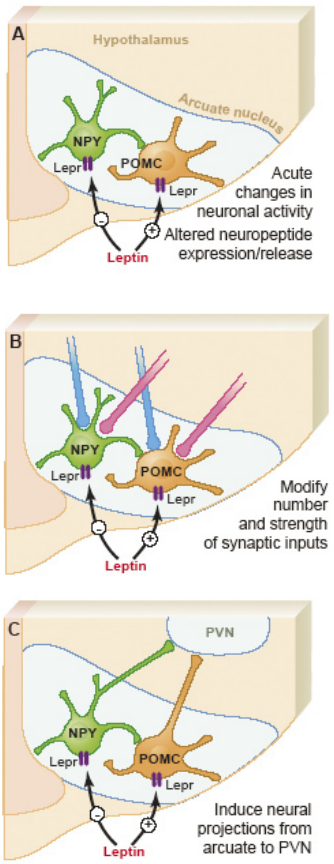
Leptin Actions on Hypothalamic Neurons & Arcurate Nucleus

Leptin decreases feeding behavior and encourages weight loss.[1] It stimulates hypothalamic neurons within the arcuate nucleus that synthesize anorexigenic or appetite-suppressing neuropeptides [proopiomelancortin (POMC) and its products α-melanocyte stimulating hormone and cocaine- and amphetamine-regulated transcript (CART)]. It also suppresses neurons that synthesize orexigenic or appetite-stimulating neurotransmitters [neuropeptide Y (NPY) and agouti-related protein (AgRP)]. These neurons then project to the paraventricular and dorsomedial hypothalamic nuclei, and lateral hypothalamic area (PVH, DMH, LHA, respectively). There, other neuropeptides propagate the feelings of hunger or satiety.[2] Leptin acts directly upon these neurons through the leptin receptor. Pinto et al identified direct anatomical functional effects of leptin upon these arcuate neurons. They transgenetically programmed wild-type (WT) and *ob/ob* mice to co-express fluorescent proteins with POMC (topaz) and NPY (sapphire). As expected each neuropeptide was expressed in a different arcuate neuron. They then examined, by patch clamp recordings in arcuate nuclear slices *in vitro*, the numbers of excitatory and inhibitory afferent inputs into these discrete neurons and quantitated by electron microscopy their anatomically distinct synapses. In *ob/ob* animals, there were far more excitatory than inhibitory impulses into (and excitatory synapses on) NPY neurons than in WT mice. There were many more inhibitory impulses into (and inhibitory synapses on) POMC neurons in *ob/ob* than WT mice. Administration of leptin to *ob/ob* mice reversed these patterns. In WT mice, administration of ghrelin, a gastric appetite-stimulating peptide,[3,4] increased inhibitory and decreased excitatory synapses into/on POMC neurons but did not appear to affect NPY-containing neurons. The authors concluded that there is "neural plasticity" in the arcuate cells containing POMC and NPY and that the effects of leptin and ghrelin are at least partially mediated by such changes.

Bouret et al examined the effect of leptin deprivation and leptin administration upon the density of the neural projections between the arcuate nucleus and the paraventricular nucleus (PVH), dorsomedial hypothalamic nucleus (DMH), and lateral hypothalamic area (LHA) in intact and leptin deficient (*ob/ob*) mice. They placed a "fluorescent ... tracer that labels axonal projections in fixed tissues" into sections of the arcuate hypothalamic nucleus then examined the pattern of fluorescent projections to the target area(s). In WT animals, the density of these projections increased with age. Relative to WT animals at all ages, leptin deficiency was associated with a greatly decreased number of projections from the arcuate nucleus to all target regions, but not to non-target areas. Administration of leptin to *ob/ob* adult mice did not alter this pattern. However, leptin given at very high doses intraperitoneally (1 mg/100 mg body weight IP) between postpartum days 4 through 12 restored the density of projections to normal by the 80th day of life. The authors concluded that leptin is essential for the development of hypothalamic neural pathways that convey leptin downstream signals and that this property was expressed in the neonatal period and perhaps promoted by the neonatal surge in leptin secretion.



Leptin and neurodevelopment. Leptin acts on the neurocircuitry of the hypothalamus in three ways. (A) Leptin acts directly on the neurons of the arcuate nucleus by binding to the leptin receptors (Lepr) that they express. The altered activity of these neurons in response to leptin results in changes in their production and release of the neuropeptide NPY and the POMC product, α-melanocyte stimulating hormone. (B) By acting on an unknown site, leptin produces rapid changes in the strength and number of excitatory and inhibitory synapses that have inputs on NPY and POMC arcuate neurons. (C) Leptin induces neurite outgrowth of arcuate neurons, stimulating projections from the arcuate to the paraventricular nucleus (PVN) of the hypothalamus during a critical postnatal period.

Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004;304:108-110.

Pinto S, Roseberry AG, Liu H, et al. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 2004;304:110-115.

Editor's Comment: *In an accompanying commentary Elmquist and Flier[4] discussed the significance of the neuroexcitatory and anatomical effects of leptin. They suggested that through the influence of leptin on the excitatory and inhibitory inputs into the arcuate neurons and by stimulation of their neural connectivity, an as yet hypothetical body weight set point might be a functional reality. In mice, there is a surge in leptin secretion in the first week after birth that is not accompanied by a decrease in food intake. The possibility that a body weight set point may be related to and perhaps programmed by the secretion of leptin in the immediate post-partum period (in mice) is intriguing. In human neonates, serum levels of leptin decline over the first 6 days of life and then do not change*

appreciably over the first 17 days after birth.[5] Serum leptin concentrations are higher in female than male infants and related to BMI through 12 months of age, but low relative to values in older children and adolescents.[6,7] If there is a set point for body weight as there is for height in man, it is unfortunately easily abridged.

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Attitudes Toward Clinical Management of Intersexuality: The Voices of 46,XY Adult Patients

Controversies regarding the care of individuals born with intersexuality prompted a stream of adult followup studies of psychosocial and psychosexual functioning. Far less attention has been directed at the attitudes held by former patients toward treatment policies. The paper by Meyer-Bahlburg et al represents a marked exception. Specifically, participants were asked about their satisfaction with assigned gender as well as their opinions regarding the desirability of a 'third gender,' and the optimal age for genital surgery.

Attitude data were collected on 46,XY adults who had presented to a pediatric endocrinology clinic with varying degrees of genital ambiguity. The study was a postal survey followed by a physical examination. A total of 72 completed the questionnaire (32 men and 40 women; 18-60 years old). Based upon appearance of the genitalia at time of referral, participants were classified with ambiguous genitalia (AMBI; 21 men, 18 women), micropenis (MICRO; 11 men, 5 women), or female external genitalia (FEG; 17 women). The AMBI group consisted of individuals born with microphallus associated with perineoscrotal hypospadias secondary to various intersex syndromes. MICRO syndromes were attributed to hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, and idiopathic types. The FEG group was made up mostly of patients with complete androgen insensitivity.

Most participants were "mainly satisfied" with assigned gender (85%). In male AMBI and MICRO 68% replied their genitalia appeared unusual, and 76% complained that their penis was too small. Whereas, in female AMBI and MICRO, 39% thought their genitals looked unusual. The majority of participants (73%) were either mainly or somewhat satisfied with sexual functioning.

Only 15% endorsed an assignment of a third gender as a strategy to avoid genital surgery. However, there was a statistical trend for those not satisfied with their own gender to endorse this. When asked about surgical correction of a hypothetical child born with ambiguous genitalia, 67% did not endorse the option of postponing genital surgery until adulthood. When asked to employ hindsight regarding their own genital surgery, 47% thought the procedure should be performed during infancy, 24% recommended postponing surgery until adolescence, and 22% thought the procedure should have been postponed until their adult years. FEG women almost uniformly endorsed waiting for surgery until adulthood.

Meyer-Bahlburg HFL, Migeon CJ, Berkovitz GD, Gearhart JP, Dolezal C, Wisniewski AB. Attitudes of adult 46,XY intersex persons to clinical management policies. *J Urology* 2004;171:1615-1619.

Editors' Comment: *Several findings of this study are noteworthy. First, the majority of the 46,XY adult patients with intersexuality expressed satisfaction with assigned gender. This finding has been corroborated in independent studies.[1] Second, 45% were mainly satisfied with their current sexual functioning (while 28% were somewhat satisfied and 27% mainly dissatisfied). Readers should be cautioned against assuming that dissatisfaction with sexual functioning is necessarily related to the quality of the surgical reconstruction. Sexual problems in the general population of men and women are reported to be high.[2] Without a healthy comparison group, the rates of satisfaction/dissatisfaction reported in this study are difficult to evaluate. In addition, the best predictors of sexual distress in women are markers of general emotional well-being and emotional relationship with the partner during sexual activity. In contrast, physical aspects of the sexual response in women, including arousal, vaginal lubrication, and orgasm, are poor predictors.[3] Because survey respondents may assign different interpretations to single questionnaire items, the precise meaning of responses await more detailed assessments. Consistent with patient advocacy groups (eg, the Intersex Society of North America), the majority of survey participants opposed a third gender option. It is reassuring that the message obtained from former patients and patient advocacy groups coalesce in this critical aspect of clinical decision-making.*

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