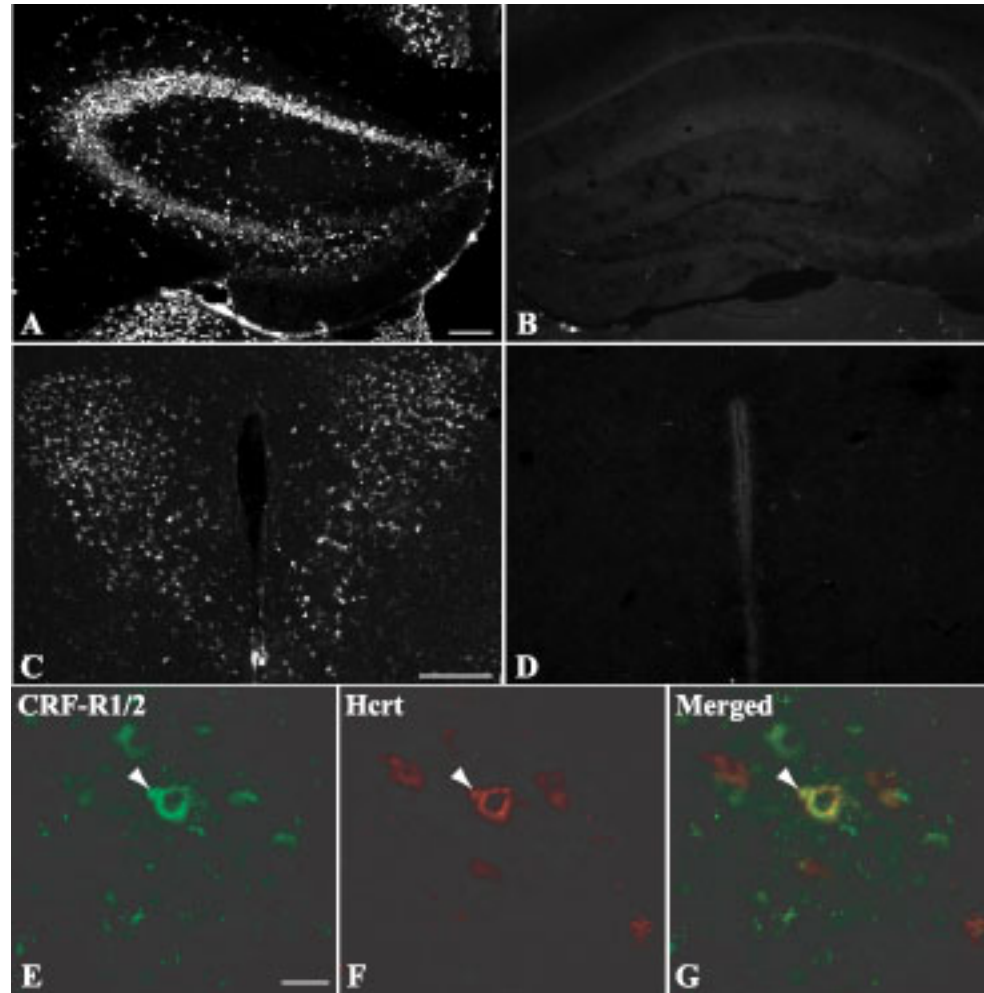
Reyes et al., 2003

CRF terminals contact HCRT cell bodies



Winsky-Sommerer et al., (2004)

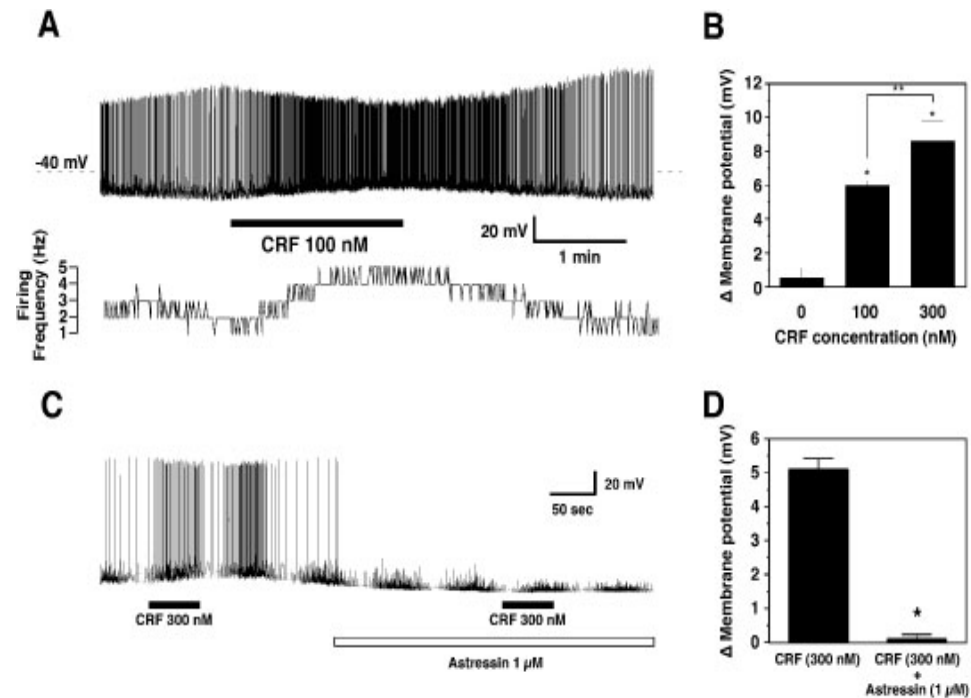
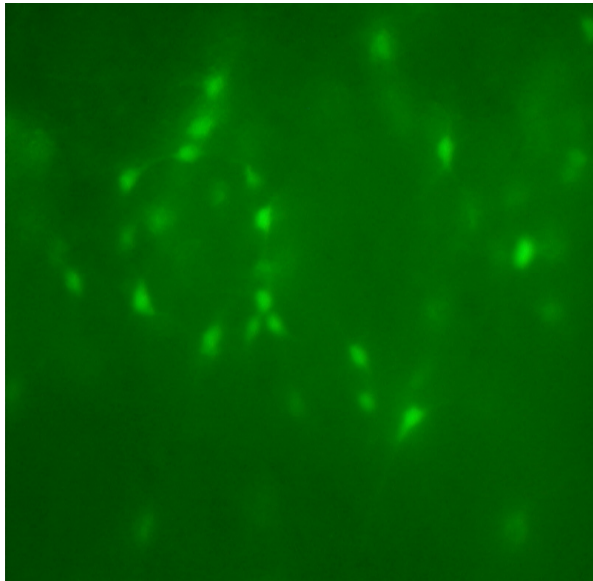
CRF receptors are expressed in hcrtn neurons



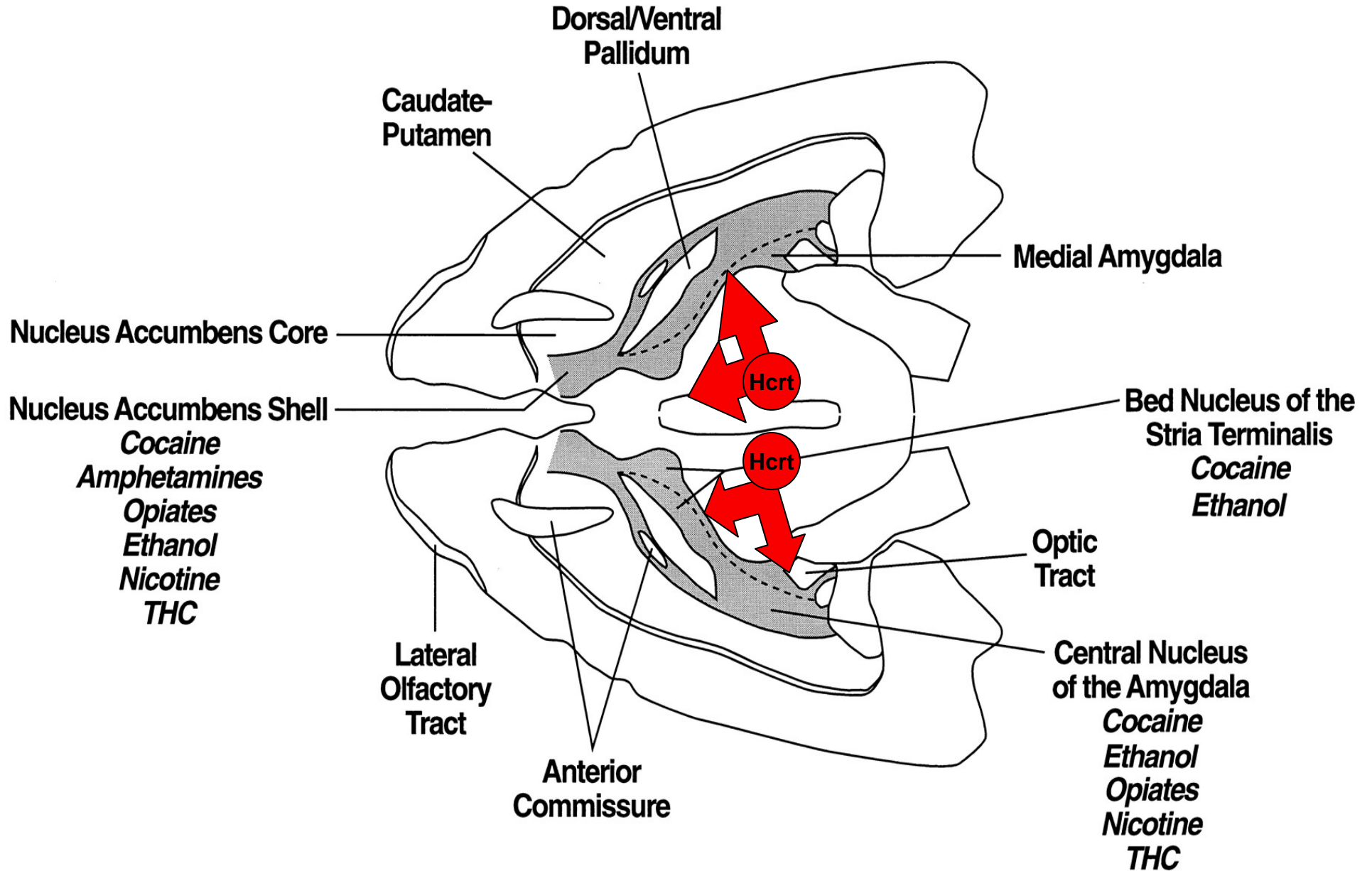
Winsky-Sommerer et al., (2004)

CRF depolarizes HCRT neurons through CRFR1

Hcrt promoter EGFP

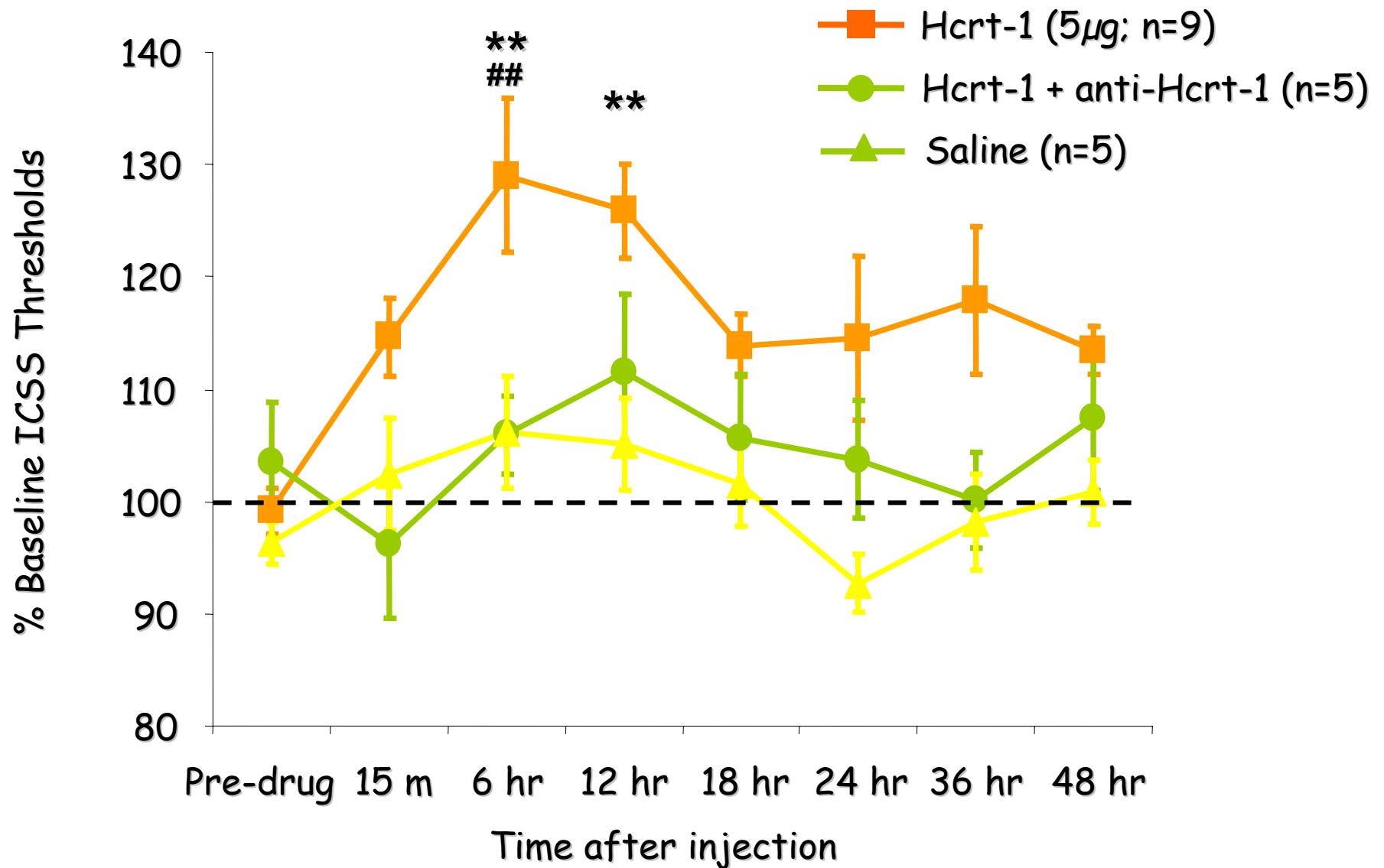


Effects of Drugs of Abuse on Subregions of the Extended Amygdala

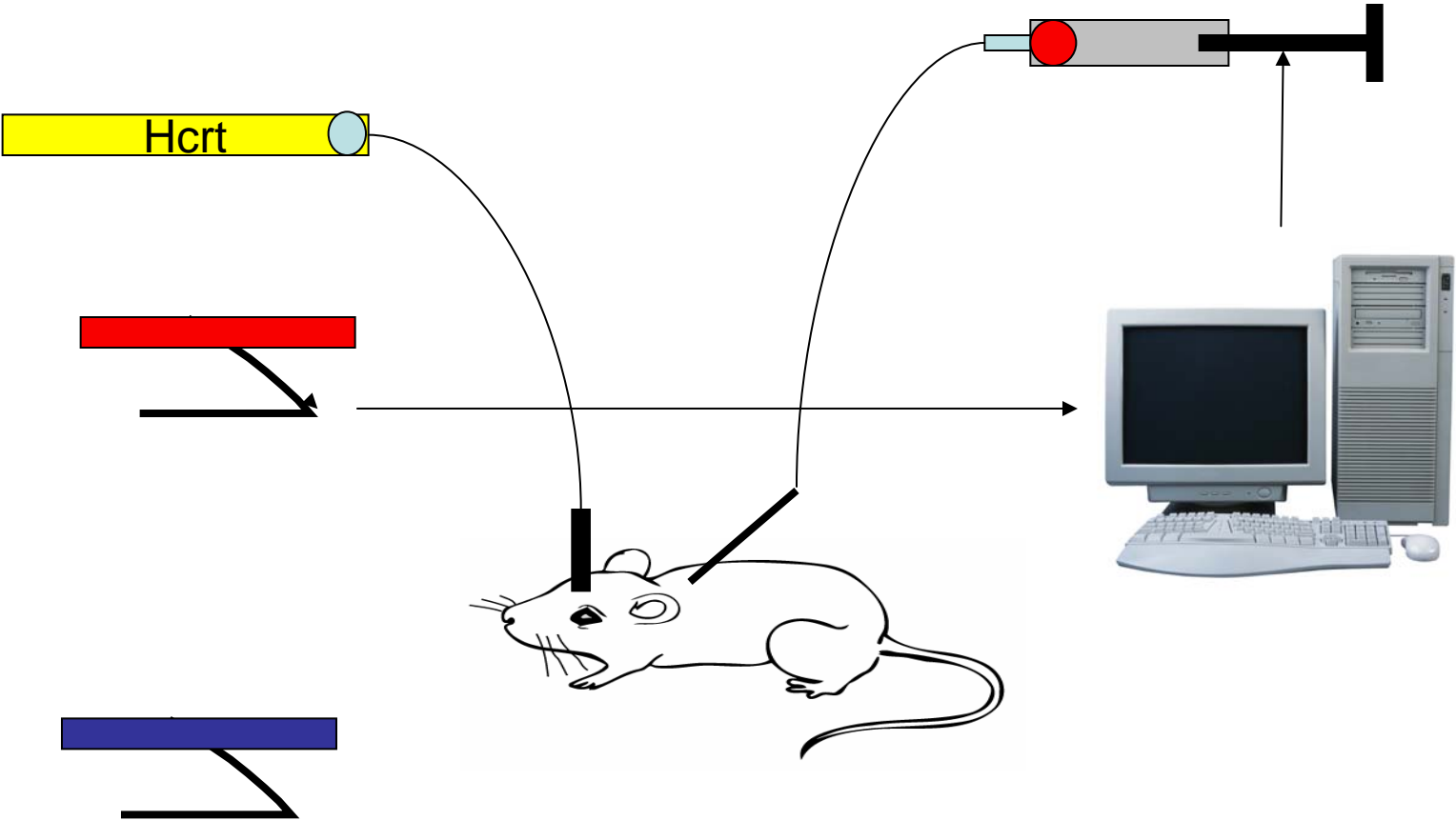


Does Hcrt affect brain reward?

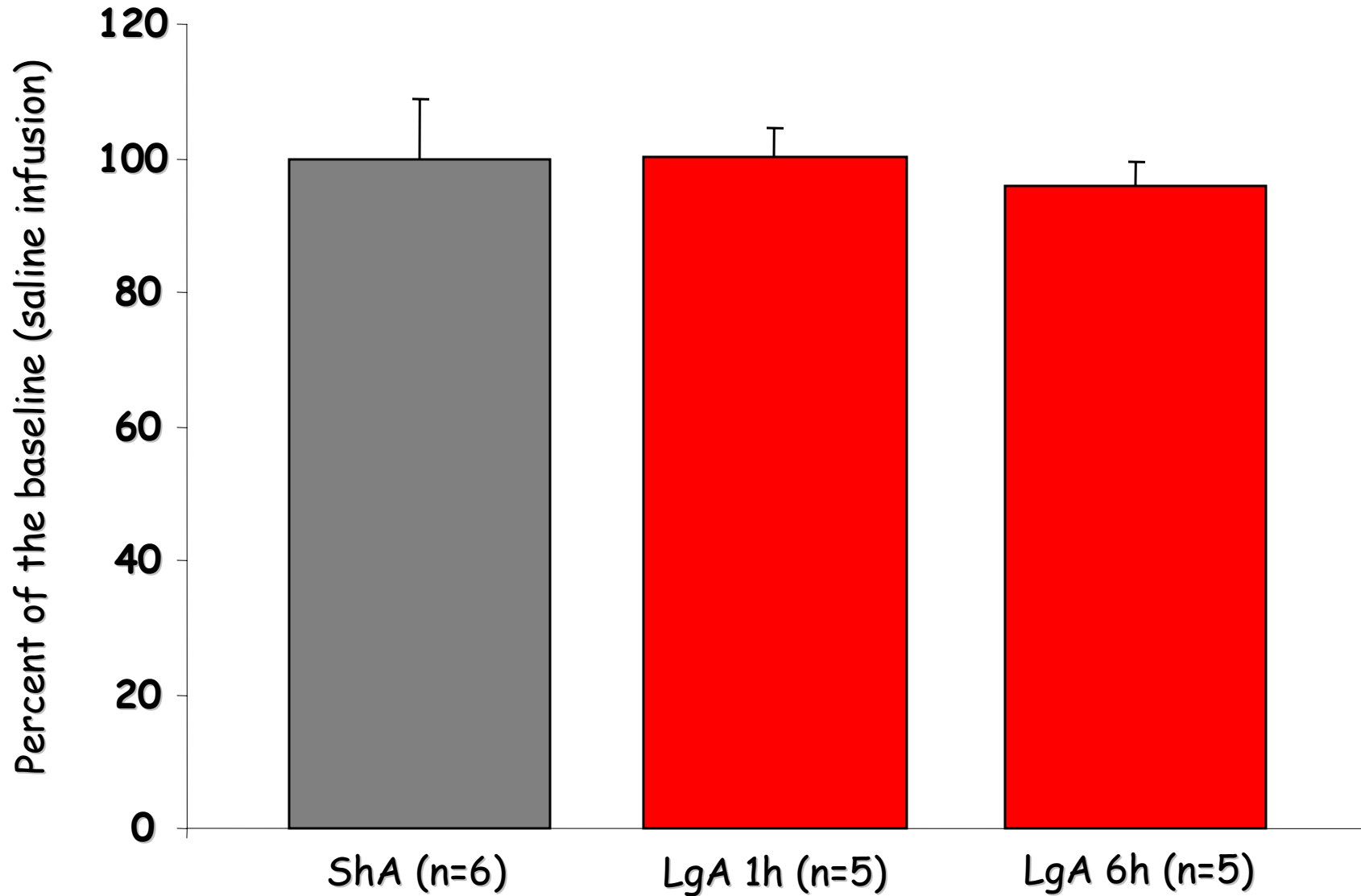
Hypocretin negatively regulates brain reward



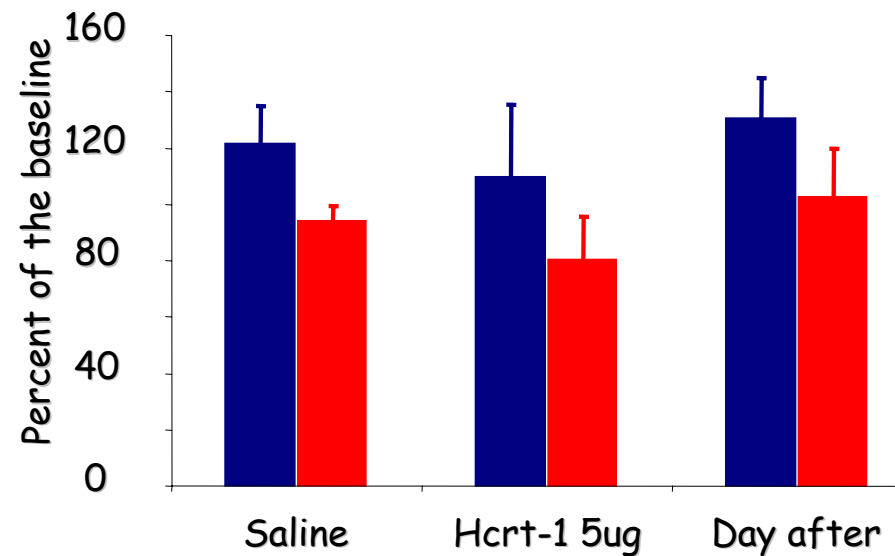
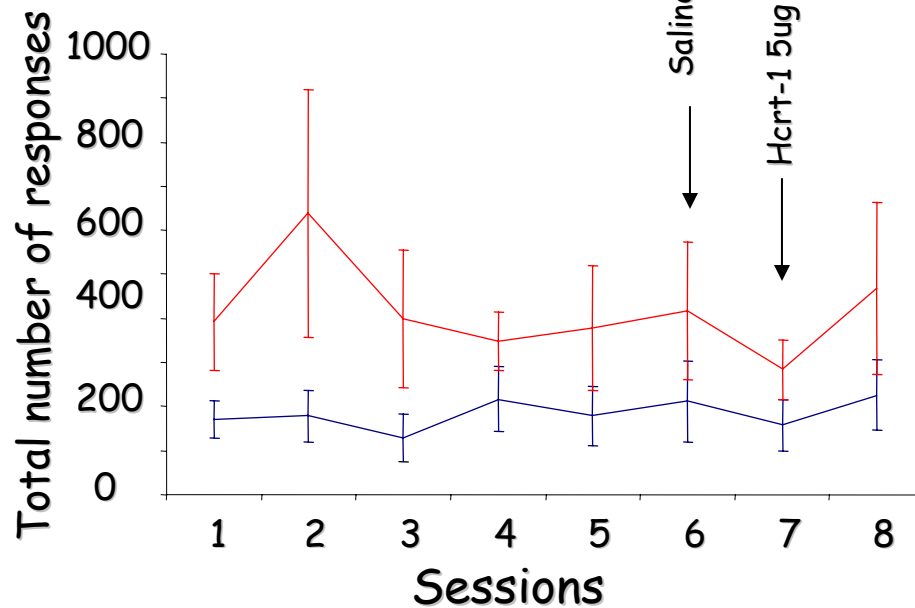
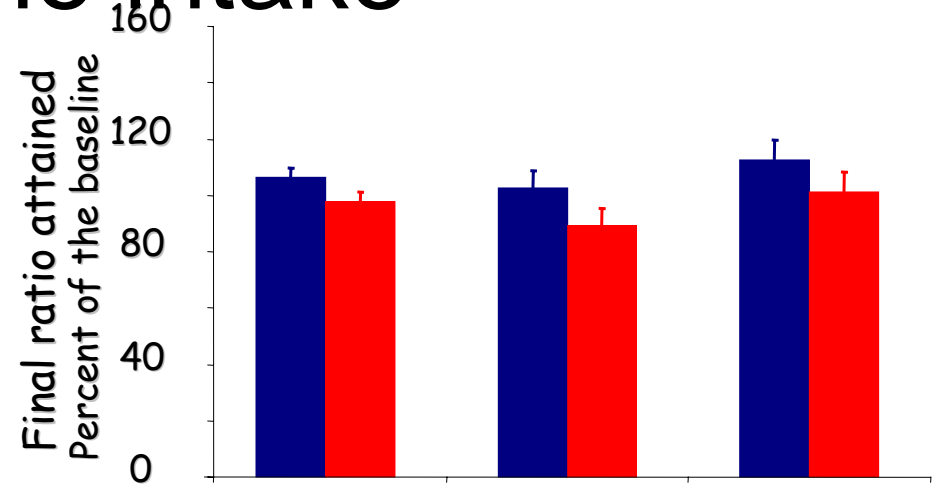
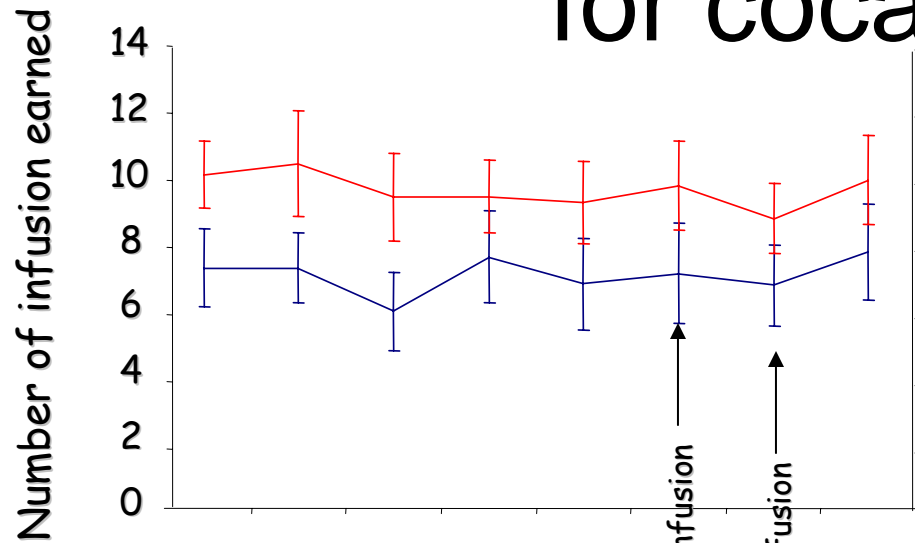
Cocaine self-administration



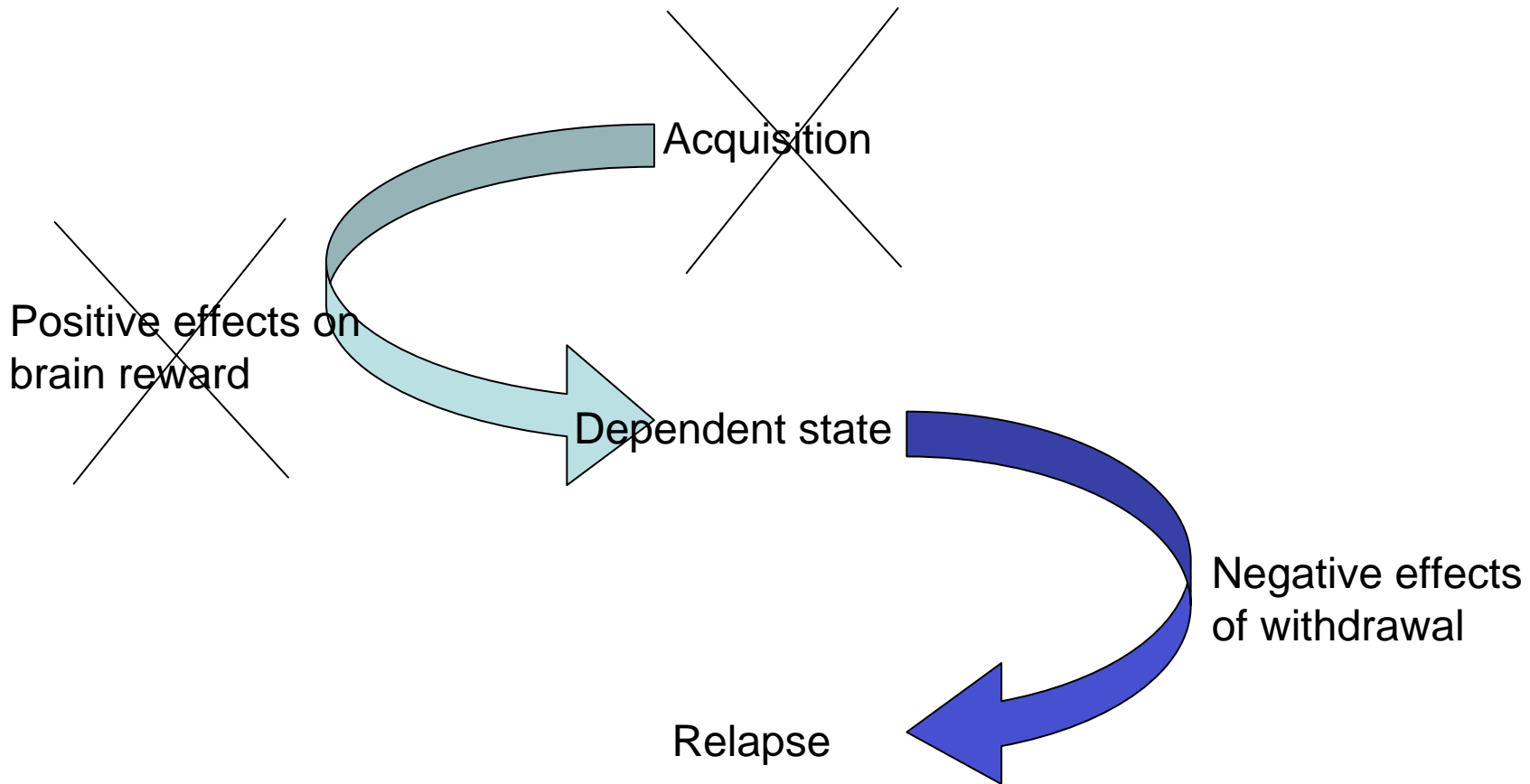
Hypocretin-1 does not affect cocaine intake



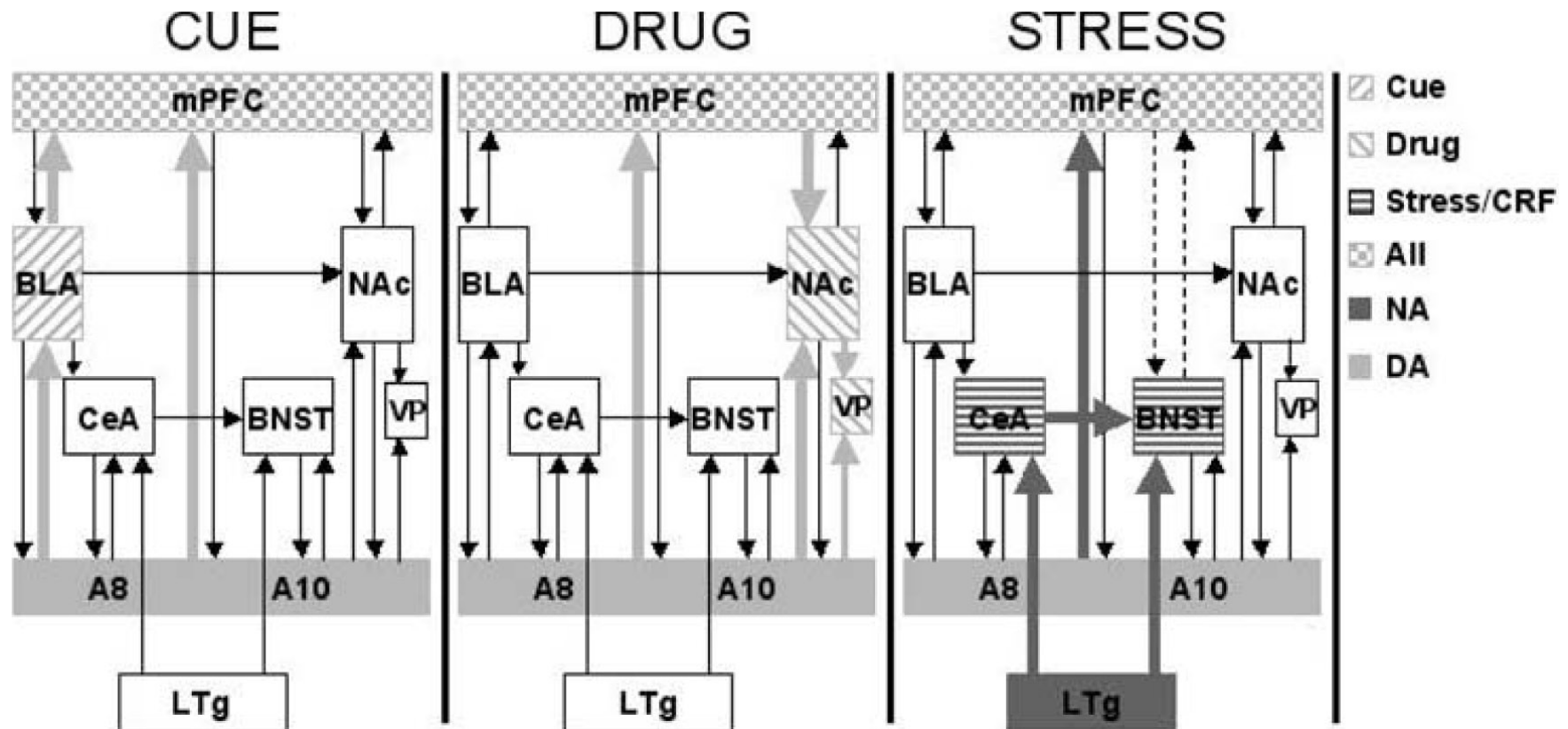
Hcrt-1 does not change motivation for cocaine intake



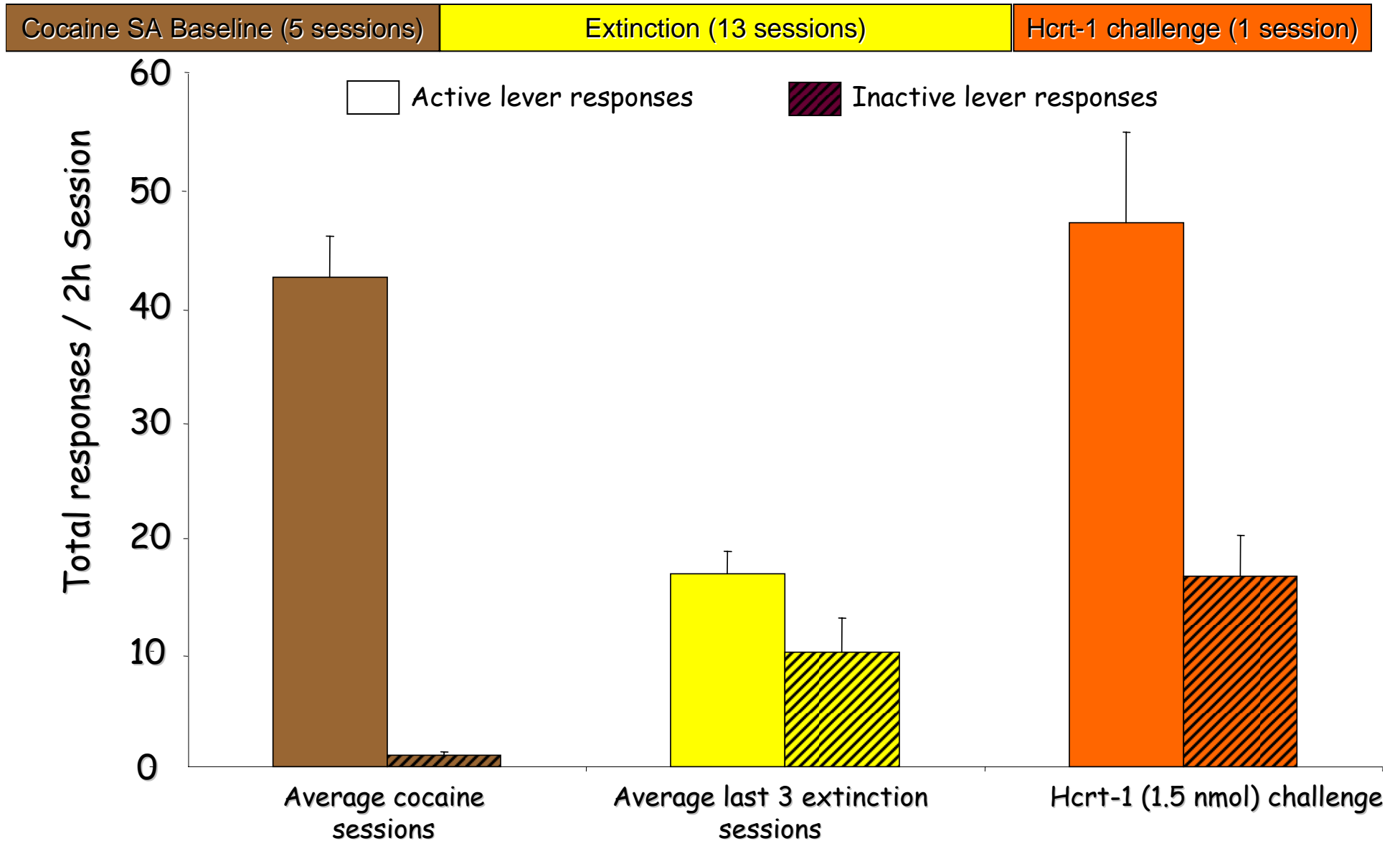
The addiction spiral



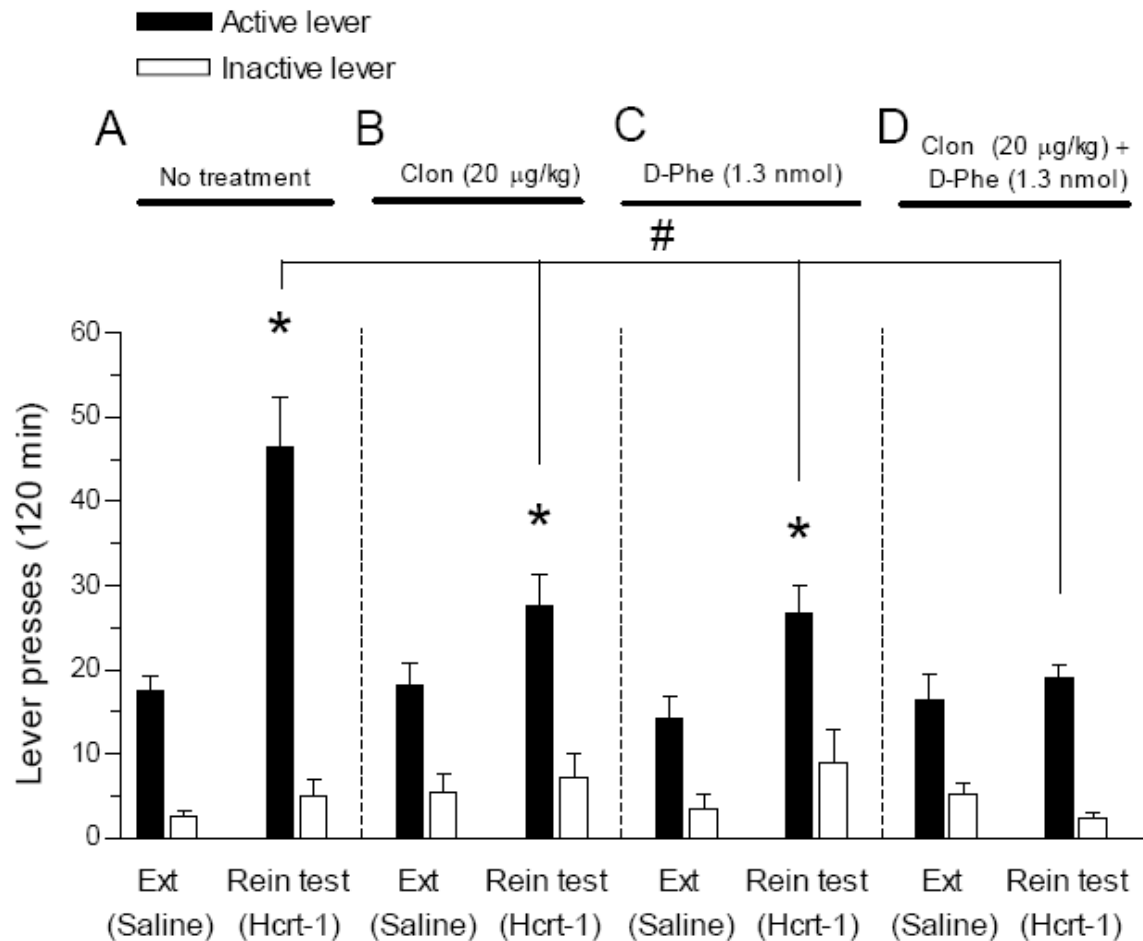
Neuronal circuits involved in reinstatement



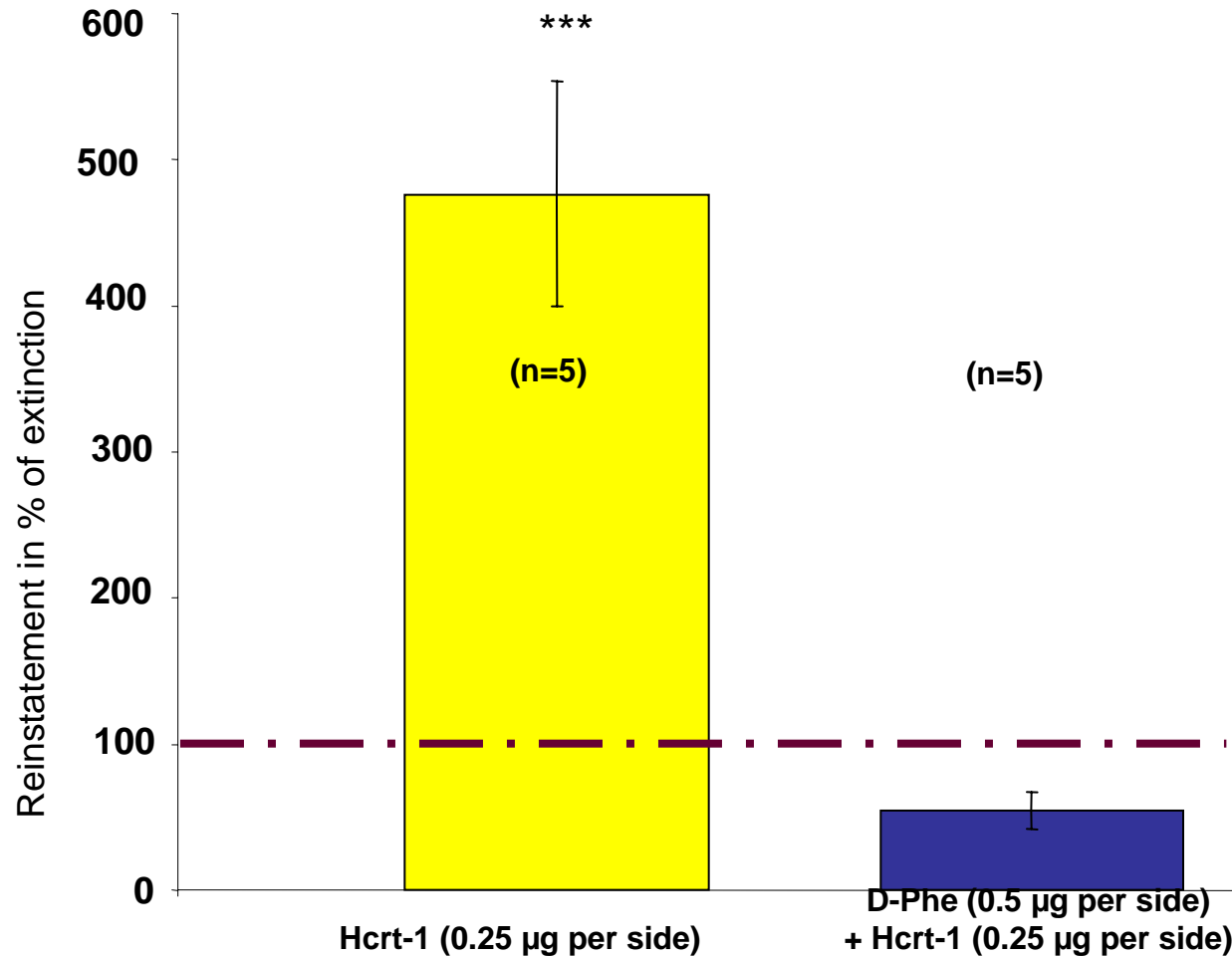
Hcrt1 (icv) reinstates cocaine-seeking behavior



Blockade of both CRF and NE prevents Hcrt-induced reinstatement

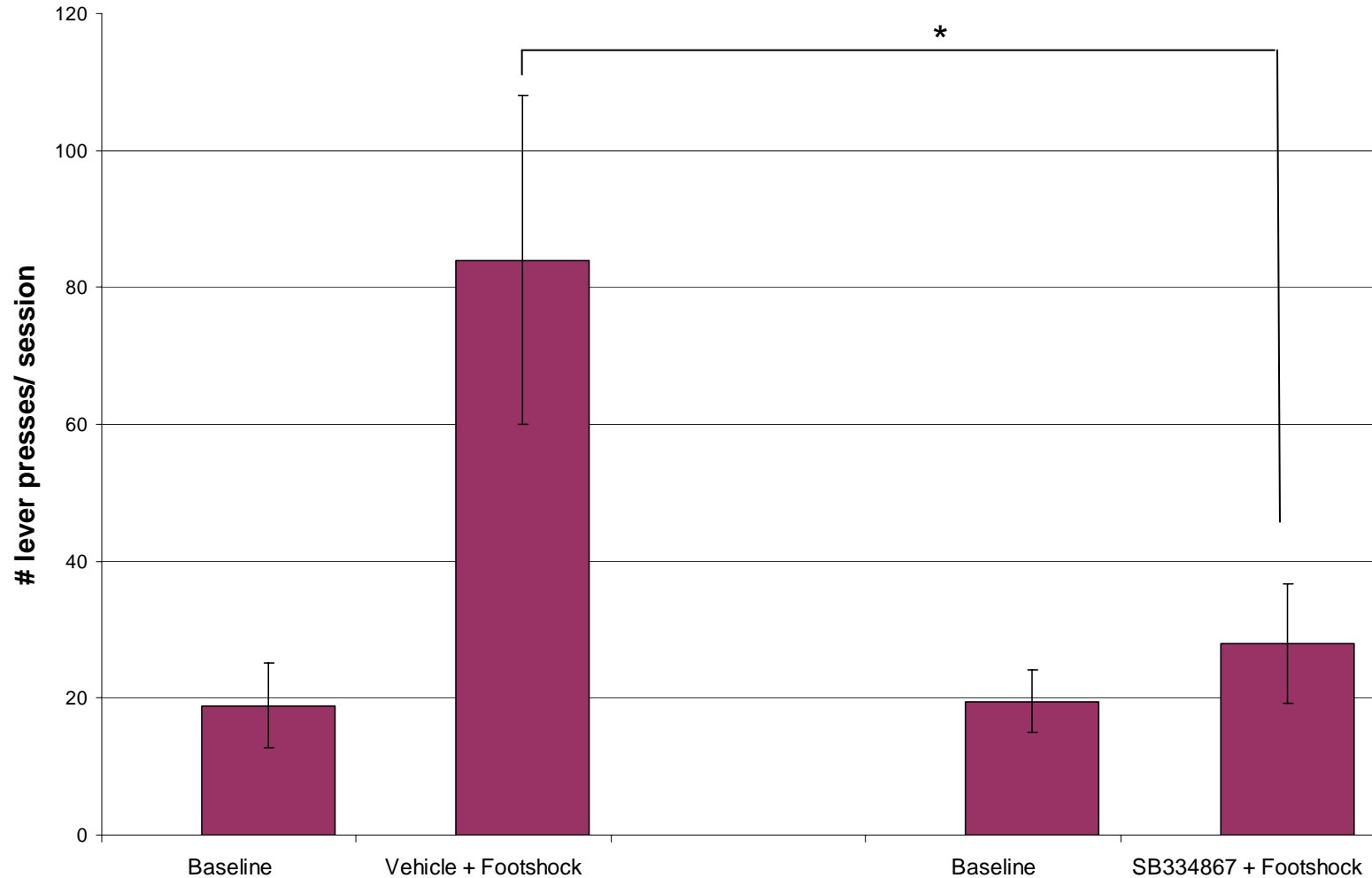


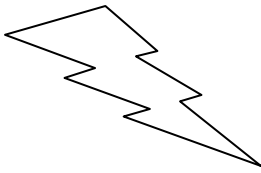
The BNST is involved in hypocretin-induced reinstatement



- Stress induces CRF
- CRF stimulates hcrt neurons
- CRF produces reinstatement
- Hcrt produces reinstatement
- CRF-R antagonists block stress-induced reinstatement
- Do Hcrt antagonists block stress-induced reinstatement?

Hcrt receptor antagonist blocks stress-induced reinstatement





Footshock stress

Addiction state



Hcrt

HPA axis



Reinstatement of Drug seeking

Acknowledgements

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