

Recognising the Role of Leptin in Disease

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Since its discovery in 1994, research in leptin has grown exponentially. Leptin was initially recognised as a regulator of appetite and body weight, but later it has been found to contribute to homeostasis of numerous other physiological functions in the body [1,2].

Leptin is a product of the *ob* gene and is mainly secreted constitutively by white adipose tissue. Its circulating levels in blood correlate positively with the amount of body fat. Its receptors are widely distributed throughout the body, including the central nervous system, reflecting its numerous functions. Leptin deficiency results in hyperphagia and severe obesity, hypothalamic hypothyroidism, hypogonadotropic hypogonadism, impaired respiratory function, increased susceptibility to opportunistic infections, impaired T cell number and function, and inverted CD4:CD8 ratio, indicative of a weakened immune system [3].

Leptin deficiency or leptin receptor mutations are, however, rare in humans, with only about sixty-six cases reported to date worldwide [4]. Obesity results in high leptin levels, in addition to exhibiting leptin resistance or decreased leptin sensitivity. Much, however, remains to be elucidated on the mechanism of leptin resistance in obese individuals. Reduced leptin receptor expression in the hypothalamus, disturbed intracellular receptor signalling in the hypothalamus, and altered transport of leptin across the blood–brain barrier, are some of the proposed mechanisms underlying leptin resistance in obesity. While leptin resistance is believed to result in obesity, prevailing evidence suggests that the

resistance is most likely central and selective, involving the hypothalamus, leaving the sensitivity of peripheral leptin receptors intact. What triggers or causes leptin resistance, the age that the resistance is observed or how resistance develops remains unknown. Epigenetics, environmental factors, dietary habits and/or life-style factors are potentially responsible. Interestingly, chronic intermittent hypoxia has recently been shown to alter leptin homeostasis, leading to leptin resistance and obesity in animals [5]. Could this trigger leptin resistance and weight gain in some individuals? Up to 5% of the adult western population may have undiagnosed sleep apnoea, which may contribute to the obesity epidemic.

Obesity is a risk factor for cardiovascular diseases, Type 2 diabetes mellitus, non-alcoholic fatty liver disease, cancer, renal disease and infertility. Evidence in the literature implicates the role of hyperleptinaemia in these obesity-related diseases. Research in recent years has demonstrated some mechanistic links between leptin and a number of pathologies associated with obesity. For example, hypertension associated with obesity is strongly linked to leptin's proinflammatory endothelial activation activities. Leptin increases endothelin-1 (ET-1) release while decreasing nitric oxide synthesis and angiotensin converting enzyme 2 (ACE2) expression in endothelial cells. It increases oxidative stress and alters renal salt handling [6]. In addition, leptin also increases sympathetic tone to blood vessels. Collectively, these are the likely mechanisms responsible for the high



prevalence of hypertension in overweight and obese individuals, where the risk of resistant hypertension is five-fold higher compared to that in normal weight individuals. The increasing level of obesity in the population is also closely associated with the rising prevalence of non-alcoholic fatty liver disease [7,8]. There is a strong relationship between persistent hyperleptinemia and the development of steatosis, fibrinogenesis and liver carcinogenesis. Obesity-related malignancies are also on the rise, and both clinical and experimental data indicate the involvement of leptin/leptin receptor axis in the promotion of tumour development and its progression, as well as reduction in the efficacy of cancer treatments [9,10]. In addition to the cell proliferative, angiogenic and inflammatory activities, recent evidence suggests that leptin, may also have carcinogenic activity and may increase the carcinogenicity of carcinogens [11]. The kidney is the major organ that metabolises leptin, and there is considerable evidence linking elevated leptin levels to chronic kidney disease [12]. Finally, the link between leptin in sperm abnormalities and reproductive dysfunction has been repeatedly reported, where leptin has been found to reversibly affect spermatogenesis, either directly or through increase in oxidative stress [13,14].

In recent times, the world has been severely affected by the SARS-CoV 2 coronavirus pandemic. COVID-19 infection has been fatal in some instances, affecting a number of key organs in the body, particularly those individuals with co-existing morbidities like hypertension, Type 2 diabetes mellitus and obesity. Obesity is a proinflammatory state, and obese individuals have an increased risk of pulmonary infections. It has been proposed that apart from the direct interaction between COVID-19 and ACE2 and transmembrane serine protease 2, compromised immune function, due to dysfunctional leptin signalling, may exacerbate the pathological changes associated with COVID-19 in the obese [14]. Leptin, incidentally, is also believed to have an important role in the 'gut-lung' axis (GLA). GLA conceptualises the interaction between lung and gut microbiota and the human immune system [16]. Gut microbiota dysbiosis is reportedly associated with obesity and increased frequency of respiratory infections [17,18]. Significant association between high

plasma leptin levels and risk of severe respiratory infections has also been reported [19].

Given the existing research, it is becoming evident that leptin has an important role in obesity related diseases. Measures need to be taken to reduce the impact of raised leptin levels on the pathogenesis and pathophysiology of disease. Using currently available pharmacological agents to block the actions of leptin might not be feasible or appropriate. Selective or organ specific leptin antagonists are therefore required. In addition, other means must be sought to reduce the level and impact of hyperleptinaemia. Adequate weight bearing or resistance exercises with reduction in body weight could help blunt some of the adverse effects of raised leptin levels on the body. Physical exercise on its own has been shown to prevent leptin-induced increase in blood pressure in rats without reduction in body weight [20]. Regular, well planned physical activity must, therefore, be a compulsory inclusion in the management of obesity-related diseases. Weight loss programmes must include both dietary and exercise regimens, and must be tailored to ensure that the weight loss is due more to loss of adipose tissue than loss of lean muscle mass. Use of more potent anti-oxidants could also help reduce the oxidative stress associated with raised leptin levels. There are currently no methods for assessing leptin sensitivity or resistance in a clinical setting. There are also no clear established criteria for the diagnosis of leptin resistance. While the mechanistic pathways that link leptin and disease are still not clearly established, acknowledging that hyperleptinemia contributes to disease is necessary if we wish to further improve the management of obesity related diseases.

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