Animal models in anorexia nervosa research

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Disposition

1. Background - Anorexia Nervosa
2. Clinical studies - Anorexia Nervosa
3. Animal models of Anorexia (Nervosa)
4. Task
Anorexia Nervosa (1)

DSM IV:
- an intense fear of gaining weight
- refusal to maintain adequate nutrition
- often associated with an erroneous image of the self as fat
- loss of original body weight to < 85% of normal
- disturbance of body image
- negative self-evaluation
- absence of at least three consecutive menstrual periods

The life-time prevalence of AN among women in the western world range between 1.2-2.2%.

90% are women (?)

AN is the deadliest of the psychiatric disorders with a mortality as high as 10-20%.
Anorexia Nervosa (2)

Complex disorder

Etiology likely involves interactions between genetic, environmental, social and cultural factors.

Two principal subtypes; restrictive & compensating
Anorexia Nervosa (3)

50-80% of AN is attributed to genetics.

First-degree female relatives of individuals with AN have an approximately 10-fold greater lifetime risk of having an eating disorder compared with relatives of unaffected individuals.

Many young girls (and boys) diet but only a small percentage (maybe those with susceptibility genes) develop anorexia.
Anorexia Nervosa (5)

Kaye, (2009), Am J Psych
Studies on AN-patients

• Genetic (blood)
• Epidemiological
• Imaging studies (brain)
• Blood analysis
Association Study of 182 Candidate Genes in Anorexia Nervosa

Andrea Poyastro Pinheiro¹, Cynthia M. Bulik¹,², Laura M. Thornton¹, Patrick F. Sullivan¹,³, Tammy L. Root¹, Cinnamon S. Bloss⁴, Wade H. Berrettini⁵, Nicholas J. Schork⁴, Walter H. Kaye⁶,², Andrew W. Bergen⁷, Pierre Magistretti⁸, Harry Brandt⁹, Steve Crawford⁹, Scott Crow¹⁰, Manfred M. Fichter¹¹,¹², David Goldman¹³, Katherine A. Halmi¹⁴, Craig Johnson¹⁵, Allan S. Kaplan¹⁶,¹⁷, Pamela K. Keel¹⁸, Kelly L. Klump¹⁹, Maria La Via¹, James E. Mitchell¹⁰,²¹, Michael Strober¹², Alessandro Rotondo²³, Janet Treasure²⁴, and D. Blake Woodside¹⁶,¹⁷,²⁵
Epidemiology of Anorexia Nervosa in Men: A Nationwide Study of Finnish Twins

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A Neural Signature of Anorexia Nervosa in the Ventral Striatal Reward System

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Georg Grön, Ph.D.
Karl Grammer, Ph.D.
Bärbel Herrnberger, Ph.D.
Edgar Schilly, M.A.
Sabine Grasteit, Dipl.-Psych.
Robert Christian Wolf, M.D.
Henrik Walter, M.D., Ph.D.
Jörn von Wietersheim, Ph.D.

(Am J Psychiatry 2010; 167:206-212)
Autoantibodies against neuropeptides are associated with psychological traits in eating disorders

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Contributed by Tomas Hökfelt, August 19, 2005

PNAS | October 11, 2005 | vol. 102 | no. 41 | 14867
Problems..

Some aspects of the AN pathology are difficult to assess in humans, such as molecular alterations in the brain or bone marrow.

Some studies are hardly conceivable in humans without prior thorough explorations and screenings in animals.
Anorexia in animals?

Rare that animals starve themselves to death voluntarily.

Prolonged self-starvation over periods of months related to reproductive behavior (seals, penguins, whales) seasonal migration (birds) or hibernation (bears).
Anorexia nervosa (4)

“harmless” dieting → Anorexia Nervosa → Chronic disorder → death

Physiological consequences: amenorrhea, bradychardia, abnormal blood pressure and temperature, depression

Other consequences: social function and adolescent development
Animal models of anorexia

- Stress model (SBA)
- Activity model (ABA)
- Genetic model (anx/anx)
- Knock-out models
- Diet restriction
Stress model: Separation-based anorexia (SBA)

Combined stress & food restriction

Decreased food intake & rapid weight loss

Eat less & lose more weight than control mice that are food restricted in the absence of the stressor.

Aberrances in neurotransmitter systems; noradrenaline, dopamine, serotonin & acetylcholine.
Activity model: Activity-based anorexia (ABA)

Combined increased physical activity & food restriction.

Low food intake, unable to compensate for energy lost during exercise and can starve themselves to death. Amenorrhea.

Unusual response, since energy expenditure is increasing at a time when food intake is limited.

The food restriction elicits the increased physical activity

Aberrances in serotonergic and cholinergic systems
Genetic model: the *anx/anx* mouse

Arose in 1976

Starvation
Emaciation
Death by week 3-5

Neurological abnormalities

Aberrances in neuropeptidergic/-transmitter systems: AGRP/NPY, POMC/CART and Serotonergic systems.

Low leptin.

Hypothalamic inflammation/neurodegeneration and mitochondrial dysfunction.
The *anx*-interval

Mutation mapped to 0.2cM interval, on mouse Chromosome 2

The interval corresponds to 1.3 Mbp

40 genes identified
The *anx/anx* mouse

Maltais et al. (1984). J Hered
AGRP-IHC IN THE anx/anx MOUSE

C. Broberger et al., (1998) PNAS
Diet restriction

Food is limited by researcher, i.e. non-voluntary food restriction.
- ad libitum for a specific time span
- access to a percentage of ad libitum, e.g. 40% or 60%

Can be used to study the neuroendocrine effects of starvation.

Aberrances in catecholaminergic-, cholinergic-, enkephalin- and dynorphin systems.
**Knock-out (KO) models**

Dopamine deficient mice
- Born normally, gradually develop hypoactivity & hypophagia, die at 3-4 weeks of age

M3 Muscarinic receptor KO
- Reduced food intake, body weight & peripheral fat depots. Aberrances in hypothalamic neuropeptides. Low leptin & insulin

MCH (melanine concentrating hormone) KO
- Hypophagic, lean & increased metabolic rate. Blunted response to food restriction.

Central cannabinoid receptor 1 KO
- Feeding phenotype after food restriction

Corticotrophin releasing hormone receptor 2 KO
- Anxiety, hypersensitive to stress, feeding phenotype only after food restriction.
Examples of studies on animal models (1)

Dysregulation of dopamine signaling in the dorsal striatum inhibits feeding

Bethany N. Sotak, Thomas S. Hnasko, Siobhan Robinson, Erik J. Kremer, Richard D. Palmiter

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Accepted 28 August 2005
Available online 13 October 2005
Examples of studies on animal models (2)

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Available online at www.sciencedirect.com

SCIENCE DIRECT

Peptides 26 (2005) 1690–1696

www.elsevier.com/locate/peptides

a-MSH enhances activity-based anorexia

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Received 2 August 2004; accepted 13 November 2004
Available online 17 June 2005
Evidence of Hypothalamic Degeneration in the Anorectic anx/anx Mouse

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Task!

Summarize the major finding of the article

Focus on introduction and discussion

What aspects, or which time point in the timeline of anorexia nervosa can the model be used to study?