The relationship between leptin and inflammation in adipose tissue determines critical points in excess nutrition

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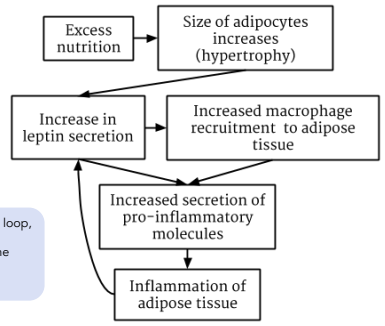
Introduction

Research has shown a significant relationship between leptin, a hormone involved in energy intake and expenditure, and inflammation in adipose tissue, the main depot of fat storage. These findings suggest an important factor in obesity: a cycle of inflammation in adipose tissue due to increases in leptin levels. This inflammation, which causes weight gain, could help to explain why lifestyle changes are often not enough to mediate obesity, now recognized as a global epidemic.

The pleiotropic role of leptin also points to its influence in immune system dysfunction as well as links obesity to its comorbidities, including type 2 diabetes, heart disease, and thyroiditis. In fact, leptin seems to be a crucial factor in the prevalence of autoimmune diseases in women. Through construction of a mathematical model of the relationships between leptin, inflammation and fat, we can better understand the role of leptin in adipose tissue inflammation, specifically in women. Insight into these relationships is necessary in better treating obesity, understanding the sexual dimorphism of immune system dysfunction, and determining risk for autoimmune disease based on amount of fat.



Excess fat is stored in adipocytes, causing a cycle of leptin secretion and subsequent inflammation.

We created the feedback loop, then constructed a mathematical model of the leptin-inflammation relationship.

Objectives

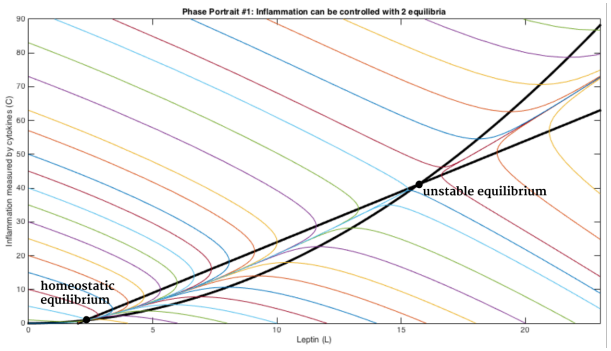
- Find a biomarker for inflammation
- Role of inflammation in obesity
- Leptin's relationship with inflammation as fat varies
- Role of sex in inflammation
- Reason for women's greater susceptibility to autoimmunity
- Applications and clinical use of mathematical model

The model: a system of differential equations

We model the rates of leptin production and inflammation by the following:

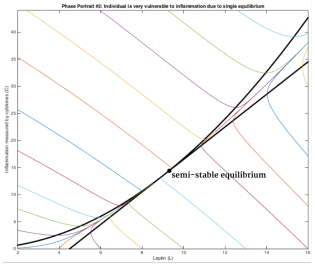
$$\frac{dL}{dt} = \alpha SAT + \beta C - \delta_1 L \qquad \frac{dC}{dt} = \gamma L^2 - \delta_2 C$$

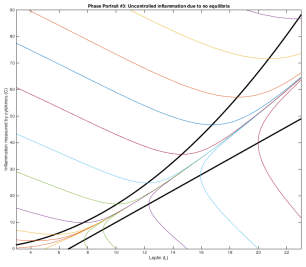
L: adipocyte-derived leptin; C: non-adipocyte-derived cytokines (inflammatory marker)
SAT: amount of subcutaneous adipose tissue; $\alpha, \beta, \gamma, \delta_1, \delta_2$: parameters

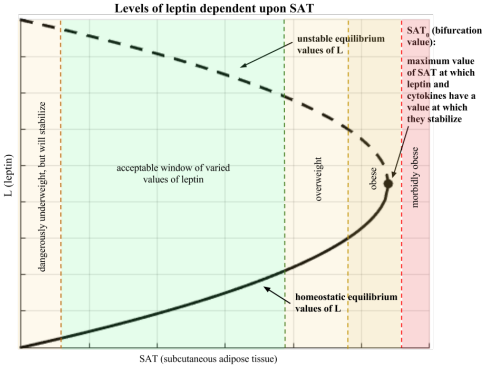


Model Analysis

- Phase portrait analysis reveals three cases based on the individual's amount of SAT:
- homeostatic and unstable equilibria, providing a window of controlled inflammation (Portrait 1)
- a semi-stable equilibrium, allowing slight changes in leptin levels to induce uncontrolled inflammation (Portrait 2)
- no equilibrium, resulting in an entirely unstable system in which inflammation is always uncontrollable (Portrait 3)







Results and applications

- Cytokines produced directly and indirectly by leptin provide an appropriate biomarker for inflammation.
- Inflammation due to leptin secreted by enlarged adipocytes increases volume of adipose tissue and contributes to, as well as exacerbates, obesity. The model, providing points of stability and instability, helps determine when medical intervention is necessary in weight loss.
- Women have higher leptin levels because estrogen favors fat deposition in subcutaneous adipose tissue, which secretes more leptin than other types of fat. We propose that this is the reason for the sexual dimorphism seen in autoimmunity.
- Using this model, we can better determine risk for autoimmune diseases, type 2 diabetes, and metabolic syndrome.

References & Acknowledgements

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