Increased leptin supply to hypothalamus by gene therapy confers life-long benefits on energy homeostasis, disease cluster of metabolic syndrome- diabetes type 1 and 2, dyslipidemia and cardiovascular ailments- and bone remodeling

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Summary. Leptin insufficiency in the hypothalamus is causally linked to increased fat accrual, diseases of the metabolic syndrome, skeletal abnormalities and shortened life-span. We show that leptin sufficiency attained with hypothalamic leptin gene therapy (i) suppressed food intake, the age-related and energy enriched diet-induced fat accrual, and dyslipidemia, (ii) attenuated episodic insulin secretion and enhanced insulin sensitivity, (iii) enhanced glucose tolerance and maintained euglycemia by concurrently stimulating glucose metabolism and non-shivering thermogenesis, even in the absence of circulating insulin, and (iv) augmented ghrelin secretion. Aside from these metabolic benefits, similar optimal leptin sufficiency in the hypothalamus (i) decreased risks for cardiovascular diseases as indicated by suppression of circulating levels of the systemic pro-inflammatory markers, C-reactive protein and interleukin-6, and hyperglycemia-induced risk factors for cardiomyopathy, (ii) improved bone health by promoting growth of long bones and reduction of cancellous bone volume in association with increased release of osteoblast-specific osteocalcin, and (iii) reduced early mortality and doubled the life-span of obese ob/ob mice. On the basis of these global long-lasting health benefits, we advocate clinical testing of central leptin gene therapy or of long acting leptin mimetics to prevent life-threatening pathophysiologic sequelae attending the worldwide epidemic of obesity and the metabolic syndrome.

Key words. Gene therapy, Hypothalamus, Obesity, Metabolic syndrome, Skeleton, Life-span
1 Historical

The potent appetite stimulating effects of hypothalamic neuropeptide Y (NPY) were discovered in the mid 1980s (Clark et al. 1984). Subsequently, a concerted effort led to deciphering of a distinct circuitry in the hypothalamus that regulates energy intake and expenditure on a moment-to-moment basis (Kalra et al. 1999, 2003). This interconnected network, primarily driven by the NPY expressing pathway, is composed of orexigenic and anorexigenic peptidergic circuitries that span the arcuate nucleus (ARC), medial preoptic area (MPOA), paraventricular nucleus (PVN), ventromedial hypothalamus (VMH) and lateral hypothalamus (LH) in the diencephalon (Kalra et al. 1999, 2003). Disruption in signaling in any component of this NPY regulatory network invariably leads to unremitting hyperphagia, abnormal rate of fat accumulation and the attendant disease cluster of metabolic syndrome and shortened life-span (Dube et al. 2007; Kalra 2008b; Kalra et al. 2003).

A further insight into the working of the NPY circuitry in maintaining energy homeostasis was gained after isolation and characterization of the anorexigenic hormone leptin produced by adipocytes, and the orexigenic hormone ghrelin produced by the stomach (Friedman and Halaas 1998; Kalra et al. 2003; Otukonyong et al. 2005b). That a dynamic minute-to-minute interplay of these two afferent signals to the hypothalamic NPY network sustain energy homeostasis was then uncovered (Kalra 2008b; Kalra et al. 2003, 2009; Otukonyong et al. 2005a; Ueno et al. 2004). The current view holds that leptin is a primary peripheral signal that imposes a stable tonic restraint on hypothalamic circuitry by a three prong control: one, by regulating the release and action of orexigenic and anorexigenic hypothalamic peptides, two, by directly countering the appetite stimulating action of ghrelin in the hypothalamus and, three, by restraining ghrelin synthesis and release into the peripheral circulation from oxyntic glands of the stomach (Kalra 2008b; Kalra et al. 2003, 2005; Ueno et al. 2004).

Finally, deeper understanding of the hypothalamic control of energy homeostasis was sparked by comprehensive new information on dynamic changes in leptin transport to hypothalamic targets across the blood brain barrier (BBB) enforced on a daily basis by aging, metabolic and nutritional imbalance (Banks et al. 1999; Kalra 2008a; Kastin and Pan 2006).

This fundamental new knowledge of the brain-body dialogue coupled with global health benefits observed after application of leptin gene therapy in the hypothalamus (Kalra and Kalra 2005), was recently synthesized into a "Central Leptin Insufficiency Syndrome" formulation to explain the underlying causality of the worldwide pandemic of obesity and attendant