Food restriction: enhancing effects on drug reward and striatal cell signaling

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Opiates, psychostimulants (DiChiara et al.) and sucrose-licking (Hajnal et al.) produce dose-related increases in extracellular dopamine in nucleus accumbens.

The propensity of animals to ingest sweet solution predicts the magnitude of their locomotor response to psychostimulants (Sills et al.) and, in some cases, their speed to acquire active self-administration (Gosnell et al.).

There is bi-directional behavioral cross-sensitization between amphetamine and sucrose (Avena and Hoebel).

Chronic food restriction enhances acquisition of drug self-administration, lowers the threshold reinforcing dose, and increases the amount consumed (Carroll et al.).
From A.E. Kelley, Neuron 44:161, 2004
### Effects of Food Restriction on Drug Self-Administration Behavior

(M.E. Carroll and colleagues from 1979 to present)

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>DRUG(S)</th>
<th>ROUTE</th>
<th>EFFECT OF FOOD RESTRICTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhesus monkey</td>
<td>phencyclidine, amphetamine ketamine</td>
<td>oral</td>
<td>↑ intake ↓ threshold reinforcing dose</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>phencyclidine</td>
<td>oral</td>
<td>↑ break-point in progressive ratio protocol</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>cocaine</td>
<td>inhalation</td>
<td>↑ intake</td>
</tr>
<tr>
<td>Rat</td>
<td>etonitazene, fentanyl</td>
<td>oral</td>
<td>↑ intake ↓ threshold reinforcing dose</td>
</tr>
<tr>
<td>Rat</td>
<td>phencyclidine, cocaine</td>
<td>i.v.</td>
<td>↓ threshold reinforcing dose</td>
</tr>
<tr>
<td>Rat</td>
<td>heroin, cocaine</td>
<td>i.v.</td>
<td>↑ intake</td>
</tr>
</tbody>
</table>
Intracranial electrical self-stimulation was discovered by Olds and Milner in 1954.

Low amplitude cathodal stimulation within the medial forebrain bundle is positively reinforcing.

Rats will learn mazes, cross electrified grids, forgo food, to access response lever.

When stimulation is delivered by experimenter it elicits: forward locomotion & vigorous sniffing, eating, drinking, mating, if appropriate goal object is available.

Drugs of Abuse Lower ICSS Threshold in a Dose-Related Manner
Positive reinforcing effects of abused drugs have been localized to VTA and/or NAc.

**Also:** Experimenter-delivered microinjections in these sites lower threshold for ICSS
ICSS curve-shift method to quantify drug reward

Rate-Frequency Function
- Maximum Rate
- Reward Threshold

Ad Libitum Feeding
- Pre-amphetamine
- Post-amphetamine
- Pre-saline
- Post-saline

Restricted Feeding
- Maximum Rate
- Reward Threshold

Post-injection Functions
- Amphetamine
- Pimozide
- Saline
Threshold-lowering effects of centrally administered drugs

**AMPHETAMINE (ug i.c.v.)**

- Restricted feeding
- Ad libitum feeding

**MK-801 (ug i.c.v.)**

**COCAIN (ug i.c.v.)**

**DPDPE (ug i.c.v.)**
Progressive Ratio Protocol

1. Fixed stimulation intensity and frequency; number of lever presses to obtain each 1-sec train is increased systematically over series of trials until responding ceases (“break-point”).

2. Break-point is particularly reflective of incentive-motivation.

3. Break-point is particularly sensitive to changes in state of dopamine system.
Effect of food restriction versus sensitization on breakpoint-increasing effect of d-amphetamine
Body weights during food restriction and recovery
1. Chronic food restriction increases central sensitivity to rewarding and motor-activating effects of diverse drugs of abuse.

2. Effect is expressed as responding for lower brain stimulation frequencies and working harder to obtain each train of brain stimulation when drug of abuse is on board.

3. Augmenting effect of food restriction seems functionally and mechanistically different from classical psychostimulant sensitization because the latter does not express in ICSS protocol and former is reversible in tandem with body weight recovery when free-feeding is reinstated.
Motor-Activating Effect of d-Amphetamine
(100 µg, i.c.v.)

Vertical Activity
(counts/30 min)

Vehicle
Amphetamine

Horizontal Activity
(counts/30 min)

Ad libitum
Food-Restricted

*
Fos immunostaining induced by i.c.v. d-amphetamine

**N. Accumbens Core**
- Saline: 100 ± 10
- Amphetamine: 400 ± 20
* p<.001

**N. Accumbens Shell**
- Saline: 20 ± 2
- Amphetamine: 60 ± 3
* p<.05

**Caudate-Putamen +1.6 mm**
- Saline: 10 ± 1
- Amphetamine: 200 ± 20
* p<.001

Legend:
- AL: Ad Libitum
- FR: Food-Restricted
- LV: Lateral Ventricle
- ac: Anterior Commissure
Fos immunostaining induced by i.c.v. d-amphetamine

**Central N. Amygdala**

- Saline
- Amphetamine

**Bed N. Stria Terminalis**

- Saline
- Amphetamine

**Ventral Pallidum**

- Saline
- Amphetamine

- *p<.001
Behavioral effects of direct dopamine receptor agonists

Horizontal Activity Counts

<table>
<thead>
<tr>
<th></th>
<th>Ad libitum feeding</th>
<th>Restricted feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinpirole (50 ug)</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>SKF-82958 (20 ug)</td>
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<td>***</td>
</tr>
</tbody>
</table>
Fos immunostaining induced by i.c.v. injection of DA receptor agonists

Number of c-fos IR Cells

CPu (m) +1.7 mm

CPu (l) +1.7 mm

Nac (core)

Nac (shell)

Vehicle Quinpirole SKF-82958

Ad libitum feeding Restricted feeding

*** **
**OBJECTIVE:** To investigate the molecular basis for enhanced cellular sensitivity to D-1 agonist treatment in the chronically food-restricted rat.
D1 DA Receptor Density/Affinity: Radioligand Binding Assays

Binding assays performed in triplicate on membranes from dissected CPu and NAc of FR (n=6) and AL (n=6) subjects. Non-specific binding measured in the presence of 1 uM SCH 23390.

**3H-SCH 23390 Specific Binding in the Caudate Putamen**

- Ad libitum-fed \( K_{D_{AL}} = 1.13 \text{ nM} \)
  \( B_{MAX_{AL}} = 692.6 \text{ cpm} \)
- Food-restricted \( K_{D_{FR}} = 1.24 \text{ nM} \)
  \( B_{MAX_{FR}} = 732.5 \text{ cpm} \)

**3H-SCH 23390 Specific Binding in the Nucleus Accumbens**

- Ad libitum-fed \( K_{D_{AL}} = 1.29 \text{ nM} \)
  \( B_{MAX_{AL}} = 582.2 \text{ cpm} \)
- Food-restricted \( K_{D_{FR}} = 1.46 \text{ nM} \)
  \( B_{MAX_{FR}} = 517.7 \text{ cpm} \)
c-fos promoter:

- ERK 1/2
- cAMP
- JNK / SAPK
- STATs
- SAP1 / SAP2
- ELK-1
- RSK-1
- PKA
- CREB
- SIE
- SRE
- CRE / AP1
- CRE / ATF2
- TATA
Stimulation of cAMP formation by SKF-82958

**CPu**

- Red dashed line: Restricted feeding
- Blue solid line: Ad Libitum feeding

**Nac**

- Red dashed line: Restricted feeding
- Blue solid line: Ad Libitum feeding

% Stimulation over Basal vs. SKF 82958 (M)
ERK 1/2 MAP kinase activation induced by i.c.v. injection of SKF-82958 (20 µg)
ERK 1/2 MAP kinase activation induced by i.c.v. injection of SKF-82958 (20 µg)
Phosphorylation of CREB by i.c.v. injection of SKF-82958
Effects of SKF-82958 on NMDA receptor and CaM kinase II activation in nucleus accumbens

**A. NMDA RECEPTOR NR1 SUBUNIT**

**B. CAM KINASE II**
Effects of MK-801 pretreatment on SKF-82958-induced signaling

A. ERK 1/2 MAP KINASE

B. CREB

C. CAM KINASE II
Effects of SL-327 pretreatment on SKF-82958-induced signaling

A. ERK 1/2 MAP KINASE

B. CREB
1. SKF-82958 produced greater phosphorylation of the NMDA NR1 subunit and CaMK II in the NAc of FR as compared to AL rats.

2. Pretreatment with the NMDA antagonist, MK-801, decreased SKF-82958-induced activation of CaMK II, ERK 1/2 and CREB, and reversed the augmenting effect of FR on activation of all three proteins.

3. Pretreatment with the MEK inhibitor, SL-327, suppressed SKF-82958- induced activation of ERK 1/2 and reversed the augmenting effect of FR on CREB activation.

4. These results point to specific neuroadaptations in the NAc of FR rats whereby D-1 DA receptor stimulation leads to increased NMDA NR1 subunit phosphorylation and consequent increases in NMDA receptor-dependent CaMK II and ERK 1/2 signaling, and NMDA receptor/ERK1/2-dependent phosphorylation of the nuclear transcription factor, CREB.
Basal and D-1 DA agonist-induced neuropeptide mRNAs in nucleus accumbens

**Pre-prodynorphin**

- Vehicle: P < 0.05
- SKF-82958: P < 0.01

**Pre-protachykinin**

- Vehicle: P < 0.025
- SKF-82958: P < 0.025
Conclusions and Speculations

1. Chronic food restriction increases central sensitivity to the rewarding and motor-activating effects of abused drugs and direct DA receptor agonists.

2. Food restriction also upregulates striatal D-1 dopamine receptor-mediated phosphorylation of the NMDA NR1 subunit, CaM kinase signaling, MAP kinase signaling and downstream activation of CREB, c-fos, PPD and PPT genes.

3. These neuroadaptations may normally facilitate behavioral approach and associative learning in relation to food-related and other salient stimuli. Drugs of abuse may exploit these neuroadaptations to produce enhanced rewarding (incentive arousal) and positive reinforcing (learning) effects.
Critical Questions

1. What are the physiological antecedents of upregulated striatal cell signaling in food-restricted subjects?

2. Is increased cell signaling (MAPK; CaMK II) necessary for behavioral expression of enhanced drug reward magnitude?

3. Is increased cell signaling necessary for facilitation of drug-reinforced instrumental or Pavlovian learning?

4. Can engagement of these neuroadaptations ever have pathological rather than adaptive consequences with regard to ingestive behavior (e.g. restriction-binge type disorder)?
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