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Metabolic Master Regulators: Sharing Information among Multiple Systems

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Abstract

Obesity and diabetes are caused by defects in metabolically sensitive tissues. Attention has been paid to insulin resistance as the key relevant pathosis, with a detailed focus on signal transduction pathways in metabolic tissues. Evidence exists to support an important role for each tissue in metabolic homeostasis and a potential causative role in both diabetes and obesity. The redox metabolome, that coordinates tissue responses and reflects shared control and regulation, is our focus. Consideration is given to the possibility that pathosis results from contributions of all relevant tissues, by virtue of a circulating communication system. Validation of this model would support simultaneous regulation of all collaborating metabolic organs through changes in the circulation, regardless of whether change was initiated exogenously or by a single organ.

The obesity crisis and weight regulation

Caloric excess alone cannot explain the current epidemics of obesity and diabetes, and the obese patient cannot be solely accountable for their obesity. These metabolic diseases represent a failure in overall metabolic regulation, and an inability of the scientific community to solve this major problem. Treating obesity as a disease will help lead to improvement in the health of our population and the development of useful drugs for the prevention or treatment of obesity.

However, excess weight does not afflict all individuals. In a Swedish study, documenting an increased incidence of obesity from 9.4% in 1990 to 17.5% in 2004, thirty five percent (5242) of the adults were found to be non-gainers (1). The chances of not gaining weight in this population correlated with older age, being female, diagnosis of diabetes, and lack of snuff use. A recent study in the US also found that although overweight and obesity continue to increase, there are still more than 30% of adults on average that are not overweight (2). In the National Health and Nutrition Examination Survey (NHANES) cohort, race/ethnicity, being female and older age correlated with not being overweight. The continued presence of subjects with apparently normal body weight regulation is useful in our quest to identify potential causes of disorders of metabolic regulation. Comparing individuals who gain weight with those who do not could help to validate or refute our hypothesis.

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Dynamic changes occur in the body in response to food (3), discussed below, sleep, exercise (4; 5), diabetes and normal living that influence energy requirements, energy expenditure and choice of fuel (6; 7). Our metabolism responds by using fuels and fuel stores to provide exactly enough ATP for all of the work of each tissue, *and not any more*, via a highly sensitive, regulated and responsive process that is mainly mitochondrial (8). To achieve the goal of providing exactly the needed amount of ATP under all circumstances, adequate fuel reserves are needed, in the form of glycogen and fat, although determinants of the size of these reserves is not fully understood (9). Nevertheless, glycogen stores and protein pools are fixed and limited, while fat stores are expandable but tend to remain stable over long periods of time, and to return to previously defended levels following either decreases or increases in their mass. In general, excursions in the reserve pool sizes occur continuously during each day, within fixed limits that vary little. Thus, depletion in glycogen and lipid stores occurs with exercise and between meals (10). Although it is possible to experience great alterations in these pools, during starvation or periods of excess consumption, this only occurs rarely. Abundant evidence exists to indicate that periods of over- or under-consumption are followed by periods of restoration of the previous *status quo*, hence the difficulty in long term maintenance of weight loss following successful diets (11; 12). In the Vermont prison study (13) where lean individuals were recruited to increase their body weight by 20%, not all volunteers were able to gain weight. However, the lean volunteers that gained weight required an average of nearly 7000 calories/day and most rapidly returned to their original weight upon termination of the study.

An important contributor to energy balance is clearly food intake. In mammals, hunger initiates food-seeking behavior followed by eating that is terminated in response to satiety signals (14; 15). Recent research has begun to clarify the mechanisms involved in regulating hunger, food seeking and satiety. Even without knowledge of the molecular mechanisms involved, normal body weight has been maintained in most individuals, through most of human history. Likewise, obesity among animals is rare. The contribution of this important component of the energy balance equation has been less explored, whereas, energy intake and physical activity are readily determined and almost exclusively considered (16; 17).

The notion that personal self-discipline is the key to body weight regulation, is not supported by compelling evidence, and is inconsistent with regulation of other major systems such as blood sugar (not usually dependent on controlling sugar intake) (18), body temperature (responsive to, but rarely regulated by, ambient temperature) (19) or electrolyte balance (responsive to but not normally controlled by salt or water intake) (20) although rare extremes can override each regulated system such as massive glucose loading, salt or water intake or prolonged exposure to extreme temperatures.

In this article, a model will be presented, based on changes in circulating redox, to provide an explanation for food or environment-induced alterations in body weight, through modifications in the regulation of energy efficiency, appetite or satiety. This model does not violate the laws of thermodynamics, but focuses rather on the non-volitional aspects of body weight regulation. Volitional behaviors are caused by information that has been processed by the central nervous system (such as choice of food), whereas non-volitional behaviors are mainly determined by chemical information and information in the nervous system, that is not adjusted (such as hunger).

“It Takes A Village**”

Defects in any of the metabolically sensitive tissues can cause obesity or diabetes. The main focus of studies on the pathosis of diabetes, since the 1980s, has been insulin resistance (21; 22), with a molecular focus on insulin signaling and signal transduction pathways in pancreatic islets (23), liver (24), adipose tissue, as well as brain, gut, vasculature, and muscle (25). As a result of this work, evidence now supports an important role for many tissues in metabolic homeostasis and the development of both diabetes and obesity. The paradox is that, it seems possible that every tissue can initiate diabetes, and the classical approach is to find the one, however, the problem may be with multiple tissues. Here, we focus on the possibility that pathosis results from contributions of all of the relevant tissues (Fig. 1), because change can be initiated by any one and communicated to all the others via the circulation leading to coordinated regulation and shared control.

How can all organs understand the metabolic state of the body and respond appropriately and synergistically to consume, release or store energy? This article hypothesizes a master metabolic regulatory system that circulates by the bloodstream and that impacts all organs. It consists of metabolites that reflect the intracellular redox state, and that can freely cross cell membranes to cause a change in the redox state of any cell (Fig. 2). Within each cell, lactate (L) and pyruvate (P) are present in a ratio of about 10 that reflects the cytosolic NADH to NAD ratio (26; 27). Equilibrium is maintained in most cells because the enzyme lactate dehydrogenase is highly expressed. The major source of lactate and pyruvate in the blood is muscle, though many other tissues also contribute. Acetoacetate (A) is produced primarily in liver mitochondria where β -hydroxybutyrate dehydrogenase is highly expressed and maintains a ratio of β -hydroxybutyrate (B) to acetoacetate of about 1, dependent on the mitochondrial NADH to NAD ratio (26; 27). All four metabolites are generally readily transported into and out of cells, due to high expression of the requisite anion transporters. The L/P and B/A ratios have been used in the past to reflect various metabolic disease states: L/P rises in metabolic diseases where pyruvate oxidation or oxidative phosphorylation is defective (28). B/A increases in type 1 diabetes when insulin is deficient, and fat oxidation is needed to provide ATP and a circulating form of acetyl CoA (29).

Is the disease communicated or is the communication diseased?

Changes to circulating nutrients and metabolites are the proposed initiators of tissue specific metabolic changes.

The pancreatic islets of Langerhans regulate secretion of insulin and glucagon. Insulin is secreted in response to elevations in glucose, fat and amino acids, while glucagon secretion is stimulated in response to a decrease in glucose levels (30). In obesity, the β -cell increases insulin production and secretion in the absence of secretory stimuli (31). Thus, an increase in the circulating redox state implies an excess of fuel availability and the need for insulin to store fuels, as was shown recently (32).

Adipose tissue controls triglyceride (TG) synthesis, breakdown and fatty acid (FA) release as well as the secretion of adipokines (33). In obesity, the adipose tissue expands excessively and eventually fails to adequately store lipid leading to ectopic fat accumulation (34), and elevated lipolytic rates.

Liver directs glycogen storage and breakdown, gluconeogenesis and ketogenesis as well as lipid packaging and secretion (35–37). The liver is the main organ that regulates blood

*Hillary Rodham Clinton, 1996

glucose and serves to also convert fuels to forms that can be utilized by all tissues. In obesity, the liver stores too much fat (38; 39) and in diabetes glucose is regulated at an elevated level implying liver malfunction in these diseases.

The gut and brain synergize to stimulate food seeking, food consumption or satiety (40), via signals transmitted by neural or circulatory routes that may be abnormal in obesity. This is a less well-explored area of investigation but the successful cure of many cases of type 2 diabetes with gastric bypass surgery suggests a hitherto unexplored regulatory mechanism (31).

The prevalent assumption is that excessive food intake initiates obesity rather than impaired maintenance or sensing of stores. However, although there is no evidence to either support or refute the proposed systemic master metabolic redox approach, there is also no evidence that body weight regulation is attributable to any single organ system, in the majority of cases, but rather seems to involve synergistic activities of many, with clear abnormalities in most.

Communication of the impaired metabolic state appears to play a key role in a pathology contributed by multiple organs. Clearly the circulation is the most widely shared information conduit in the body. Changes to circulating nutrients and metabolites are the proposed initiators of tissue specific metabolic changes.

In a well-regulated system, depressed circulating fuel levels or empty stores should stimulate a systemic response that begins with ingestive behavior that in turn increases insulin secretion leading to the replenishment of stores and the induction of satiety (Fig. 3). If such signals are not generated, inappropriate eating will occur: examples include leptin or leptin receptor deficiency (41). If such signals are generated but not sensed appropriately, maladaptive eating will occur, e.g., gold thio-glucose that induces lesions in the ventromedial hypothalamus and impairs the ability to sense satiety (42). A possible role for similar types of defective signaling due to systemic responses to misinterpreted environmental agents has not been carefully explored in common obesity.

The concept that circulating signals mediate alterations in metabolic health through adaptive responses in all metabolic organs is an attractive hypothesis that could explain the observed changes. We propose the redox metabolome as the basic communication system consisting of pyridine nucleotides and thiol redox systems (Fig. 4), which reflect the intracellular redox state and are altered in response to nutrients and activity. The intracellular redox state is the ratio of reduced NAD(P)H and thiols (SH) to their oxidized partners NAD(P) and thiols (SS) (Fig. 4). The main cellular thiol is glutathione (SH or SS) and the main circulating thiols are cystine and cysteine (43). Additional members of the intracellular thiol redox family include thioredoxins and peroxiredoxins. These redox compounds are interconnected through the mitochondrial transhydrogenase (44) and do not normally pass in and out of cells, but are in equilibrium with metabolites that do move across membranes. So we can know what the ratio in the cell is from the ratio of these indicator metabolites. The thiol redox state is more complicated and is distributed among all compartments (see reviews by Dean Jones [42–45]). A major consequence of increased mitochondrial redox, in the absence of a fall in ATP, is the generation of reactive oxygen species (ROS), since the generation of $O_2^{\bullet-}$ within the mitochondrial matrix depends critically on NADH and the mitochondrial membrane potential (32; 45). Thus when we refer to an increase in redox, we also imply an increase in ROS (32; 46).

Mitochondria and energy efficiency

A less studied but important element in regulation of body weight is energy efficiency, which is defined as the percentage of actual/perfect efficiency. Perfectly efficient mitochondria should produce three molecules of ATP for every molecule of NADH consumed. This never occurs. It has long been established that mitochondria have a variable proton leak, and that increasing this leak, decreases energy efficiency (47).

In most cases, the site of the leak, the specific proteins involved, and the mechanisms that regulate the leak, are not entirely clear. The exception is the uncoupling protein UCP-1, in brown adipose tissue (BAT). BAT, that uniquely expresses UCP-1, is specialized to produce heat in response to cold, and UCP-1 facilitates dramatic changes in energy efficiency and heat production by regulating proton flux across the mitochondrial membrane (47). Less dramatic alterations in energy efficiency also contribute to protecting body weight during starvation (48), in hibernating mammals (49), and migratory birds (50). In addition, continuous variation in mitochondrial energy efficiency or proton leak occurs in all mitochondria even without the challenges noted above (47). Several specific proteins have been documented to play roles in this process, including cyclophilin D which regulates the mitochondrial permeability transition pore (MTP) (51), and the nicotinamide nucleotide transhydrogenase (NNT) (44). NNT is proposed to play an important role in redox-mediated regulation due to its major role in maintaining the thiol redox state and linking the NADH/NAD ratio to the NADPH/NADP ratio. Interconversion of NADH and NADPH is achieved at the expense of a proton leak operating in a manner energetically similar to ATP synthase (Fig. 5). This serves to match the rate of ROS production with provision of GSH (Fig 5).

Our changed environment

Many things have changed since the onset of the obesity epidemic. Those who would “explain” obesity as the outcome of gluttony and sloth (twin capital sins of early biblical and medieval origins) are giving great credence to concepts with limited scientific basis. The prevailing concept that personal self-control is the key to body weight regulation is not supported by compelling evidence (see references 12, 13, 41, 42). In seeking alternatives to gluttony and sloth, we considered things that have changed since the epidemic began, with a particular focus on those that might have systemic effects, and deregulate the system that, until modern times, has effectively regulated our body stores. This does not imply that a change in energy intake relative to energy outflow has not occurred, but rather ingestion and activity are not simple variables. The important concept of variable energy efficiency has been largely ignored, particularly during the transition periods of active weight gain.

Changes have occurred in our foods, living conditions, activity levels and the air we breathe (46). Do any of these changes impact the signal transduction or redox states? In particular, it is not known whether food processing, plastics, toxicants that may enter our bodies, air conditioning, antidepressant prescriptions, or average home temperature (52), impact metabolic efficiency or any of the signals that regulate components of the hunger to satiety pathway. Because of the widespread nature of metabolic diseases across all age groups and culture, it seems unlikely that our air or unique living conditions are the main culprits. Likewise, the differences in activity levels among boys and girls, old and young, and different workers make it unlikely that decreased activity can be the major explanation (53).

Food, however, and processed food in particular, is now shared across the globe. Differences in food today compared to the past, include thousands of new agents that have entered our food supply intentionally or inadvertently. Almost none of these agents have been evaluated as potential causes of obesity or diabetes in humans. In addition, with the dramatic improvements in agriculture and animal husbandry, the average weight of cattle has

increased, as it has in humans, while the percent body fat has actually declined (54). In poultry, the average age at market has decreased from 112 days to 42 days, while the average weight has more than doubled, due to an increase in feed efficiency (55). The question therefore arises: could such increased efficiencies in food animals influence human weight?

The role of minerals in metabolic disease is not clear either, however, it may be important to note that the mineral content of fruits and vegetables has also changed, probably due to improved and standardized growing conditions (56–59). There is now evidence that some plasticizers, possibly from packaging and preparation of our food, can impact metabolic health (57–59). Many foods now days contain preservatives, emulsifiers, flavor enhancers, food coloring and other fillers (60–62) that have not previously been consumed in significant quantities, and it is not known whether they impact body weight; indeed, these non-food additives have not been carefully evaluated for a potential causative or contributing role in the obesity and diabetes epidemic.

Does the blood redox metabolome change?

Elegant work by Dean Jones has shown that potential regulation by the redox state is exerted by reduced to oxidized thiol ratios involving glutathione and cysteine (63–66). Changes in thiol redox correlate with aging, diabetes, heart disease and some cancers. Thiols also regulate intracellular signal transduction, cell growth and mitochondrial ROS production.

Thus, it is important to consider redox as an integrated system that involves linked changes in the pyridine nucleotides, glutathione, thioredoxins, peroxiredoxins, and multiple thiol redox sensitive proteins (67). The redox potential of phosphatases and a detailed description of the cascade involved has been elegantly described (67). The NADPH to NADP ratio is connected to both the thiol redox state and the NADH to NAD ratio, because NADH and NADPH are interconverted and influence the oxidation state of glutathione (Fig. 4) and other thiols.

Diabetes and obesity are associated with increased circulating levels of several metabolites that are known to alter redox and influence tissue specific functions. These include free FAs (FFA), the redox indicator lactate, and the essential branched chain amino acids (BCAA) (68–70). FFA, lactate and BCAA all generate increases in mitochondrial NADH through their metabolism. Recent metabolomic studies by Wang et al and LaFerrère et al, measuring hundreds of blood metabolites, have emphasized a strong and predictive association with BCAA (71; 72).

An increase in mitochondrial redox has previously been documented, indicated by the β/A ratio in liver, that occurs in response to the ketoacids of BCAA, as well as lactate, and was found to be exaggerated in the presence of elevated FFA (73–77). Since, elevated BCAA, FFA, lactate, and combinations of these metabolites are associated with diabetes (71; 72) and increase the liver redox state, they are expected to increase the blood redox state, reflected in the β/A ratio (Fig. 2). Such an increase in redox could contribute to metabolic alteration in other organs, activation of redox sensitive transcription factors such as sirtuins, SREBPs and PPAR γ (78), altered fuel selection for ATP production and sustained hyperinsulinemia in the β -cell. It has also been shown that imposing extracellular changes in β -hydroxybutyrate, changes intracellular redox (79). Similar findings also have been documented following infusion of ketones (80; 81). Thus, the blood redox metabolome varies with both food intake and circadian rhythms (82).

Have environmental influences changed redox state?

A key unanswered question is “do environmental influences affect the blood redox metabolome and do changes in these parameters influence function?” Because most of the thousands of new environmental agents and food additives have not been tested, we cannot answer these questions, yet. However, a decrease in glucose oxidation rate in response to an increased mitochondrial redox state has been documented (79). There is also increasing evidence that bisphenol A increases basal insulin secretion and disrupts glucose homeostasis, by causing insulin resistance (83; 84). In isolated β -cells, increased redox in response to a common food additive, mono-oleoylglycerol, that leads to increased ROS production and that also increases basal insulin secretion, has been shown (32). Similar data have been obtained with some artificial sweeteners and excess iron (46). Effects of ROS scavenging to inhibit both insulin secretion (32) and lipolysis (85) have been shown. It seems likely that other of the untested agents might also play a role in the impairment of metabolic health.

Concluding remarks

A change in redox will influence different organs in important ways either directly through ROS production, or indirectly by modifying proteins or lipids. Well-established targets of ROS and redox include transcriptional regulators such as sirtuins, SREBPs, PPARs, and many others, that in turn regulate long-term translational components including hormones, metabolic enzymes and adipokines (78). This is conceptually a highly refined system that assures that after ingestion of a meal, all the metabolically important organs in the body respond appropriately both in the short term: β -cells secrete insulin, liver stores glucose, adipose tissue increases fat storage and the brain signals satiety; and in the long term: insulin is synthesized, and adaptive metabolic enzymes are induced.

The focus on a coordinated systemic mechanism for regulation of metabolic health (Fig. 1), rather than a specific tissue defect, emanates from the reality that something has changed in our environment to cause an epidemic, and we have been unable to determine what changes are most critical. Here we present a hypothesis suggesting that the circulating redox state is a metabolic master regulator that senses and communicates fuel and energy status to all organs via the blood stream, and assures that the energy state is similarly perceived by all relevant tissues. A change in redox will influence each organ in specific ways to affect organ-specific function (Fig. 3).

Our concept is of a master metabolic regulatory failure as the cause of obesity. We suggest that this failure is caused by environmental factors communicated to all organs in the body via the blood stream in the form of the redox metabolome. This is feasible, testable and potentially modifiable by dietary means. The work ahead, demands that we determine the effect of food additives and environmental agents (and combinations thereof), on the blood redox metabolome and the development of obesity and diabetes. Identifying and eliminating any potent redox modifiers from our environment will help us re-establish an optimal redox state.

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BOX: Outstanding questions

- Are new agents in our food or environment present in humans and do they correlate with metabolic health?
- What are the normal and disease-related characteristics of the blood redox metabolome as defined by frequent sampling?
- What are the characteristics of observed changes in blood redox metabolites?
- Do blood redox metabolites alter organ specific functions: e.g., hepatic glucose production; β -cell insulin secretion; adipocyte lipid handling; the gut secretome; or hunger and satiety?
- Will redox manipulations such as ROS scavengers, methionine to change thiol redox, or medium chain FAs, be beneficial in establishing an optimal redox state?

Figure 1. Information sharing among metabolic organs via the bloodstream

An interplay among organs in which changes that occur in one organ are transmitted to other organs via the circulating redox system. L/P (lactate/pyruvate); B/A (β-hydroxybutyrate/acetoacetate); SH/SS (reduced thiol cysteine/oxidized thiol cystine; ROS (reactive oxygen species).

Figure 2. Blood as redox communication system

Interaction of mitochondrial, cytosolic and circulating redox indicators: L/P (lactate/pyruvate) indicates the cytosolic redox state determined mainly by muscle; β/A (β -hydroxybutyrate/acetoacetate) reflects the mitochondrial redox state determined mainly by liver. The circulating thiol redox state is represented by the cysteine/cystine ratio and the mitochondrial and cytosolic thiol redox state is represented by reduced (GSH) and oxidized (GSSG) glutathione.

Figure 3. Predicted changes in response to fuel depletion and excess

An oxidized state will occur when ATP need exceeds available fuel, as during fasting. In this case, the α -cell will secrete glucagon, adipose tissue lipolysis will be stimulated, the liver will produce glucose and a sense of hunger will prevail. A reduced state will occur when fuel supply exceeds the need for ATP synthesis as at the end of a meal. In this case, excess fuel will be stored through secretion of insulin to stimulate adipocyte fat storage, glycogenesis in liver and muscle and satiety.

Figure 4. Linkages among the redox couples and glutathione

NADH and NADPH are interconverted by the nicotinamide nucleotide transhydrogenase (NNT). NADPH generated by NNT reduces GSSG formed as a result of scavenging H₂O₂. NAD and NADH equilibrate with lactate and pyruvate in the cytosol and acetate and β-hydroxybutyrate in the mitochondria. Transport of reducing equivalents between cytosol and mitochondria occurs via several anion carriers not shown (86).

Figure 5. Nicotinamide Nucleotide Transhydrogenase (NNT)

The rate of leak through the electrogenic NNT pore is determined by the rate of ROS production. ROS is detoxified by GSH converting it to GSSG. GSSG requires NADPH to reduce it to GSH and the NADPH is provided by substrate-generated NADH.