

Obesity: a case-study in systems biology The prevalence of obesity has roughly doubled in the last quarter century, with a significant proportion of adults now being overweight. Excess adiposity is not only implicated as a risk factor in diabetes, cardiovascular disease, and various forms of cancer, but severe complications are also more likely to develop in obese patients as a result of mutually exacerbating interactions between various organ systems.

Obesity usually develops as the accumulated effect of a relatively small perturbation in the daily energy balance. For this reason, it is imperative that we gain a detailed, quantitative understanding of the neuroendocrine regulation of food intake and the disposition of nutrients among the organ systems in the body, both in health and disease.

Nutrient disposal involves a plethora of choices. For instance, a nutrient molecule can serve as fuel or as a building block. Glucogenic nutrients can be converted into lipids for the purpose of long-term storage of energy reserves. Skeletal muscle also serves a dual role, combining structural and storage functions: in the short term, it acts as a major immediate buffer for glucose and amino acids, whereas in the long term it attains a mass appropriate for the average level of resistance load at the prevailing body size. Similarly, while the endocrine control systems protect plasma homeostasis in the short term, in the long term they govern the rate at which mass is gained by bones, soft tissues, muscle, and adipose stores. These choices are deeply intertwined: each choice is contingent on whole-body nutritional status. A proper understanding of nutrient disposition and utilization therefore requires a treatment which does justice to its intrinsic dynamical nature, and which adopts a system-level point of view.

Macrochemical dynamics Mathematically, the challenge is to relate the short term dynamics that govern the diurnal cycle of feeding and fasting to the long term changes in body composition. The latter time scale is associated with growth and changes in muscularity and adiposity at the gross anatomical level. At these scales, the problem can be addressed in macrochemical terms, i.e. simply as dynamic shifts in chemical composition. To a good first approximation, only nitrogen and carbon need to be taken into account. However, due to a fundamental biochemical constraint, carbon has to be treated as two distinct species of pseudo-element: glucoplastic and ketoplastic carbon. This distinction is closely related to the commitment of glucogenic compounds to use as fuel or long term storage as lipid reserves. Interestingly, this long-term dynamics of the macrochemical state is determined almost completely by stoichiometric constraints, combined with classical scaling rules on nutrient supply and demand, and physiologically plausible assumptions on hierarchical protection of set points. From these few basic rules five dynamical “modes” emerge. These modes correspond to distinct nutrient limitation regimes, including several distinct starvation syndromes. The most important regime, however, is the *adipodynamic* mode which applies when ketogenic energy reserves are available.

While the basic rules almost completely determine long-term dynamics, a few loose ends do remain. First, there are two external forcings: these are the the availability of nutrients, which depends on the environment, and the average resistance load on the muscles. A final missing link is the feedback from adiposity to modulate appetite, basal metabolic energy expenditure, and adipose storage capacity. This feedback is part of the *adipostat*.

Endocrine regulation of nutrient disposition The macrochemical dynamics representation contains relatively few fluxes which can be thought of as the time-averaged, net result of a much larger number of biochemical transformations and exchanges between organ systems, which evolve on a much shorter, sub-diurnal, time scale as the organism progresses through the physiological stages associated with ingestion, digestion and assimilation. A central process on this short term time scale is (neuro)endocrine regulation of plasma nutrient levels and the attendant management of reserves. At the heart of this homeostatic regulation lies the key hormone *insulin*, which stimulates the clearance of plasma glucose into various tissues, as well as the formation of the storage polymer glycogen from glucose in the liver. Insulin also stimulates the disposition of triglycerides in adipocytes and of essential amino acids in muscle.

As insulin is involved in the post-prandial disposition of all major nutrients, its effects can be thought of as the primary endocrine action, modulated by the additional effects of other hormones, which include *adipokines* such as *resistin* which counteracts insulin and *leptin* which enhances the actions of insulin; *glucocorticoids* which protect glycogen stores under energy stress by stimulating gluconeogenesis and glycogenesis in the liver, antagonizing insulin extra-hepatically, and mobilizing glucogenic energy

from muscle protein; *glucagon*, which safeguards a minimum plasma glucose level by mobilizing liver glycogen, stimulating gluconeogenesis and stimulating fatty acid oxidation by mobilizing adipocyte lipid reserves; *epinephrine* which synergizes with glucagon and in addition stimulates glucogenic energy mobilization from muscle while inhibiting muscle proteolysis; *thyroxine* which stimulates turnover of protein and glucogenic energy stores in muscle, as well as lipid reserve mobilization and basal metabolic rate; *growth hormone* which mobilizes both lipid and glycogen energy reserves, stimulates protein synthesis and the production of *insulin-like growth factors*. Ultimately, these endocrine factors are, of course, just tokens of nutrient availability and requirements in various anatomical locations. From a dynamical point of view, the hormones act to coordinate the exchange fluxes of nitrogen, glucoplastic carbon and ketoplastic carbon between the various organs.

Dynamics on the physiological time scale A detailed analysis of how the short-term dynamics of the endocrine system form the basis for long-term macrochemical shifts in composition is forthcoming. To understand its operation in broad outline it is convenient to regard the system as composed of three interlocking modules: the *glucostat*, the *myostat*, and the *adipostat*, corresponding roughly to glucoplastic carbon, nitrogen, and ketoplastic carbon. The glucostat forms the hub of the system and has been described above.

The myostat regulates the disposal of nitrogen. Skeletal muscle protein is the major nitrogen store in the body. Moreover, the skeletal muscles are important glucoplastic carbon buffers. They alternate between states of net amino group depletion and accretion. The depletion flux is channeled towards either fueling (via alanine and hepatic gluconeogenesis) or biosynthesis (of purines, pyrimidines, and non-essential amino acids via glutamine/glutamate) depending on the sarcoplasm's energetic status (damming up of pyruvate in β -oxidation and enhanced proteolysis in starvation). The "anabolic drive" of the accretion flux is governed by the resistance load, which in turn depends on activity and bone length. Under sufficiency of energy and nitrogen intake, muscle mass is able to adapt to this load, whereas under energy stress, increased depletion (with concomitant cachexy) can occur to fulfill energy requirements.

The timing of growth hormone relative to ingestion and assimilation of nutrients ensures that muscle regeneration/accretion effectively takes precedence over proliferation in other tissues which is regulated by insulin-like growth factors; the availability of essential amino acids in the plasma governs the "gain" of growth hormone-stimulated production of insulin-like growth factors. Thus the average post-absorptive level of essential amino acids over many cycles determines the macrochemical growth rate. Under energy insufficiency, these levels fall as muscle retains a larger proportion to compensate for fueling depletion, and growth ceases. As the glucoplastic reserves become increasingly depletion stressed by energy insufficiency, the ACTH-cortisol axis becomes more active and shifts the nitrogen accretion/depletion balance of muscle into the red.

The third major division of the nutrient disposition system is the adipostat. In the well-nourished organism lipids stored in adipose tissue represent the body's major energy reserve. In addition there are glucoplastic reserves, most notably in skeletal muscle and the liver, which serve to replenish plasma glucose levels (in the case of muscle, via glycogenolysis to three-carbon compounds which are the substrates for gluconeogenesis in the liver). The glucoplastic reserves have limited capacity, and surplus glucoplastic nutrients that exceed this capacity are converted into lipids by the liver and the adipocytes themselves. While each adipocyte can accumulate a relatively large amount of lipid, the adipose stores have a maximum capacity which is ultimately attained under a sustained high-energy diet.

Capacity signalling (via leptin) by adipose tissue results in various compensatory effects: an increase in glucoplastic turnover in muscle and other organs (via potentiation of insulin signalling, thyroxine activation and stimulation of sympathetic tone) resulting in expansion of glucose disposition in these tissues, a reduction of food intake (via hormone-sensitive neurons situated in the arcuate nucleus of the hypothalamus). Moreover, it is clear that pre-adipocyte proliferation leading to an expansion of adipose storage capacity must be an essential part of the response to sustained high-energy supply. At present, this key component of the adipostat is only poorly understood. Phenomenologically, adiposity (lipid store volume relative to body size) appears to relax towards an equilibrium density that is proportional to the energy density of the diet. It can be shown that the brain disposes, in principle, over sufficient information to regulate adipocyte growth in a manner that is consistent with the observed first-order dynamics of adiposity (this is nontrivial since information about fluxes at the whole-body level is not readily available to individual cells).

Central control of the adipostat Simple rules almost completely fix long term macrochemical dynamics. The short term system (composed of glucostat, myostat and adipostat) can be viewed as merely implementing these rules; its apparently byzantine complexity can be explained by the need to maintain homeostasis under the constantly shifting demands that accompany the diurnal cycle of nutrient acquisition, disposition and utilization. Two regulatory interactions are not fixed by the basic rules and at present only partially understood: these are control of adipocyte growth and modulation of appetite. These are under the control of a group of hypothalamic nuclei which include the arcuate nucleus and the paraventricular nucleus.

The “set points” of the adipostat can be taken to be the adiposity level attained for a given energy density in the diet and the feeding drive at a given adiposity level. From a physiological point of view, these set points arise as emergent properties of the input/output response characteristics of the hypothalamic nuclei.

In particular, the arcuate nucleus contains at least two populations of neurons which are sensitive to bloodborne signals: NPY/AgRP cells which tend to promote feeding and POMC/Cart cells which tend to inhibit feeding. These neurons are known to be responsive to various hormones which include insulin and leptin. The arcuate neurons are furthermore suspected of being sensitive to the plasma glucose level. These observations have prompted the working hypothesis that capacity stress in glucoplastic and ketoplastic stores is indicated by the relative proportions of the AUCs (area-under-curve) of insulin, leptin and glucose during the various stages of nutrient disposal (e.g. absorptive, post-absorptive). This hypothesis is currently being investigated by characterization of the response of the arcuate NPY/AgRP and POMC/Cart neurons to insulin, leptin and glucose. The ultimate aim is to define precisely what physiological signals are monitored, and how they are processed, in the regulation of food intake and adipose capacity. Such a characterization should make a fundamental contribution to our understanding of obesity.
