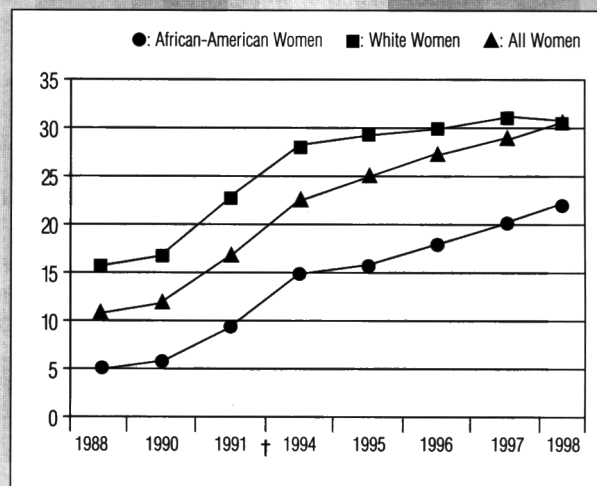


**Editor's comment:** Although this is primarily a descriptive report, the information provided is of significant importance not just to pediatric endocrinologists but to all physicians. In this editor's personal experience, I have seen 2 such children in the past 6 months (1 who was 13 months of age and 1 who was 4 years old). Of interest, the 4 year old was referred for evaluation of short stature and failure to thrive. His lower limb bowing and metaphyseal flaring were obvious at cursory inspection.

With the significant increase in breast-feeding, accompanied by a significant increase in public health warnings regarding the effects of excessive sunlight and the subsequent use of sunscreen on many infants, it is important that all physicians be aware of the possibilities of vitamin D-deficient rickets and that children be supplemented appropriately. In addition, it is important that the community and physicians be reminded of the signs and symptoms of this easily treatable cause of short stature. A study of subclinical rickets in both white and black infants who are breast-feeding would very possibly determine that the incidence of clinical or subclinical rickets is very significant in the latter group.

William L. Clarke, MD

Figure



Incidence of breast-feeding in African-American women in North Carolina, 1988 to 1998. Information for women seen for the maternal postpartum WIC visit. †Data not available for years 1992 to 1993.

Reprinted with permission from Kreiter S, et al. *J Pediatr* 2000;137(2):153-157.

## The Central Melanocortin System Affects the Hypothalamo-Pituitary Thyroid Axis and May Mediate the Effects of Leptin

In the fasted rodent, in the genetically leptin-deficient mouse (*ob/ob*), and in the genetically leptin-resistant mouse (*db/db*), there is secondary hypothyroidism. Kim and collaborators hypothesize that leptin may act through the melanocortin system (MS) upon pituitary thyroid-stimulating hormone (TSH) secretion in adult rats. The basis for the hypothesis is that the MS is known to mediate the inhibitory actions of leptin on feeding.  $\alpha$ MSH was administered by cannulae into the third intracerebroventricular (ICV) or into the intraparaventricular nucleus (IPVN), which regulate the secretion of pituitary TSH. Also, similarly injected was the *agouti*-related peptide (Agrp), which is an endogenous antagonist of melanocortin 3 and 4 receptors (MCR-3, MCR-4). When activated by  $\alpha$ MSH, these receptors inhibit feeding.

In vitro, Agrp significantly decreases plasma TSH concentrations in the *fed* animal when injected into the ICVN or IPVN. In contrast,  $\alpha$ MSH increased TSH levels in fasted rats. In vitro,  $\alpha$ MSH increased the release of thyrotropin-releasing hormone (TRH) from hypothalamic slices (Figure), an effect blocked by Agrp. In this in vitro system, leptin increased and Agrp blocked the release of  $\alpha$ MSH and TRH.

Therefore, the investigators concluded that leptin stimulates thyroid function by enhancing the production of  $\alpha$ MSH from pro-opiomelanocortin and possibly by blocking the synthesis of Agrp.  $\alpha$ MSH stimulates release of TRH, which increases TSH secretion. Consequently, the regulatory pathways for the

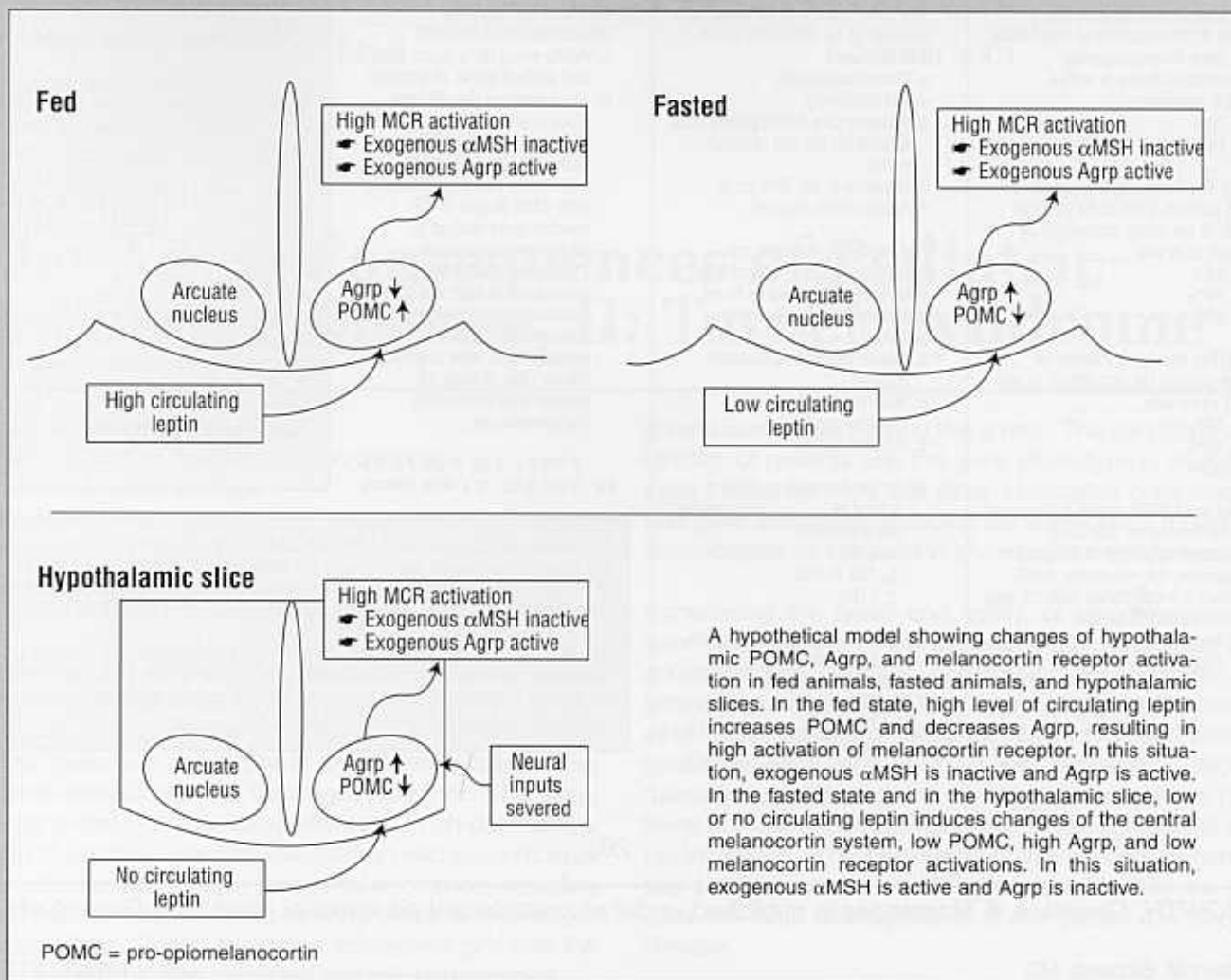
control of energy balance via food intake and food metabolism are linked.

Kim MS, et al. *J Clin Invest* 2000;105:1005-1011.

**Editor's comment:** In the starved state, the expression of TRH in the paraventricular nucleus is dramatically decreased, a response that can be reversed by the administration of leptin. In addition to the pathway through pro-opiomelanocortin and  $\alpha$ MSH synthesized in the arcuate nucleus, leptin likely acts directly on transcription of the gene encoding TRH (Figure).<sup>1</sup> Thus, changes in leptin secretion mediate the metabolic responses characteristic of the fed or starved states. Interestingly, MCR-3 and MCR-4 mediate different aspects of leptin- $\alpha$ MSH actions: MCR-3 affects feed efficiency—that is, the quantity of weight gained per calorie ingested—while MCR-4 influences the quantity of food ingested (or appetite) and energy utilization.<sup>2</sup> Not only does leptin mediate feeding behavior and energy expenditure by its central action, this fat-derived protein also influences bone mass in this manner. ICV administration of leptin inhibits bone formation in *ob/ob* mice by unknown mechanisms, while patients with a loss-of-function mutation in MCR-4 are obese and have a high bone mass.<sup>3</sup>

Besides its effects on melanin synthesis and dispersal by keratinocytes and on feeding mediated primarily by MCR-4,  $\alpha$ MSH, acting through 1 of 5 MCRs, reduces a number of

Figure



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inflammatory processes by lowering the production of several proinflammatory cytokines (including interleukin-1β and -6, tumor necrosis factor-α, and interferon-γ) and the nuclear transcription factor NF-κB.<sup>4</sup> Serum concentrations of αMSH are elevated in a number of inflammatory illnesses, including HIV infection, suggesting that αMSH may be an important component of our innate host defense mechanisms. Melanin-concentrating hormone (MCH) is a hypothalamic neuropeptide that in fish causes the aggregation of melanin within melanophores and thus lightens the color of the fish scale, an effect opposite to that of and opposed by αMSH.<sup>5</sup> Acting through G-protein coupled receptors, MCH increases food intake in rodents, an effect opposite to that of leptin and αMSH. MCH also acts within the pituitary, where it stimulates corticotropin secretion. Thus, the regulation

of feeding and energy metabolism is becoming ever more complex.

William L. Clarke, MD

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