FOOD REWARD AND MODULATION BY NUTRITIONAL STATUS, INSULIN AND LEPTIN

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Model for regulation of body adiposity
Hypothalamic Areas Regulating Energy Balance

Arcuate Nucleus
Abundant leptin and insulin receptor expression
Neuropeptides involved in energy homeostasis and regulated by adiposity signals.
Downstream of the Arcuate Nucleus:
VTA/SNC

Striatum/
NAcc

Pallidum

Motor
Programs

Amygdala/
Hippocampus/
PF Cortex

PBN

NTS

Oral sensory
and Motor
Programs

PPTN
Insulin and leptin act directly in the CNS to decrease performance in ‘reward behavior’ paradigms:

1. Brain self-stimulation (Fulton 2000; Carr 2000)

2. Food-restriction stress induced relapse to drug-taking (Shalev 2001)
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1. Brain self-stimulation (Fulton 2000; Carr 2000)

2. Food-restriction stress induced relapse to drug-taking (Shalev 2001)

3. Food reward/motivation (Lattemann lab)
Conditioned place preference (CPP) evaluates learned association of a place with a rewarding experience.
Sucrose or chow pellets condition a place preference in food-restricted but not *ad lib* fed rats.
Low leptin levels contribute to CPP in food-restricted rats.

Figlewicz et al. 2001
IVT insulin and leptin block CPP to high fat diet in *ad lib* fed rats.  
Figlewicz et al, 2004

![Graph showing CPP scores with ad lib fed rats.](image-url)
IVT insulin and leptin block CPP to high fat diet in *ad lib* fed rats.
CPP to High Fat Diet Reward
in ad lib Fed Rats

CPP score (sec)

Total kcal Fat Reward Consumed (max=90)

○ CSF
CPP to High Fat Diet Reward in ad lib Fed Rats
Self-administration evaluates the motivation (willingness to work for) a reward such as drugs, intra-cranial electrical pulse, or food.
Sucrose self-administration: evaluating the motivating qualities of food.

1. “Constant schedule” bar pressing—see above.

2. “Progressive ratios”—rats press the bar an increasing number of times to obtain a sucrose reward.

Grimm and Shaham, NIDA
Motivated work for sucrose solutions is modified by nutritional status.
IVT insulin and leptin decrease 5% sucrose self-administration in non-deprived rats.
Motivated work for food reward (baseline performance) may be increased by a more palatable food reward (chocolate Ensure).
Motivated work for food reward (baseline performance) may be enhanced by a higher-fat chronic diet.
The effectiveness of IVT insulin or leptin can be modified by changing the rewarding food or changing the chronic diet of the rats.

# PRESSSES ON ACTIVE LEVER
AS % OF CSF DAY (WITHIN-SUBJECTS)

5% SUC n=30 5% SUC/SSM n=13 10% SUC n=23

* p<0.05 vs. CSF
Where in the CNS are insulin and leptin acting to modulate food reward?

1. Via Arcuate/PVN circuitry
2. LH
3. VTA/NAc
4. Amygdala
Cellular and behavioral evidence supports the possibility that the VTA DA neurons can be direct targets for insulin or leptin:

1. Presence of insulin and leptin receptors
2. Activation of the PI3 kinase/PKB pathway
3. Regulation of a key synaptic protein, the DA re-uptake transporter
4. Suppression of sucrose ‘treat’ feeding and chow intake.
The VTA/Substantia Nigra Circuitry

Paxinos 1995
SN TH and GAD neurons
VTA TH and GAD neurons

Figure 40

Interaural 3.80 mm

Bregma -5.20 mm
Insulin receptors and leptin receptors are expressed on VTA dopamine neurons. Figlewicz et al., 2003
Insulin receptors may be expressed in GABA neurons within the VTA. (Naleid, unpublished)
Insulin and leptin increase PIP3-immunoreactivity within the VTA.
Top panel: In situ, low power showing Lepr (ObR) mRNA in the VTA of rat

Middle panel: In situ, higher power, showing that Lepr is in TH neurons only (but clearly not all TH neurons)

Bottom panel: Western showing pSTAT3 response in VTA punches 2h after IP leptin (2mg/kg) treatment of mice
DA Terminal and Synapse: The DAT terminates DA signalling by clearing DA from the synapse.
In vitro Voltammetry of DA Uptake in Striatum

1.5 μM Dopamine

1.5 μM Dopamine + Mazindol or Cocaine

3 minutes
IVT insulin increases the expression of the DA reuptake transporter (DAT) in the VTA.
Figlewicz et al. 1994
Acute food deprivation results in decreased expression of the DAT in the VTA.
Acute food deprivation results in decreased activity of the DAT in the striatum, which is restored by insulin *in vitro.*

\[\text{Patterson et al 1998}\]
Insulin stimulates DA uptake by recruiting DATs to the cell membrane. (A. Galli and colleagues)
Mu opioid agonists stimulate feeding in the VTA by inhibiting GABA neurons.
Intra-VTA DAMGO injection stimulates food intake which is blocked by D1 DA antagonist in the nucleus accumbens.

MacDonald, Levine and Billington 2003
Unilateral intra-VTA insulin or leptin reverse the effect of a mu agonist to stimulate sucrose intake.
Bilateral VTA injection of leptin decreases 24 hr chow intake. (Ralph DiLeone and colleagues)
Concluding Remarks

1. Insulin, leptin, and other metabolic signals (ghrelin) can modulate food reward:
   a. Feeding caused by direct stimulation of reward circuitry;
   b. Learned association between place and rewarding food;
   c. Motivated work for rewarding food.

2. IMPLICATION: Our findings suggest that all of these aspects of food reward (learning/motivation/”wanting”) may be amenable to pharmacological or pharmacotherapeutic intervention.
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