Obesity.

TL:DR

Obesity is a non- linear thermodynamic systems problem.

There is nothing more fundamental to life than energy, consequently the body has developed systems to protect that energy.

Stresses on the system consume energy.

These stresses come from the environment, both inside and outside the body.

To an aerobic diurnal organism it is vital that oxygen/energy supplies are linked to demand.

Demand varies from organ to organ during the day and night.

Systems are in place to allow for efficient supply of energy to meet these demands.

Obesity is the body's adaptive response to a loss of energy.

Most people understand obesity as a metabolic problem, due to the overconsumption of energy (food), and not enough "work" being done, however, this is an example of linear thinking.

Whereby, the current paradigm focuses on CICO (calories in calories out).

People eat too much and exercise too little get fat, so the simple linear solution is:-

“Eat Less and Exercise More”!

A systems view would see it differently:

Stress on system requires energy to deal with it.

Stress response triggers the immune system (inflammation - cytokines etc)

Chronic stress requires a longer term solution to deal with energy supply and demand problem - protective mechanisms of Leptin resistance and insulin resistance are activated.

So obesity can be viewed as the body’s response to a loss of energy - it attempts to store more and more and makes it more and more difficult to access.

Some people can get really obese because they have relative insulin sensitivity, whereas, others develop insulin resistance when they are not even overweight (TOFI) - hence it is non-linear.

If you take a bioenergetic systems approach you begin to see that the nervous system, immune system, hormone system, as well as the metabolic system is involved - (l would also add the Microbiome/Virome to this list)

A stressed out (hypoxic) fat cell leads to an increase in ROS, this hypoxia is a signal for HIF-1 which then activates the immune response - so we see an increase in cytokines and an increase in angiogenesis and permeability to divert oxygen/energy to the cell.

This enables the adipose cell/tissues to either expand (hypertrophy) to relieve some of the pressure inside, or produce more fat cells (hyperplasia).

Eventually, the signal is also given for Insulin Resistance, to prevent any further glucose from entering the cell.

In addition, Leptin Resistance is also triggered:

Leptin is the “Master Hormone” of the brain.

This hormone helps to regulate the nervous system, the immune system and metabolism.

At a central level it communicates with the hypothalamus (brain) to decrease hunger and increase metabolism.

At a local level its secondary functions are: modulation of energy expenditure, activation of immune cells and beta islet cells, and growth factor angiogenesis in fat cells, to allow this hyperplasia and hypertrophy to take place.

Circulating leptin affects the hypothalamic–pituitary–adrenal axis (HPA axis) in the brain giving leptin a pivotal role in the stress response.

Chronically high leptin levels are also associated with obesity, overeating, and inflammation related diseases, including; hypertension, metabolic syndrome and cardiovascular disease.

All of these conditions also demonstrate some degree of Leptin Resistance.

What then increases Leptin?

Interestingly, there is recent evidence suggesting hypoxia is a key driver for leptin.

For example, the hypoxic environment in the placenta associated with pre-eclampsia also produces an increase in Leptin, as well as gastric ulcers which upregulate Leptin to assist in the healing process.

If Leptin is associated with hypoxia you would also expect it to be linked with HIF-1.

It is:

https://link.springer.com/content/pdf/10.1007/s00125-002-0804-y.pdf

HIF-1 is not only a master regulator of the innate immune system and oxygen homeostasis, it is also cross talking with the nervous system and metabolism.

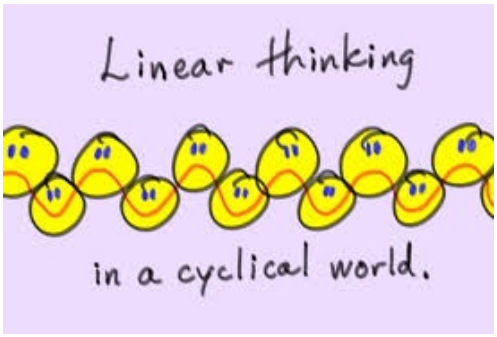
https://www.ncbi.nlm.nih.gov/pubmed/23988176

The body always identifies and responds to stress, in whatever shape or form it may take.

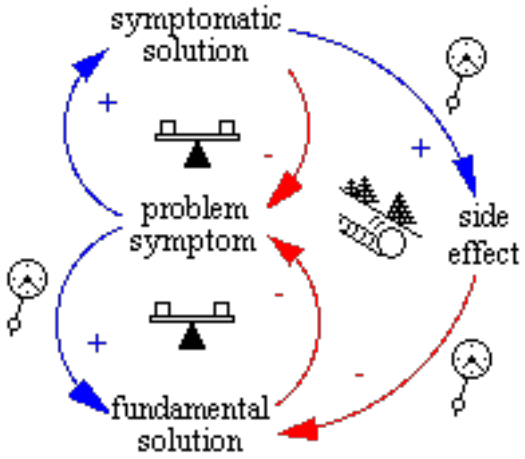
HIF-1 obesity https://www.frontiersin.org/articles/10.3389/fnins.2018.00813/full

As already stated, it is linear thinking which leads to the mistake in management.

A non-linear thermodynamic/bioenergetic systems approach

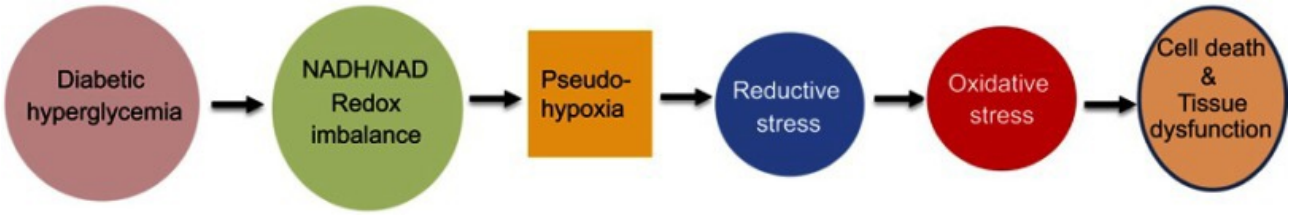


would manage it differently.



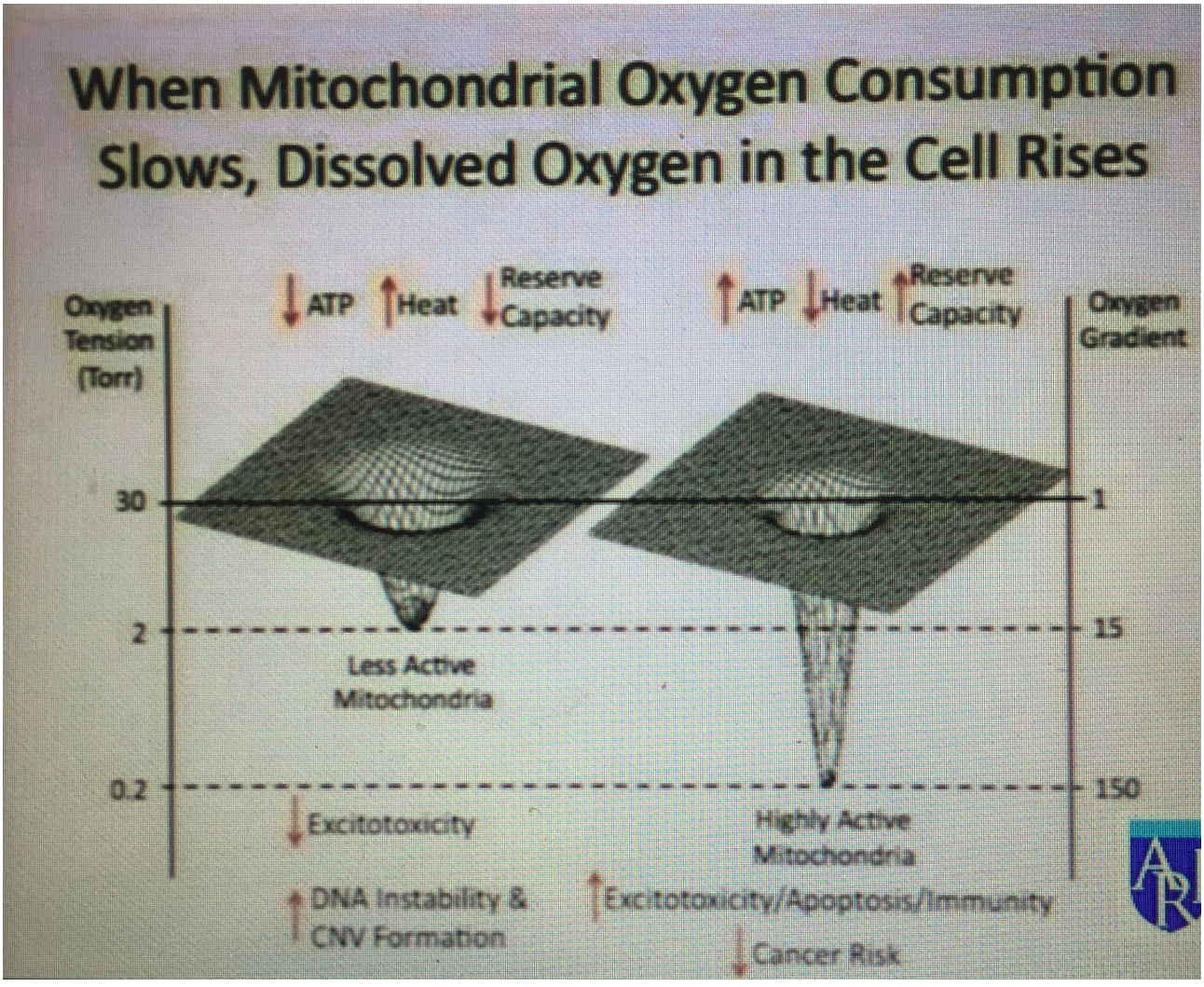
At a Metabolic level oxygen is sensed by the Mitochondria in each cell.

Under acute hypoxic conditions, OXPHOS energy production is inactivated and anaerobic glycolytic activity increases to produce ATP eg high intensity exercise



Under chronic hypoxia/pseudohypoxia conditions we see a shift from OXPHOS to aerobic glycolysis occur, making cells more dependent on glucose for growth and survival. (Warburg effect)

The Mitochondria respond by slowing down the ETC (oxygen is terminal electron acceptor in ETC) as a protection mechanism. This leaves more oxygen in the cell rather than mitochondria and increase ROS production.



Chronic hypoxia stimulates the sympathetic nervous system and adrenal medulla this causes depletion of thiamine in the mitochondria https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3758298/

When thiamine is reduced pyruvate can't be used as much in glycolysis

This means lactate increases - lactate is emerging as a key player in driving immunosuppression.

Lactate is a potent signaling molecule that promotes stabilization of hypoxia inhibitory factor alpha (HIF-α) this increases vascular EGF expression and angiogenesis and is thought to be involved in the

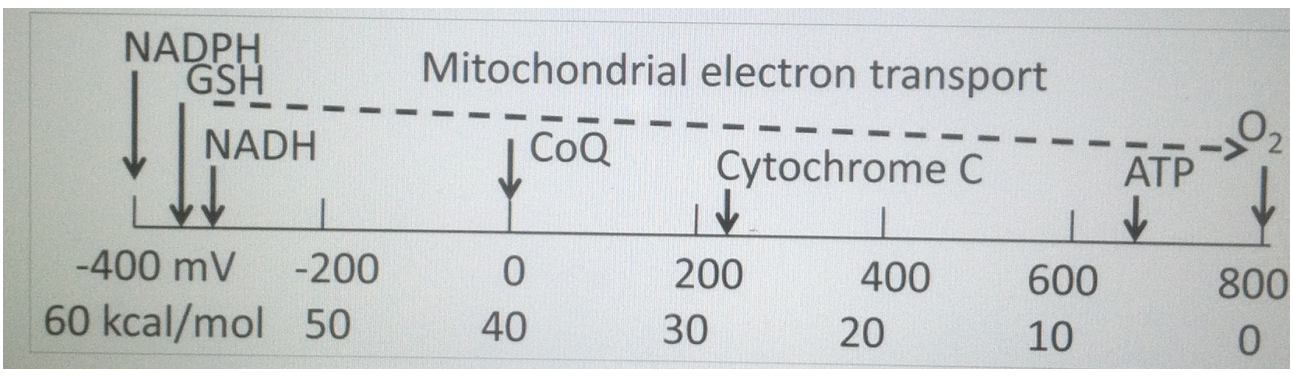
$$\frac{[NAD^+]}{[NADH]} = \frac{[pyr]}{[lac]} \cdot \frac{10^{-pH}}{K_{Eq}}$$

development of certain cancers.

https://www.sciencedaily.com/releases/2020/01/200115093435.htm

When Pyruvate cannot be used because thiamine is absent, lactate rises causing NAD+ to drop steeply and with it redox potentials in the mitochondria.

When redox potentials drop energy drops.
Hypoxia due to obesity is a stress on the cell - system responds (adaptation/symptoms), this response requires energy for transport, manufacture (proteins), communication and monitoring.



The mitochondria react as if oxygen levels have dropped (hypoxia) and slow down the production of energy so less oxygen is used - this is a survival tactic/mechanism.

However, oxygen levels haven't actually dropped which means there is more oxygen dissolved in the cell. It is therefore called pseudohypoxia.

Oxygen is a highly reactive molecule and this can cause a lot of stress/confusion inside the cell. ⬆️ ROS and RNS are generated.

These are used by the cell for both redox signalling and oxidative stress.

Oxidative stress ➖ ⬆️HIF-1 ➖ ⬆️NRF2 ➖ ⬆️HO-1

When the body detects stress this triggers the sympathetic nervous system to take action. It starts to manufacture more glucose which can then be used by the cell, with or without oxygen, to produce energy.

We will see non-linear responses because people have different engines (mitochondria) depending upon their haplotype- some will be tightly coupled (high efficiency) and others will be uncoupled as an evolutionary response to generate more heat energy to survive in colder climates.

However, with chronic hypoxia - long term measures to protect the body are required - this involves epigenetic changes related to immunometabolism, proliferation, and angiogenesis, which help to supply oxygen/energy to the cell/tissue.

There are 2 further important factors to take into account that enables a cell and the body as a whole to match up energy demand with energy supply.

Circadian rhythms and Light.

Circadian clocks are a highly conserved evolutionarily timekeeping mechanism that allow organisms to anticipate and adapt their behaviour to predictable changes in the environment.

Each cell in the body has its own molecular clock that works by rhythmically cycling the levels of different molecules. Proteins called CLOCK and BMAL1 trigger the production of proteins PER and CRY.

As levels of PER and CRY rise, they interfere with CLOCK and BMAL1, essentially switching off their own production.

Then, levels of PER and CRY fall and the cycle starts again.

Thus, these molecules rise and fall throughout the day to drive circadian rhythms, similar to how a pendulum swings back and forth to keep a clock ticking.

It has been demonstrated that Organisms which have a circadian period matched to their environment, actually grow faster and survive longer than those that have a mismatch.

It is generally accepted that metabolism regulates these cellular clocks by diurnal oscillations in the redox potentials.

There is now evidence that this link between metabolism and circadian rhythms is achieved by NRF2 - with activation of NRF2 occurring at peak times of ROS production.

Hydrogen peroxide (ROS) is a byproduct of cell metabolism, and leads to an increase in NRF2 which in turn leads to epigenetic changes in the cell.

The appropriate timing and magnitude of this ROS signaling coupled with NRF2, helps to ensure energy demands are temporally coupled with energy supplies.

When intracellular redox potentials decrease this leads to the accumulation of oxidants with a corresponding reduction in intracellular pH which is the trigger for activation of NRF2

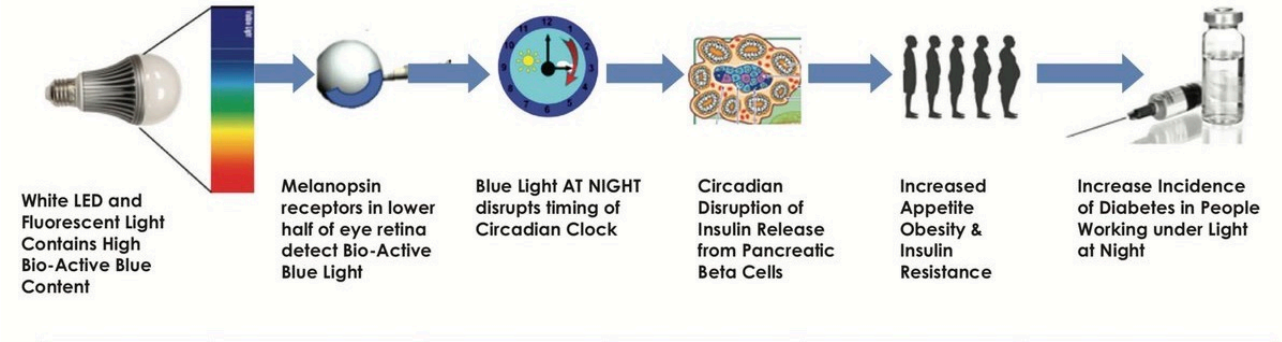
The oxidative activation of NRF2 coupled with the cellular clock allows energy production and utilisation to be matched to the environmental light-dark cycle.

This matching of energy to the light-dark cycle is achieved via photo receptors which are present in the retina, skin, capillaries and fat cells.

The most relevant photo receptor is called melanopsin, which is predominantly activated by wavelengths of light in the blue spectrum.
Blue light is most prevalent in natural sunlight at midday and it's percentage changes during the day, it is therefore a reliable way for a biological system to keep track of time.

The melanopsin receptors in the retina are linked to the suprachiasmic nucleus (SCN) via the retinohypothalamic tract.

The SCN acts as the central clock in the body and communicates with all the peripheral clocks in the cells.



From this diagram, we can see how a mismatch between light and circadian rhythms could disturb the metabolism of a cell and lead to metabolic disruption and disease.

⬆️ Blue 💡 ➖ ⬇️Melanopsin ➖SCN (Brain) ➖ ⬆️ PER2 ↔️➖⬆️ HIF-1 ➖Met Syn ➖obesity.

The final piece in the jigsaw involves the relationship between melanopsin and melatonin.

Melatonin production and suppression is very sensitive to light and primarily the blue light which stimulates melanopsin.

⬆️ Blue 💡 ➖⬇️Melanopsin ➖⬇️ Melatonin ➖ ⬇️ Sleep➖⬇️ Immune function

So, here we have a very interesting evolutionary connection between light and sleep (dark) which links HIF-1/NRF2 with Circadian rhythms (PER2), and allows the changing thermodynamic demands on the system that occur from day to night and from hot to cold, to be met by metabolic adaptations.

Day time (Light) is when the body is set up to play the game of life and deal with all its stresses and strains, whereas darkness is the time reserved for rest, recovery and growth.

By linking the day and night light conditions with hypoxia pathways a thermodynamic system is able to ensure energy production is matched with oxygen consumption, so not too much ROS or inflammation is generated and energy is conserved.

However, once you start disrupting this energy homeostasis, perfected over millions of years of evolution, you start to generate chaos and entropy, ROS and inflammation and run down the mitochondrial batteries necessary for life.

It seems logical that if the body senses energy supplies (oxygen) are under attack and extra energy is being used or required for protection on a long term basis (chronic inflammation) then it will endeavour to conserve and store energy in the form of fat.

This is achieved initially by HIF-1 and NRF2 oxidative stress defences and then by Leptin and insulin resistance.

For any thermodynamic biological system, energy is the key to life, generating both movement and structure, from which we get function and when that system is an aerobic organism, nothing matters more than oxygen.

https://link.springer.com/article/10.1007/s00018-019-03039-y

https://europepmc.org/article/pmc/pmc6715538

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261999/#!po=20.8333

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https://pubmed.ncbi.nlm.nih.gov/30697806/