

(Metre)leptin in anorexia treatment

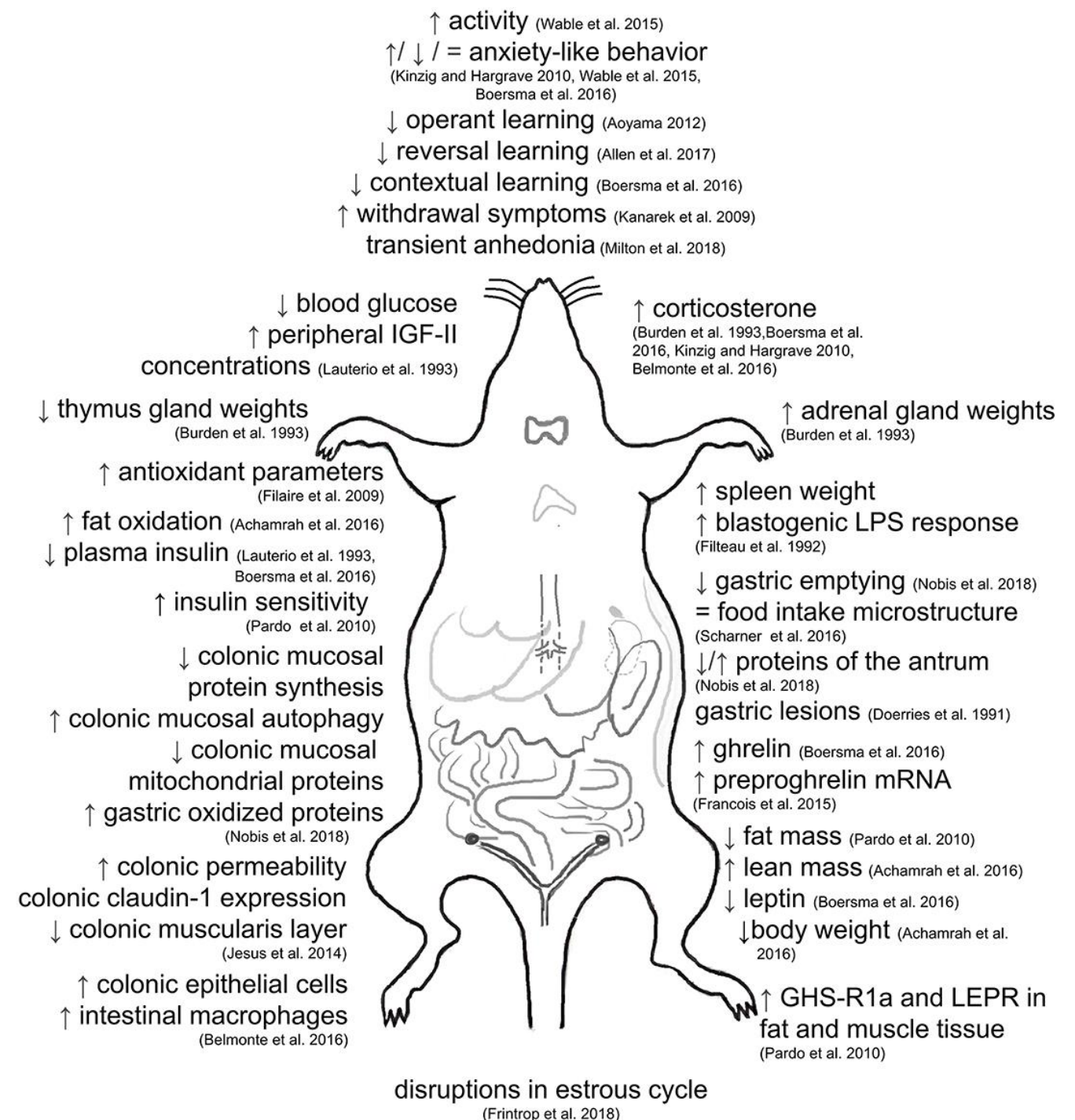
Dr Elizabeth Roberts,
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The activity-based anorexia (ABA) model

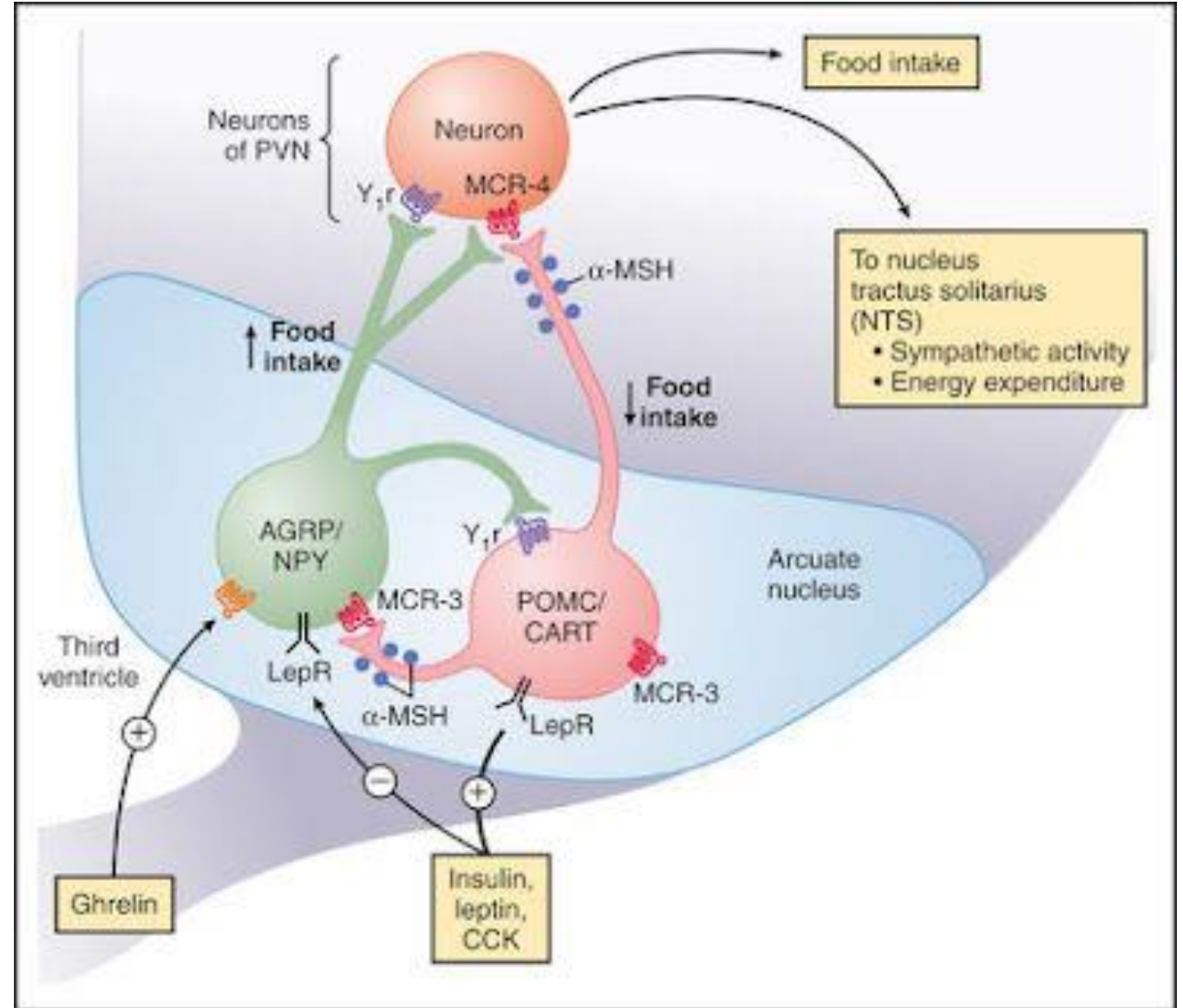
- Food restriction to one hour per day in rats or 2–4 h per day in mice = increased wheel running + decreased food intake = weight loss, which can exceed 30% of baseline weight (Hall and Hanford, 1954; Routtenberg and Kuznesof, 1967; Ross et al., 2016).
- Food restriction to 60% of ad libitum intake termed semi-SIH also results in increased wheel running by 300–400% within days (Exner et al., 2000).
- Both ABA and SIH can ensue in the death of the rodent due to starvation (Routtenberg and Kuznesof, 1967).
- In contrast, rats in cages without a running wheel survive the restricted access to food.



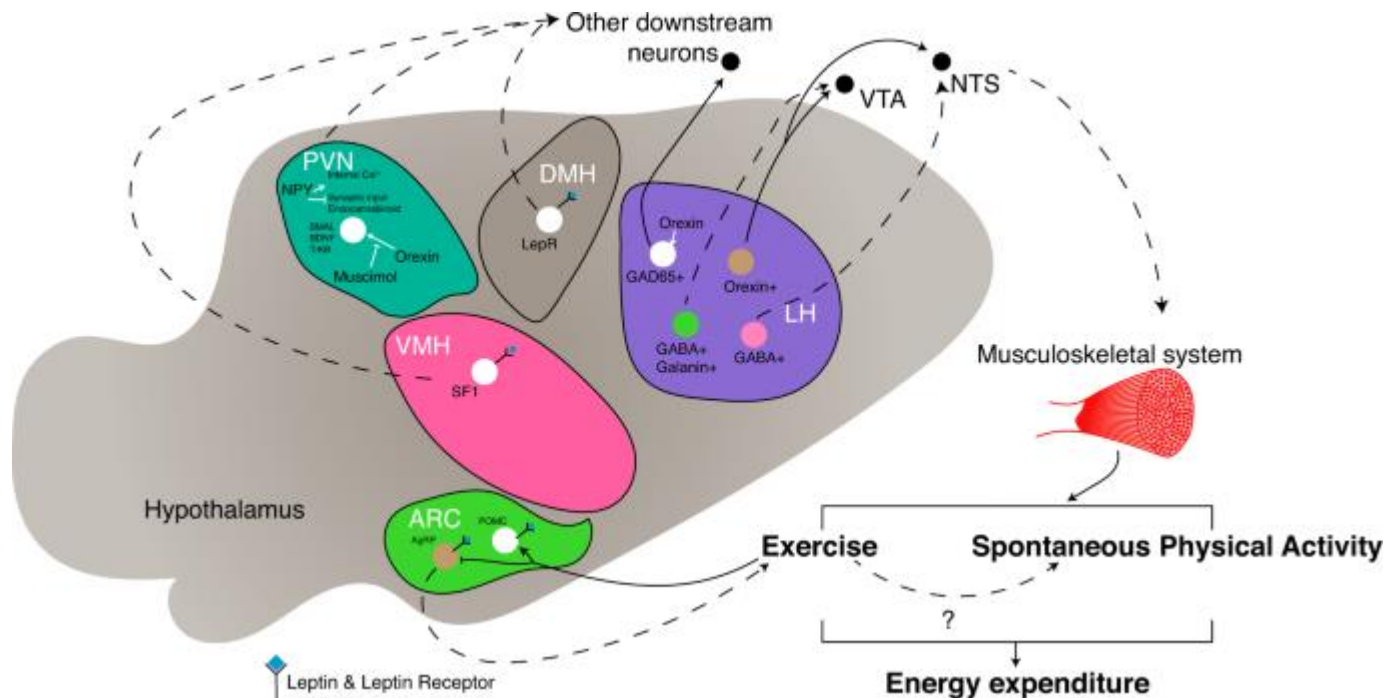
Various versions of ABA protocols are described. Consequently, several influencing factors such as pre-exposure, ambient temperature and sound, handling and maternal separation, diet and food access, activity, sex, strain and genetics have been described able to affect food intake, activity and thus body weight loss during the development of ABA.



The melanocortin system



AgRP neurons in the ARC and neurons in the lateral hypothalamus control spontaneous physical activity

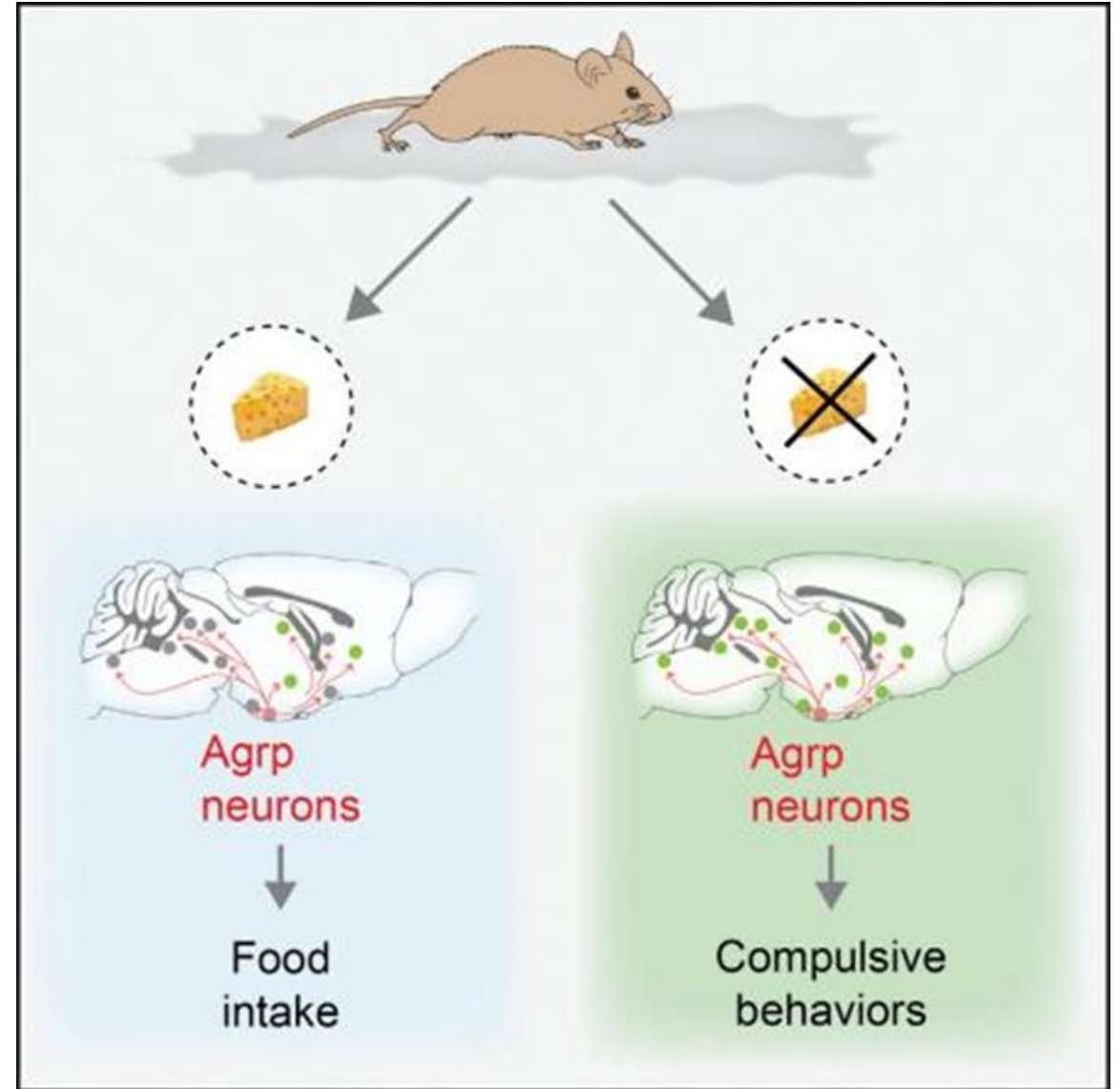


- AgRP neurons in the hypothalamus are quickly inhibited within 30 s at the end of a voluntary running session, while POMC neurons are activated.
- Using the activity-based anorexia (ABA) mouse model, the impaired activation of AgRP neurons in response to a negative energy balance induced compulsive exercise, and this sustained exercise led to death.
- Activation of AgRP neurons in female mice running under the ABA paradigm increased the running counts and abilities of the food-restricted mice.
- These findings provide one line of evidence for the role of AgRP neurons in compulsive exercise in individuals with anorexia nervosa.

Starvation and stereotypical behaviours

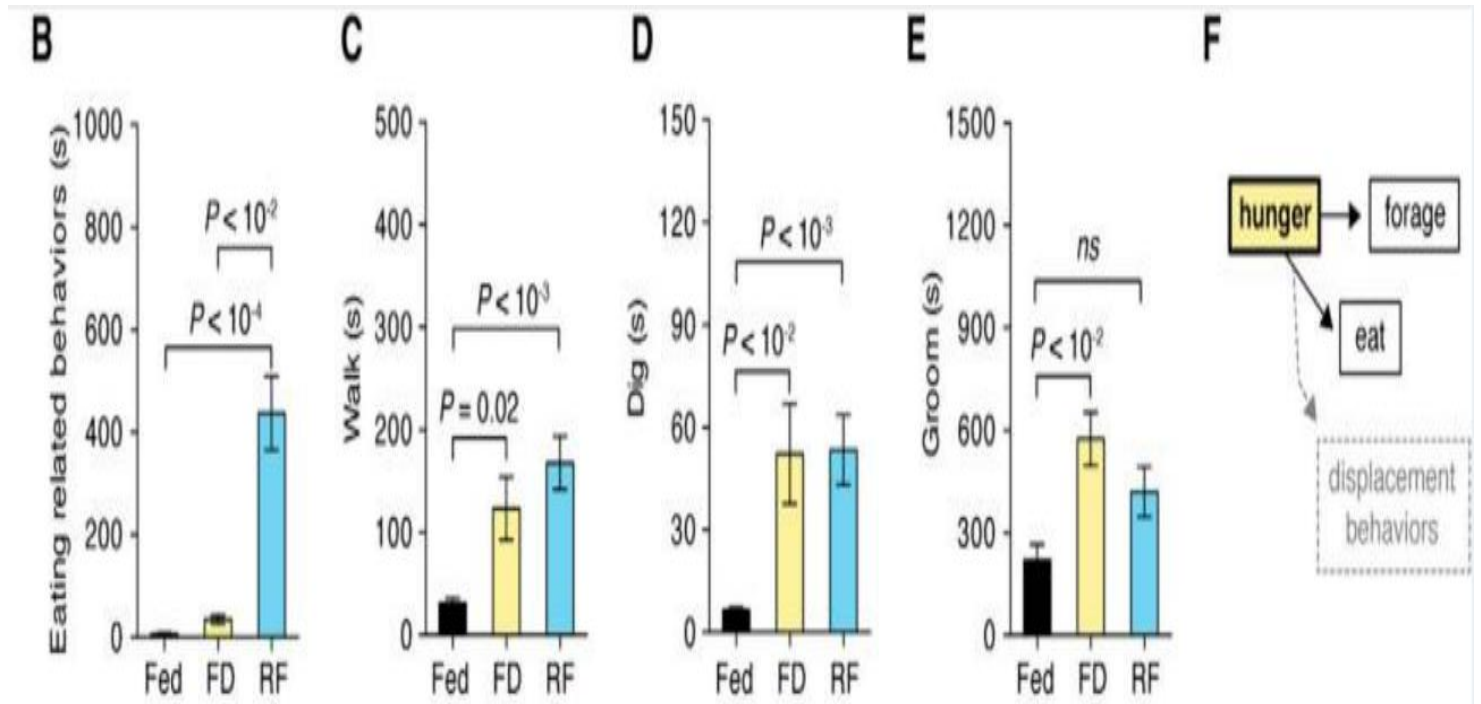
- Feeding and eating behaviours (time spent in the eating zone and chewing)
- Foraging behaviours (running/walking and digging)
- Displacement behaviours (marble burying and grooming)

Marcelo O. Dietrich, Marcelo R. Zimmer, Jeremy Bober, and Tamas L. Horvath. Hypothalamic Agrp Neurons Drive Stereotypic Behaviors beyond Feeding. Cell. 2015 Mar 12; 160(6): 1222–1232.



How does starvation and refeeding effect rat behaviours?

- Because the hypothalamus is an evolutionarily conserved brain region, it is likely that these results are relevant to higher-order organisms, including humans.
- Our findings place interoceptive regions of the mammalian brain, such as the arcuate nucleus of the hypothalamus, as crucial mediators of repetitive and stereotypic behaviors.



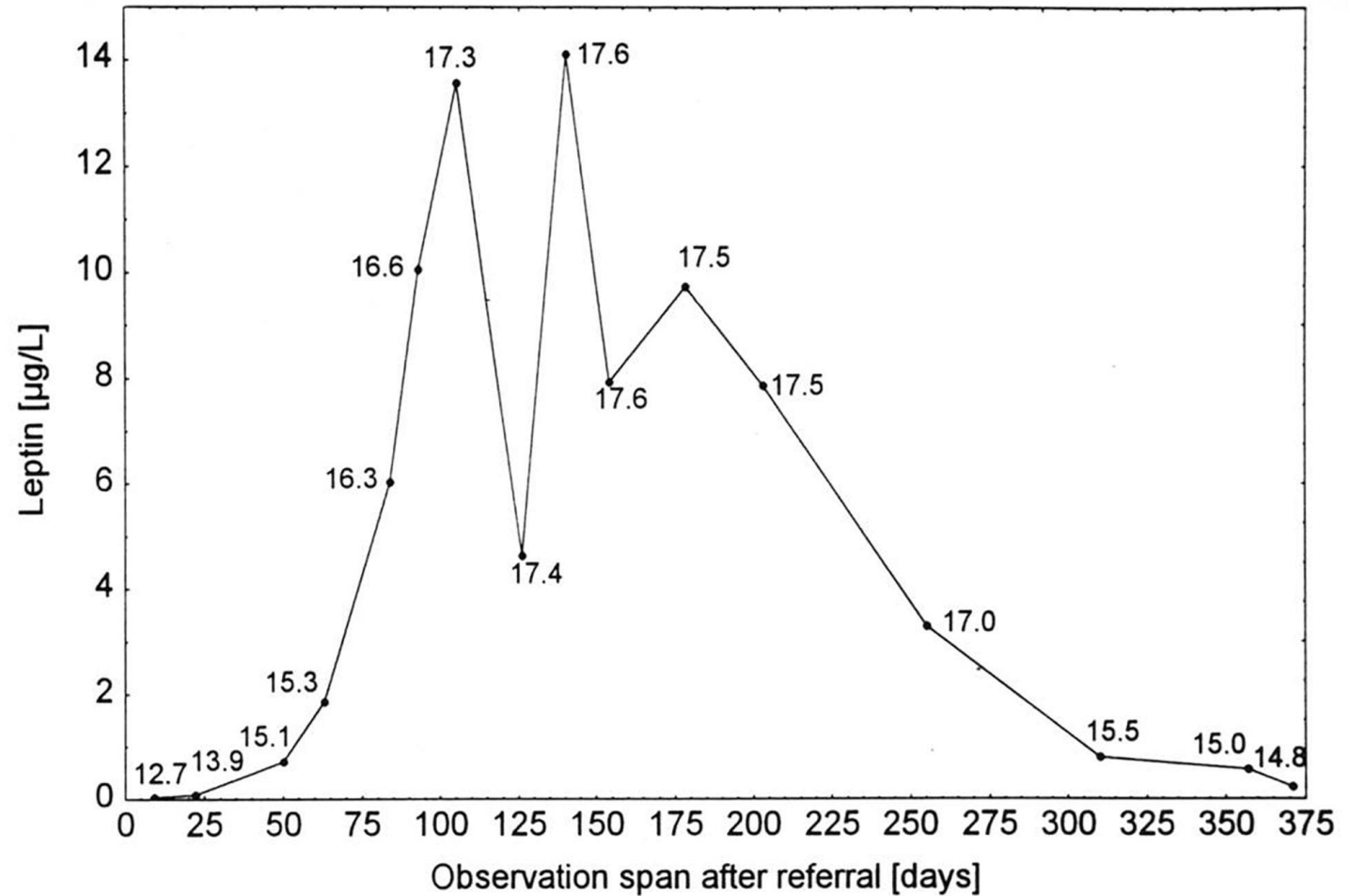
What does this mean in anorexia?

- Patients with anorexia nervosa have elevated circulating blood levels of Agrp compared to controls (Merle et al., 2011; Moriya et al., 2006) and Agrp levels are associated with cognitive rigidity in these patients (Sarrar et al., 2011).
- Anorexic patients have depleted fat stores, low leptin levels, and a reduction of cerebrospinal leptin levels (Hebebrand et al., 1995, 1997; Grinspoon et al., 1996; Mantzoros et al., 1997), neuropeptide Y is elevated (Kaye et al., 1990) as is ghrelin (Ariyasu et al., 2001; Otto et al., 2001).
- Hypoleptinemia is associated with weight-related rumination (Wronski et al., [2022](#), [2023a](#), [2023b](#), [2023c](#)).

Hebebrand's leptin trials

- Patients with AN present hypoleptinemia in accordance with both their reduced energy intake and fat mass (Hebebrand et al., 1995, 1997, 2007; Grinspoon et al., 1996).
- Consistent with results obtained in normal weight and overweight individuals, serum leptin levels in patients with AN show a higher correlation to body fat than to BMI (Grinspoon et al., 1996; Mathiak et al., 1999).
- The serum levels are below those of age, BMI, and sex matched controls including constitutionally thin females (Hebebrand et al., 1997; Eckert et al., 1998; Kopp et al., 1998; Germain et al., 2007; Föcker et al., 2011).
- A serum leptin level of approximately 2 $\mu\text{g/L}$ predicts both AN and a lifetime history of secondary amenorrhea in underweight females (Kopp et al., 1998; Föcker et al., 2011).

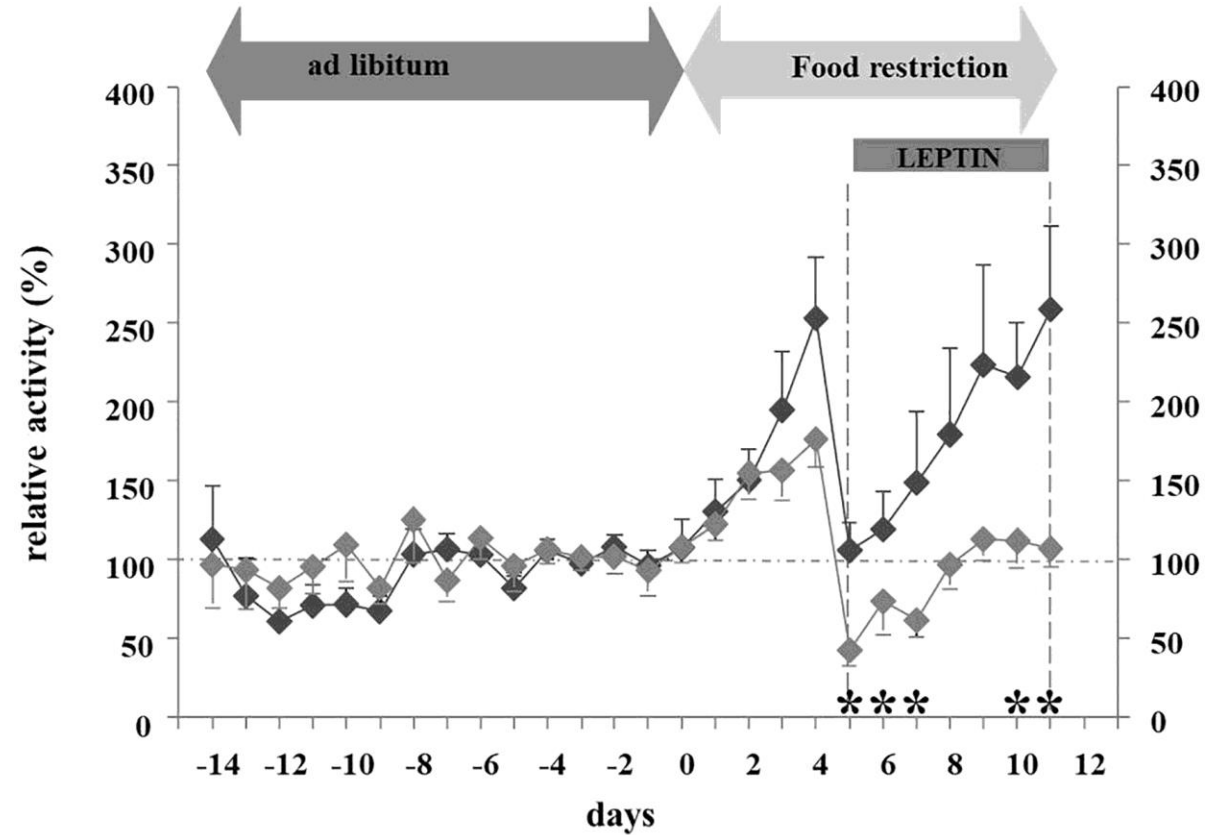
Serum leptin concentrations of a patient with anorexia nervosa at admission for inpatient treatment, during weight gain, intermittent weight maintenance, and renewed weight loss (numbers indicate BMI in kg/m^2).



Hebebrand, J., Blum, W. F., Barth, N., Coners, H., Englaro, P., Juul, A., et al. (1997). Leptin levels in patients with anorexia nervosa are reduced in the acute stage and elevated upon short-term weight restoration. *Mol. Psychiatry* 2, 330–334. doi: 10.1038/sj.mp.4000282

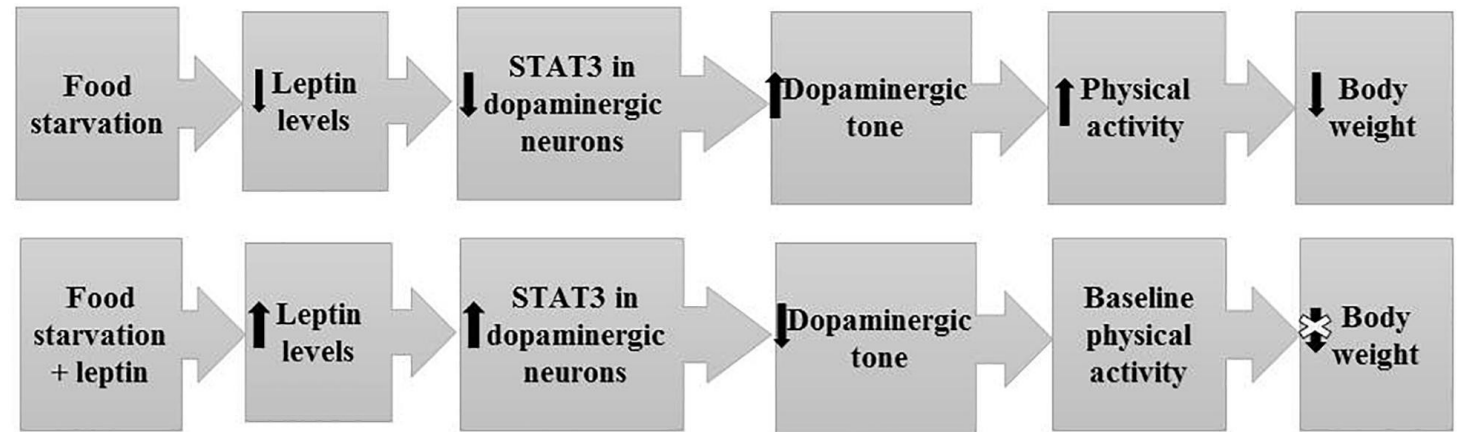
Administration of leptin suppresses ABA in rodents

Upper part of the figure displays the pathway of rodents exposed to food starvation with a subsequent loss in body weight due to elevated physical activity. The lower part of the figure displays the pathway of rodents who first developed SIH and were then treated with leptin via a mini-pump.



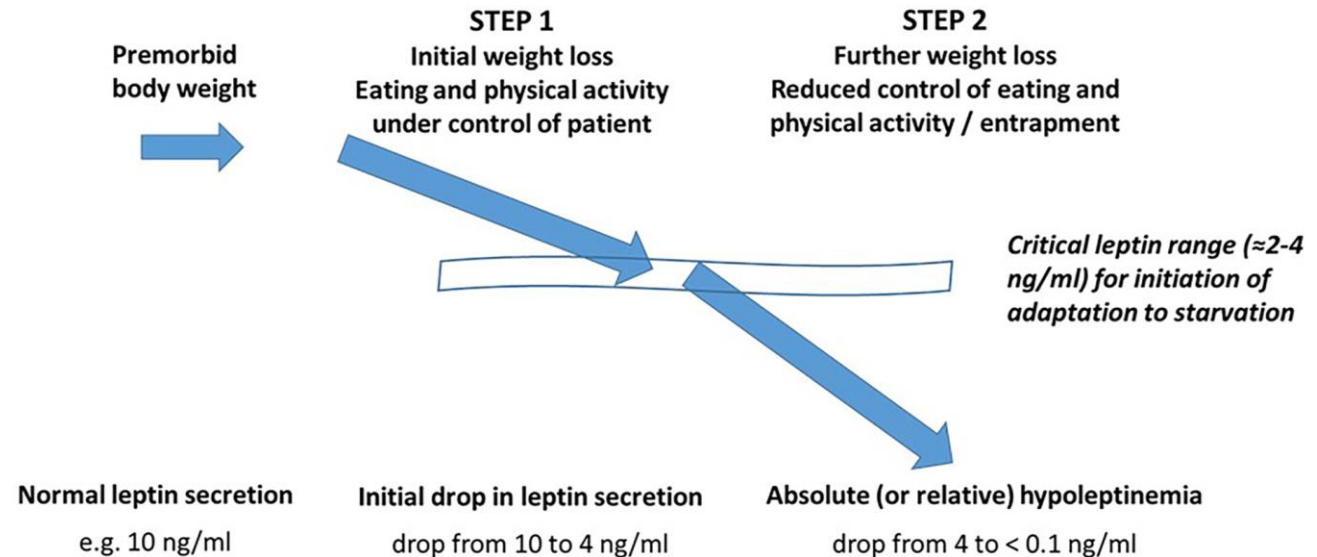
Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, Schweiger U, Blum WF, Preibisch G, Heldmaier G, Klingenspor M. Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. *Mol Psychiatry*. 2000 Sep;5(5):476-81. doi: 10.1038/sj.mp.4000771. PMID: 11032380.

One hypothesis for how starvation induces hyperactivity

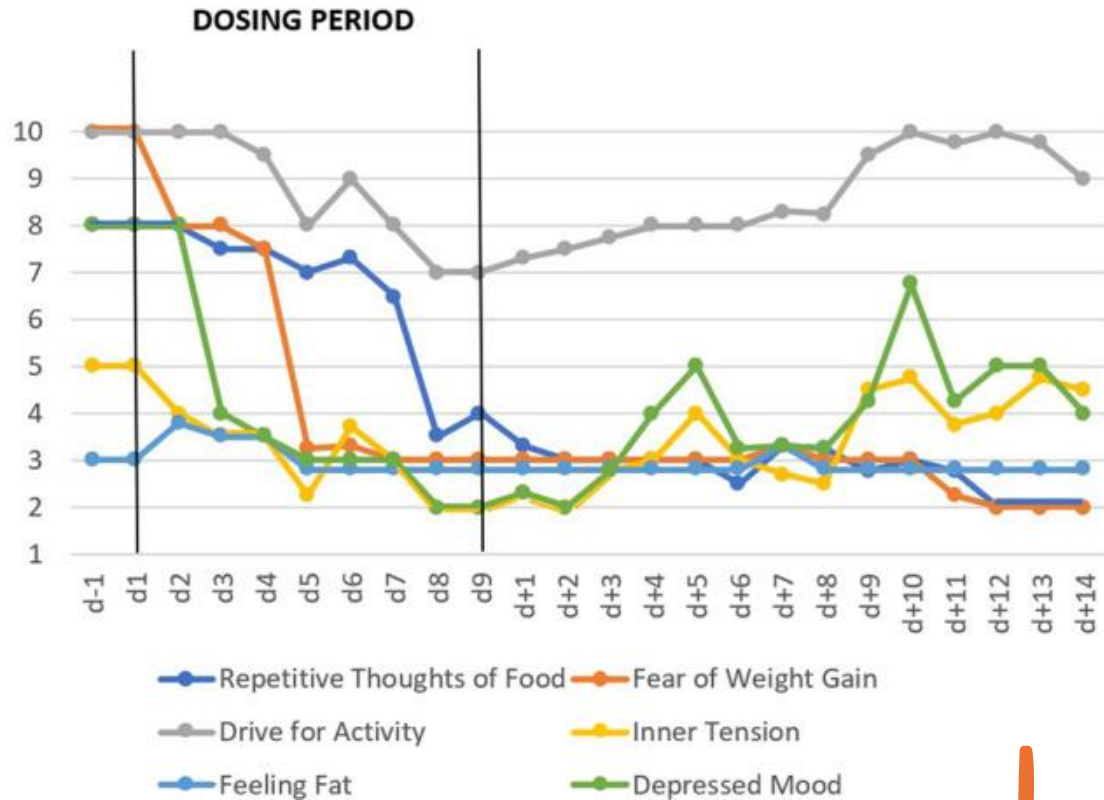


Hypoleptinaemic 'entrapment'

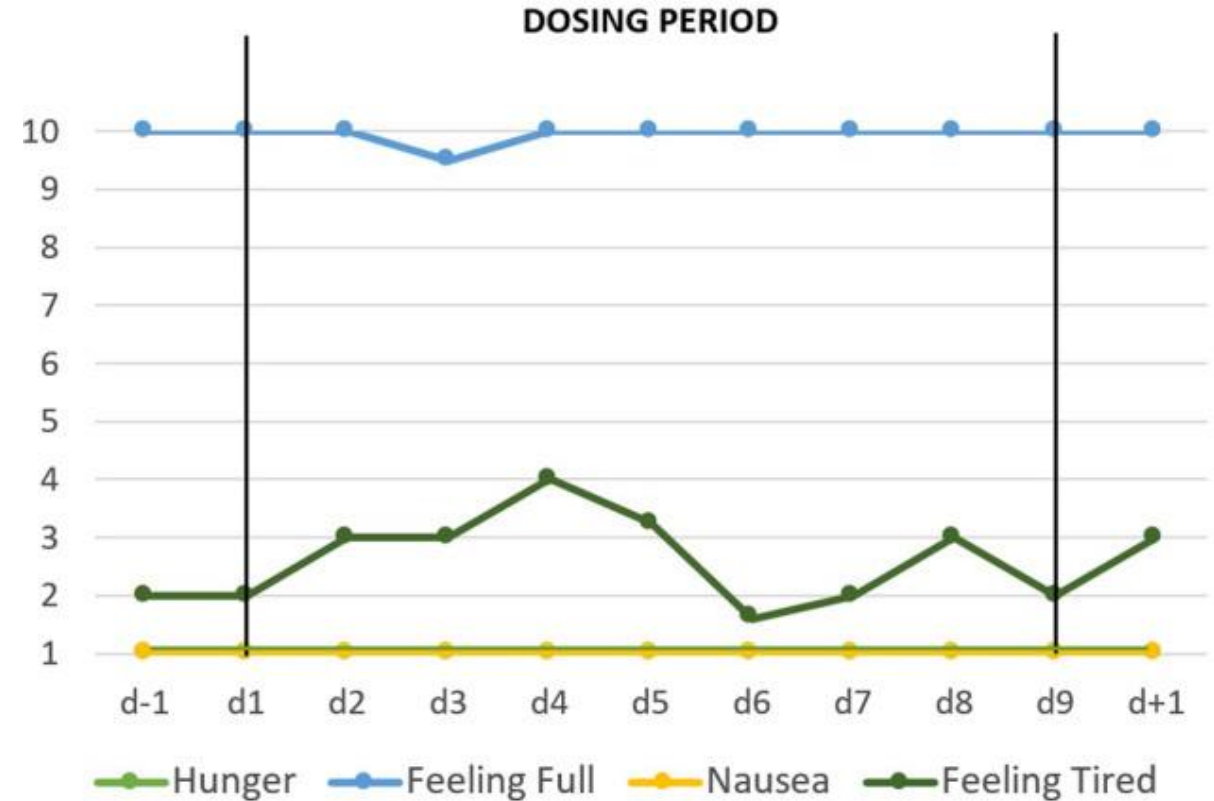
Hebebrand, J., Plieger, M., Milos, G., Peters, T., Hinney, A., & Antel, J. (2024). Does hypoleptinemia trigger entrapment in anorexia nervosa? Etiological and clinical considerations. *European Eating Disorders Review*, 32(3), 557–574. <https://doi.org/10.1002/erv.3071>



Patient A



Patient A

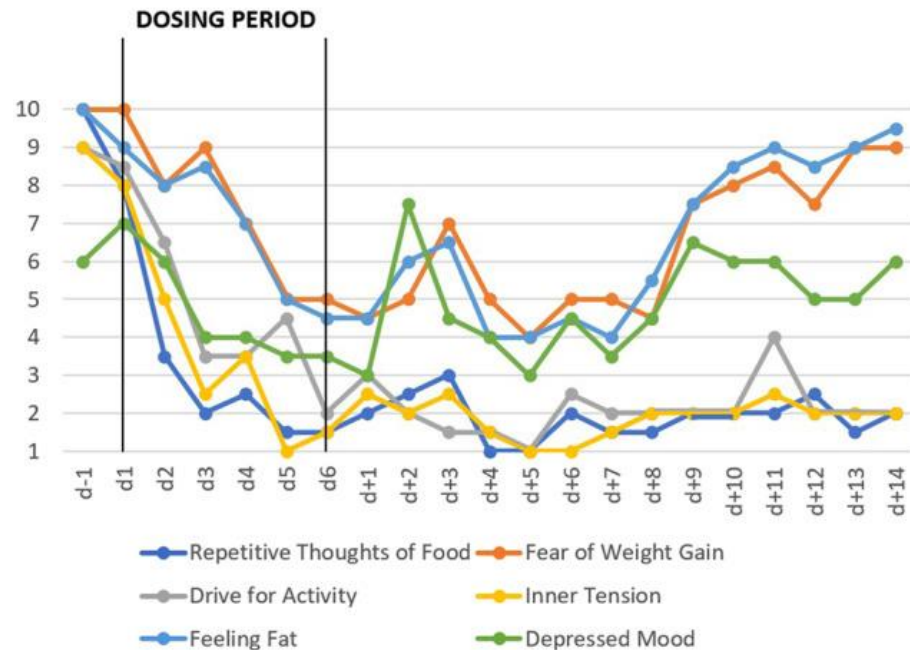


Case study treatment with leptin patient A

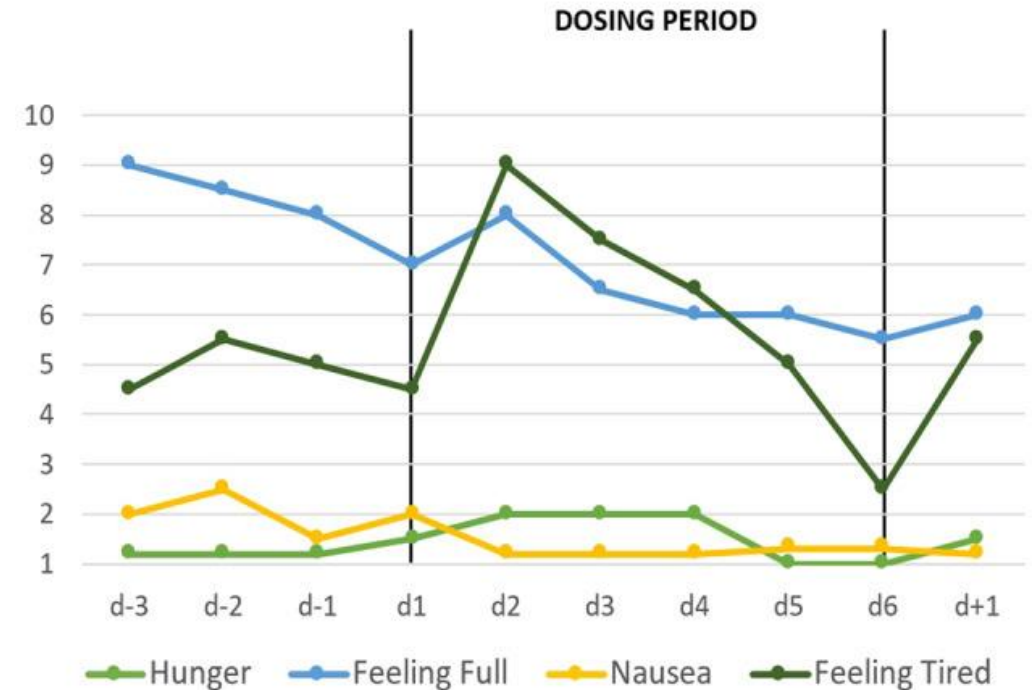
Milos G, Antel J, Kaufmann LK, Barth N, Koller A, Tan S, Wiesing U, Hinney A, Libuda L, Wabitsch M, von Känel R, Hebebrand J. Short-term metreleptin treatment of patients with anorexia nervosa: rapid on-set of beneficial cognitive, emotional, and behavioral effects. *Transl Psychiatry*. 2020 Aug 27;10(1):303. doi: 10.1038/s41398-020-00977-1. PMID: 32855384; PMCID: PMC7453199.

Case study treatment with leptin patient C

Patient C



Patient C



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