

Oxygen is the Molecule of Life. # Don't Mess with Oxygen!

TL:DR

Chronic stress uses up energy and weakens your ability to deal with infection.

The body is a non-linear bioenergetic/thermodynamic system.

The virus is a stress on that system.

Hypoxia/Pseudohypoxia is an even bigger stress on an aerobic system.

The system responds to stress.

This response requires energy.

When there is not enough energy to respond, the body dies.

<https://www.sciencedirect.com/science/article/pii/S0042682219300509?via%3Dihub>

I keep hearing all this talk of a “War” on the Coronavirus - well, you might as well declare war on a biro, for all the good it will do.

Because this virus, in fact any virus, is not a living thing - it is just information in the form of a single strand of RNA, and because it is new information to the body it's generating an enormous amount of panic and confusion, far more than is healthy for a human body or, indeed, a World Economy!.

The important thing here, is to understand what is actually going on:

In technical terms: It's a very serious non-equilibrium thermodynamic systems problem that is affecting every individual, every business, and every country, across the globe - It is not the apocalypse or WW3.

In simple terms: The defensive and energy systems of the human body, together with the medical services, have been weakened by years of chronic stresses and environmental pollutants, and are now unable to cope with a novel virus that is simply looking for a place to stay.

So great is the chaos and mayhem being created, thousands of people are dying both directly and indirectly (collateral damage) and from a simple thermodynamic point of view, this virus is generating a tremendous amount of entropy, burning off a tonne of energy and leading to Heat Death - a state whereby no energy is left for life.

All that being said, I thought I should sum up what I think is going on with this particular Coronavirus pandemic in layman's terms, and just to make clear, I consider there to be a number of contributing factors, non of them causal, but all are related to our modern lifestyle and environment.

These include, in no special order; Air pollution, Electrosmog, Junk food, modern lighting, indoor living and sedentary lifestyles.

Every geographical region is going to have different factors, making differing contributions, but the overall effect will be an overstressed nervous system, a weakened immune system and a

reduction in energy flow, resulting from a condition called pseudohypoxia.

So called because the body isn't actually hypoxic, in terms of having a low oxygen concentration in the blood - it just think's it is!

Environmental Pollutants.

When oxygen is breathed in through the lungs it goes to tiny air sacs and from there it enters the blood stream via tiny capillaries. Once in the blood it is transported to the cells of the body to supply the oxygen needed for energy production in the mitochondria (cell batteries).

Any change in the structure of the oxygen molecule for whatever reason can effect this process.

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.

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.

This is fine in the acute setting eg exercise - however when it becomes chronic, things start to go astray.

For example, thiamine (Vit B1) starts to be depleted because it is required for this type of energy production.

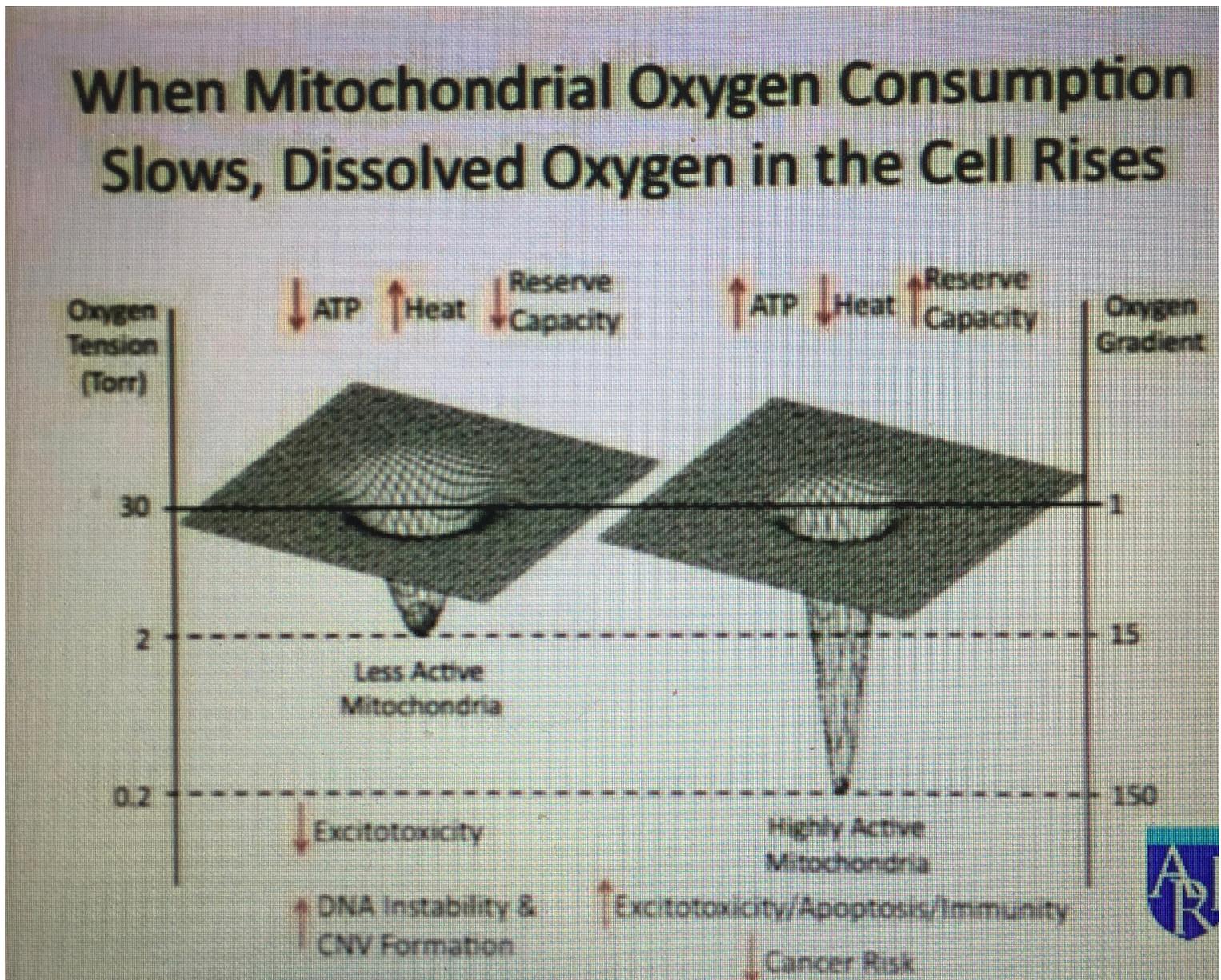
When thiamine levels drop, this means you get even less energy production from the mitochondria and an increase in lactate in the cell.

The increase in lactate is another hypoxic stress signal in the body and leads to another defensive response to save energy - reduced immune system function! (This process is thought to be related to the development of many cancers).

Now consider what might happen when a virus infects the lungs under these circumstances and causes an actual hypoxia - the body is in a much weaker position to deal with it because it has already played its hypoxic defensive card and is now a busted flush, needing to go all in with what little chips it's got left!

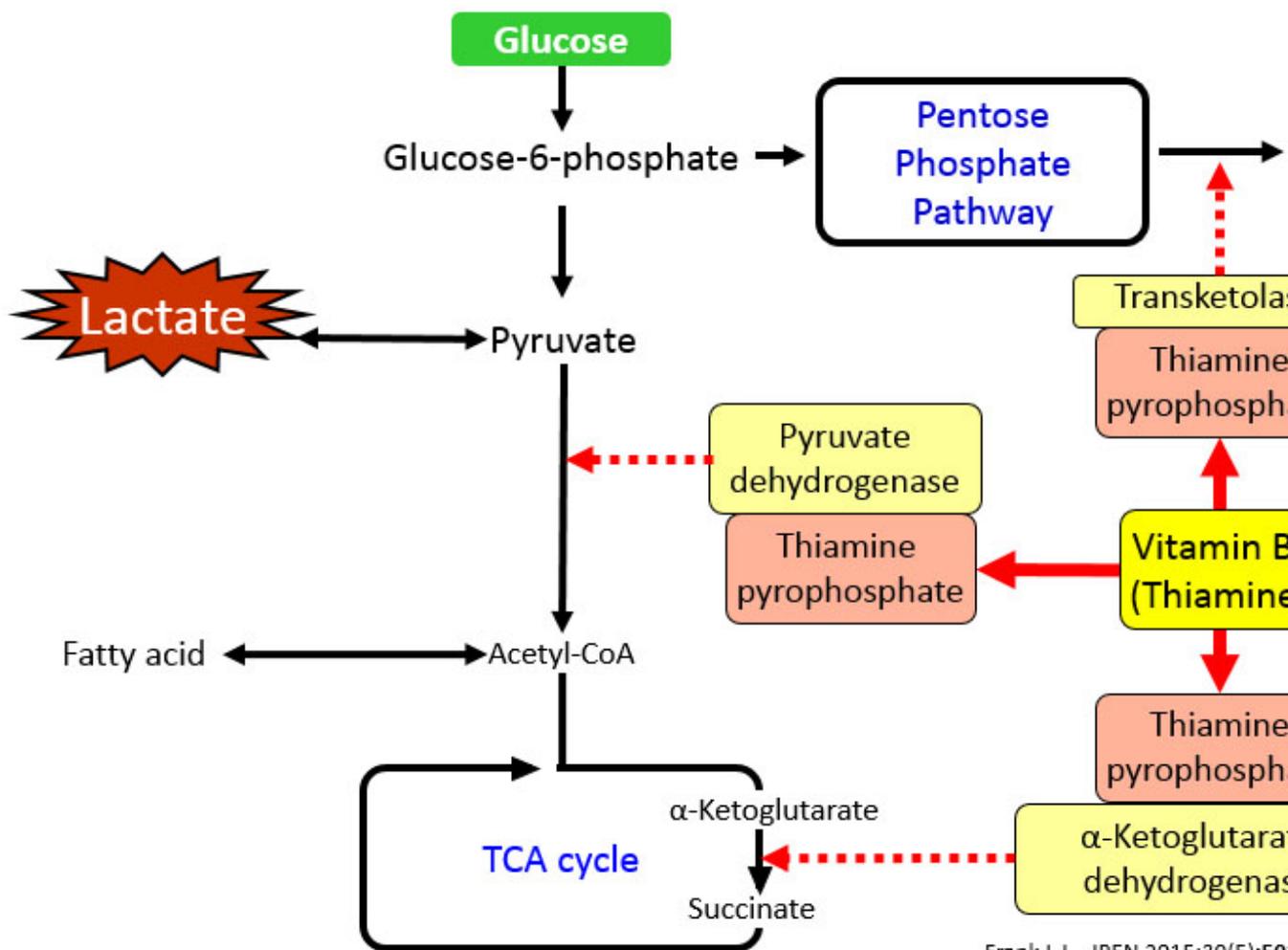
Technical explanation:

Pollutants in the atmosphere affects oxygen binding to haemoglobin - enters blood - transported to cells and mitochondria - signals hypoxia/pseudo hypoxia - mitochondria responds by slowing down 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/>

Enzymes in which thiamine serves as a cofactor in carbohydrate metabolism

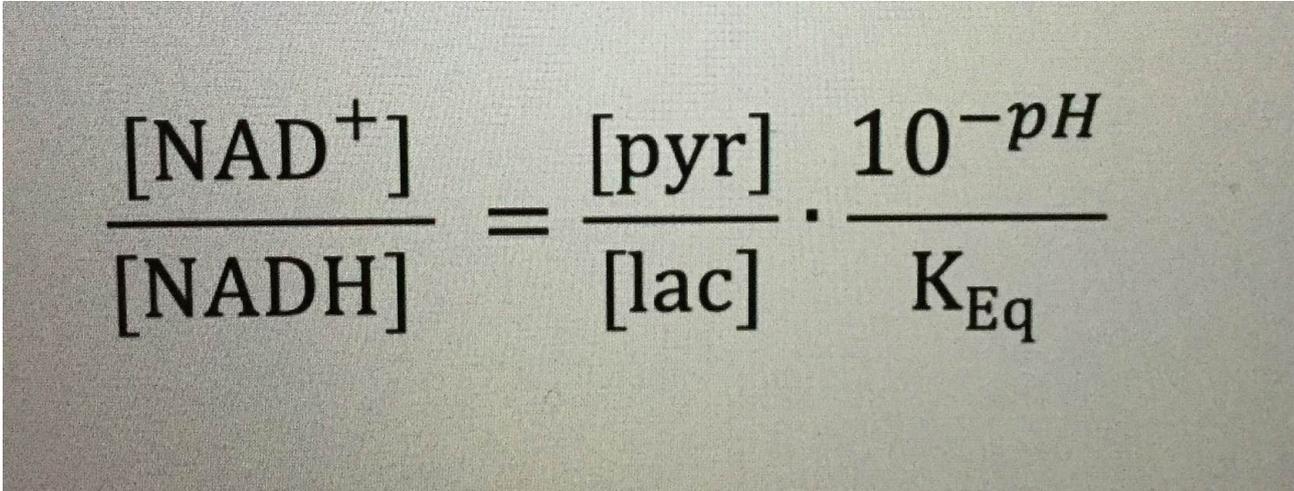


Frank L.L., JPEN 2015;39(5):50

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.

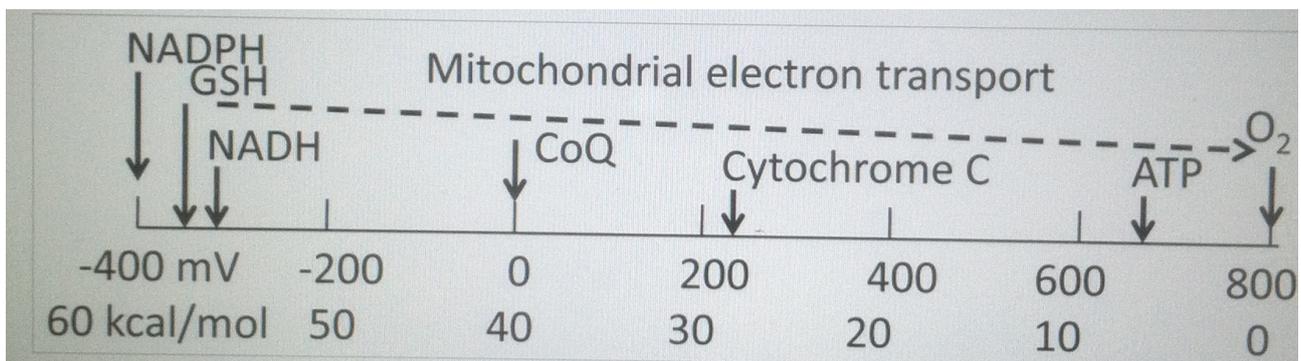
Lactate is a potent signaling molecule that promotes stabilization of hypoxia inhibitory factor alpha (HIF- α) this increases vascular EGF expression and angiogenesis and is thought to be involved in the development of certain cancers.



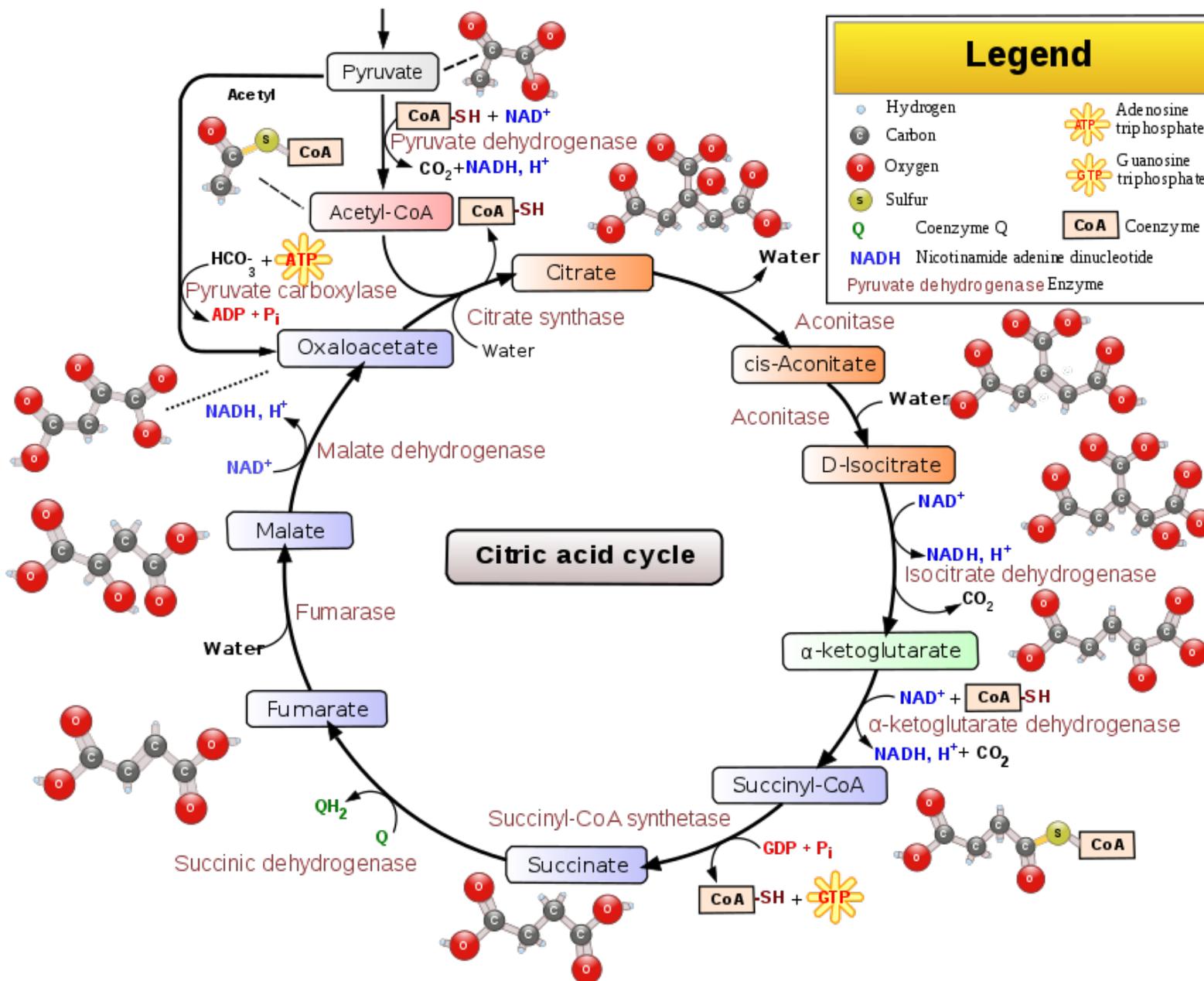
<https://www.sciencedaily.com/releases/2020/01/200115093435.htm>

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

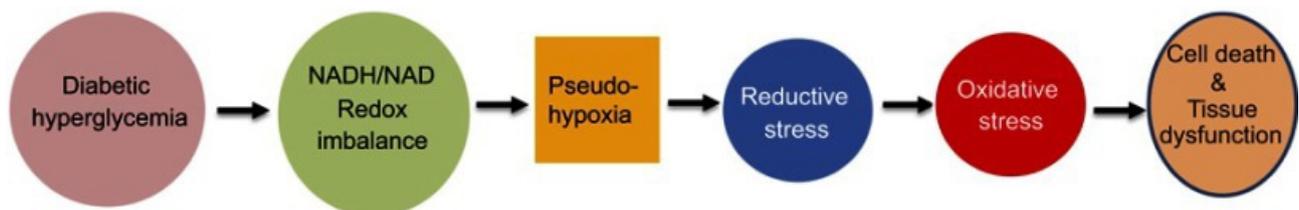
When redox potentials drop energy drops.



A similar pseudohypoxia can also be seen in chronic overconsumption of fats and sugars.



NADH/NAD redox imbalance can overload the mitochondrial electron transport chain, leading to excess production of reactive oxygen species (ROS).



This is the type of pseudohypoxia also seen in type 2 DM.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6560198/#CIT0007>.

Then, when the Coronavirus enters the pneumocytes and starts replicating, it causes an actual hypoxia - This is a massive and confusing signal to the defences of the body - because they thought they were already dealing with an hypoxic scenario in the cells - and now they are faced with a more acute and serious systemic problem.

This generates a massive overreaction from both the nervous system, immune system and Microbiome, leading to a Cytokine storm and overwhelming the metabolic capabilities of an already tired and weary body.

Thiamine:

TL:DR - Thiamine deficiency powers down your Batteries.

Thiamine is a rate-limiting cofactor in the production of 5 enzymes involved in the production of ATP in the mitochondria via the glucose, fat and amino acid pathways - deficiency therefore causes a reversible decrease in energy production.

Clinically, thiamine deficiency is seen in Alcohol induced Beriberi and Wernicke's encephalopathy - which is why thiamine is given to people with alcohol dependency.

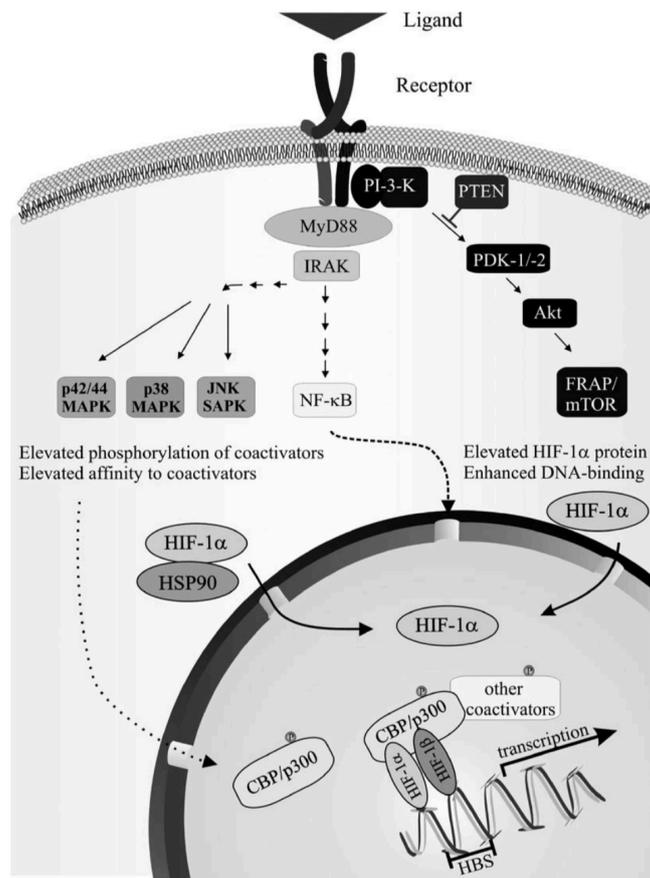


FIG. 2. Pathways involved in ligand-induced receptor signaling leading to increased HIF-1 function exemplarily shown for IL-1 and IL-1 receptor/IL-1R accessory protein (IL-1R/IL-1RAcP). The main pathway leads to the activation of NF-κB. To this end, the MyD88 adapter protein serves as a docking platform for IL-1 receptors-associated kinase (IRAK), which is of particular importance for NF-κB activation. Downstream from IRAK there are cross-links leading to the activation of p42/44 MAPK, p38 MAPK, and JNK/SAPK. Moreover, the PI3K signaling pathway is induced by IL-1/IL-1R/IL-1RAcP independently from MyD88/IRAK. PI3K activates PDK-1/-2, which in turn initiates Akt and subsequently FRAP/mTOR activity. PTEN phosphatase silences this pathway by dephosphorylation of phosphatidylinositol(3,4,5)P₃. Loss of function mutations in PTEN lead to constitutive activation of the PI3K pathway and to elevated HIF-1α protein. Besides these pathways, HIF-1α is stabilized by association with such molecular chaperones as HSP 90.

It is significant that some of the key features of wet Beriberi are similar to those with SARS-CoV2 namely :-

Shortness of breath

Rapid heart rate

Cardiovascular complications

There is also an even more acute version called Shoshin Beriberi, which sees a more rapid deterioration in cardiovascular functioning.

And, this too is characterised by a right sided heart failure, pulmonary hypertension, low blood pressure, renal shutdown and a severe metabolic acidosis.

Representing some of the hallmarks of those acutely unwell with SARS-CoV2

History tells us that Beriberi was commonly mistaken for a mysterious infection.

In one instance, Japanese workers suddenly developed symptoms all together when exposed to sunlight and nobody could explain why?

With hindsight it has been hypothesised that the stress of ultra violet light on a nutrient deprived (thiamine) body precipitated the disease.

I highlight this case, not because I think this is beriberi, but because I think there are lessons to be learnt.

New Paradigm:

The current medical model is treating this as a simple linear infection problem:

Virus - causes infection in lungs - causes pneumonia - causes low oxygen and sepsis - causes death.

Therefore cause of death is virus .

The weaker the immune system, the more vulnerable the patient, the more likely they are to get a severe infection and die.

All this is true, however, there are some cases of young healthy people catching the virus and dying and equally vulnerable people not dying.

The virus is the proximate cause of death, it is not the root cause, and unless you address the root cause you will fail to treat it properly.

By this I mean the virus is another stress on the body, and the body responds producing symptoms - fever, cough, sore throat breathing problems etc - these symptoms should be viewed as the body's defensive/adaptive action to this particular stressor.

The prevailing medical model seeks to counteract the body's response.

eg - fever - give paracetamol to lower it.

Joint aches - initial advice take ibuprofen

Low oxygen levels = give high flow oxygen to increase oxygen

However, by treating just the symptom you can make matters worse.

For example, giving paracetamol has been shown to prolong the duration of infection because the body is using the higher temperature to allow both an immune response and a energy response - a higher temp allows more oxygen/energy to be supplied to the cells fighting the infection (Bohr effect).

We know that giving ibuprofen is detrimental in this instance, because its anti-inflammatory properties are reducing the immune systems response to the infection.

It is linear thinking which leads to these mistakes.

A non-linear thermodynamic/bioenergetic systems approach would view the situation differently.

Virus is a stress on the whole system - system responds (adaptation/symptoms), this response requires energy for transport, manufacture (proteins), communication and monitoring.

If any part of this system is not functioning correctly you get inefficiencies and energy is wasted.

The body only has so much energy - once energy supplies are low it has to prioritise the most vital departments - brain and heart - energy is diverted away from other areas eg immune system or kidneys.

Just as the world economy would very quickly fall apart without an energy supply, or any business without cash flow/money, the bodily system can also not function properly without fuel.

Indeed, in order to understand what is happening on the inside, perhaps we need to look at what is happening on the outside.

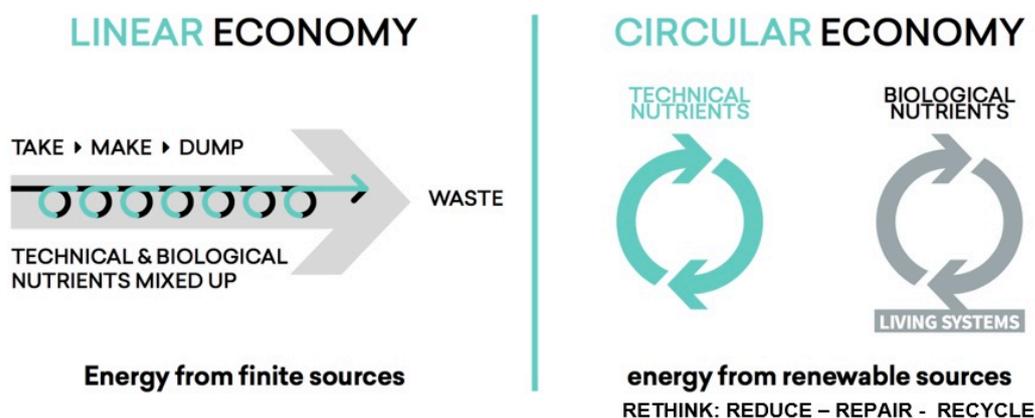
Because the “Environment” is always the key!

The lack of PPE for protection, represents a poorly functioning innate immune system.

The lack of Testing for surveillance, represents an overworked Nervous system.

And finally,

The severe Economic collapse, reflects the total Chaos and Energy crisis that is occurring inside many bodies right now!



In a linear economy, waste is generated without recycling and energy gets depleted, so when demand is high (eg PPE) supplies run out.

In a circular economy supplies get replenished to meet demand

Oxygen - The Molecule of Life!

Over millions of years of evolution our cells have adapted to face many diverse stresses and strains in the game of life, many of which challenge the vital delivery of oxygen and energy.

The ubiquitous player in this game was finally awarded the Nobel Prize in 2019, and, given all those years of experience, you will not be surprised to learn, plays a pivotal role in how the body performs.

The name of that player is: Hypoxia Inducible Factor is **HIF**.

Oxygen is the key high-energy molecule driving the energetics of aerobic life, and HIF is charged with the important task of detecting it and ensuring it is always in supply.

It gives the body the ability to direct oxygen and therefore energy to where it is needed most, via vasodilation, angiogenesis, vascular permeability, glucose uptake and glycolysis.

Under hypoxic conditions, the rate of O₂ supply limits the rate of O₂ consumption, and aerobic metabolism is reduced.

And, in cases of severe O₂ deficiency, the respiratory chain succumbs, risking cellular death, and HIF-1 is charged with the job of supplying the cell with the oxygen and energy producing substances it needs for survival.

In the kidneys and liver it signals the production of EPO to produce more oxygen carrying red blood cells. It also stimulates

the production of extra capillaries to get the oxygenated blood to where it is needed (via increase in VEGF and NO)

At the cellular level, hypoxia increases the production of enzymes involved in glycolysis eg lactate dehydrogenase and PGK-1 as well as increasing the number of glucose transporters (primarily GLUT-1) to provide more substrates for glycolysis and energy production.

NB Glycolysis requires much less oxygen than fat oxidation.

It is therefore a key regulator of Metabolism as well as oxygen homeostasis.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2906567/>

In addition, HIF is also a mediator of the immune system.

For example:

High levels of HIF-1 are found in macrophages in rheumatoid tissue. <https://www.ncbi.nlm.nih.gov/pubmed/11465705>

This is also the underlying reason why anti inflammatory medications like ibuprofen have an adverse outcome in Covid-19 - They do not allow the immune system to function efficiently.

Here we have the interplay between the immune system and metabolism, collectively referred to as; immunometabolism.

In which Cytokines and metabolic hormones such as insulin, IGF-1 and vasoactive peptides, such as angiotensin 2, work together in defence of the body.

Now, there is another key factor with the SARS-CoV2 virus which links it in with HIF-1 and immunometabolism and that is its point of entry, the ACE2 receptor, which is vital to the workings of the Sympathetic Nervous System and its response to stress.

When the body is under stress it requires more energy to deal with the problem.

Energy stress caused by hypoxia leads to an increase in ACE2. This then gives the virus more access points into cell.

Furthermore, ACE2 is also intrinsically linked to the immune system as well as the SNS, as it has an anti-inflammatory action, which dampens down the immune response.

So, we find the nervous system linking up with the immune system, which in turn links up with the metabolic system in a collective defence of the organism.

SARS CoV2 itself down regulates ACE2 and in so doing sends Angiotensin II rocketing which increases aldosterone and causes a loss of potassium via urine excretion, which is a key characteristic of covid-19.

These ACE2 receptors can be found all around the body - most notably the; lungs, kidneys, brain, fat cells, gastrointestinal tract and they are also elevated in men!

This would therefore explain, both the symptom profile of the disease, and highlight those most at risk from severe symptoms and death.

Symptoms:

Shortness of breath

Dry cough

Temperature

Headache

Diarrhoea

Bloating and nausea.

Loss of taste and smell.

Conditions most associated with increased ACE2 include:

Male

Hypertension.

Obesity

Heart disease - heart failure

Type 2 DM / Insulin resistance.

All of the above are tied in with metabolism and metabolic syndrome and all have been shown to be risk factors for adverse outcomes with SARS-CoV2

Another key point to note here, is the likelihood that HIF-1 also regulates this RAS/ACE2 pathway - more on this later.

But first, let us do a Strengths and Weakness analysis of the 2 teams involved, to allow us to decide the best strategies to use:

Away Team - Opponent: Virus

Strengths:

Structure - Very small, (invisible), resilient, can survive on many surfaces.

Movement - Fast - air borne - easily spread

Tactics - attacks ACE2 receptor. Targets metabolism and immunity.

Weaknesses:

Structure: Simple - easily killed eg UV, High Temp, Humidity, Alcohol, Copper!

Movement: Unable to move by itself

Tactics: One trick pony - vulnerable people easy to spot - therefore self isolation.

Home Teams - Host

It appears that the big modifiable risk factors are; hypertension, type 2 DM, heart disease and obesity, all of which can be classified under the umbrella of metabolic syndrome.

Along with 2 non modifiable risk factors - old age, and Male.

Sixty-three per cent of patients in intensive care in UK hospitals due to covid-19 are overweight, obese or morbidly obese.

37 per cent are under the age of 60

So, what's going on here then?

Why would a metabolic condition make you more vulnerable to a tiny virus.

Simple: It adversely affects your energy supply.

Because, metabolically stressed out cells have a pseudo hypoxic environment, they are less robust and capable of handling an energy crisis.

Evidence for this pseudo hypoxia is the involvement of HIF-1 the oxygen sensor in all of these metabolic conditions.

HIF-1 insulin <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570255/>

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

HIF-1 Heart disease <https://www.ncbi.nlm.nih.gov/pubmed/23988176>

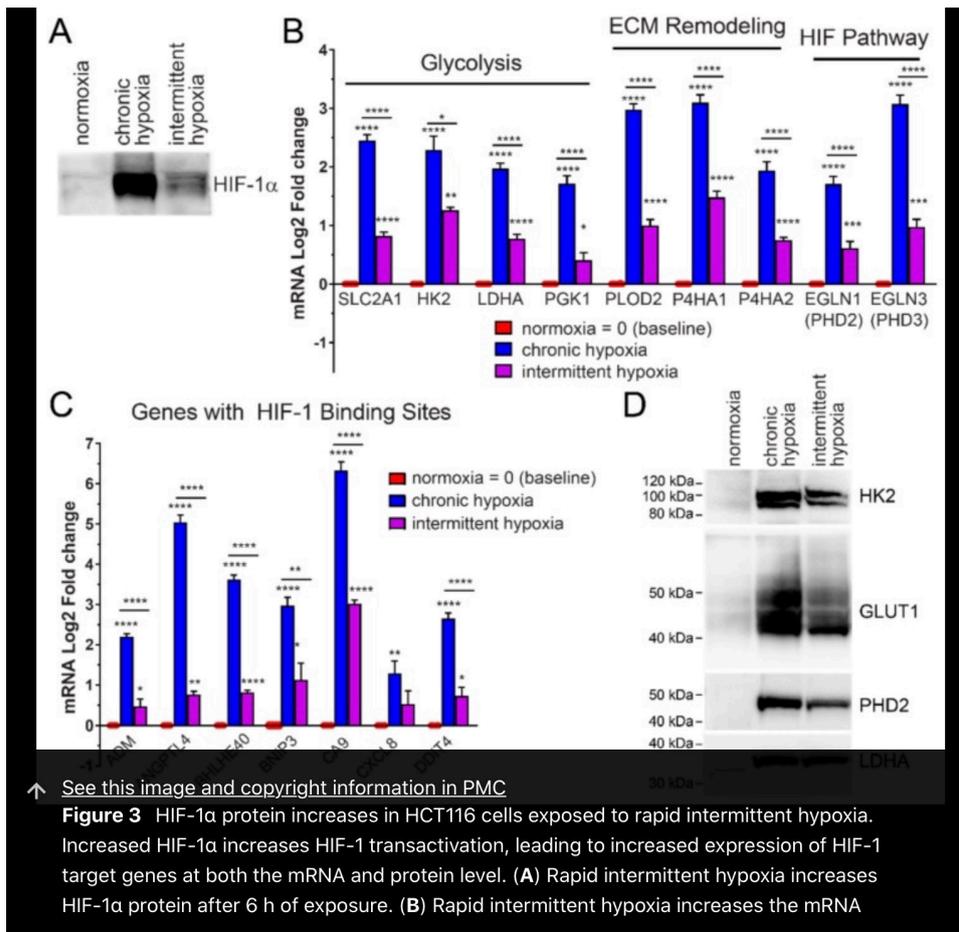
HIF-1 Sleep apnoea <https://www.ncbi.nlm.nih.gov/pubmed/30669593>

Again, all can be viewed as protective mechanisms by a bioenergetic system.

Further evidence for the involvement of hypoxic mechanisms and HIF-1 in the regulation of the ACE2 pathway can be found here:

<https://journals.physiology.org/doi/full/10.1152/ajplung.90415.2008>

From an adaptive system view point, this makes perfect sense - An oxidative stress is sensed thermodynamically by the mitochondria in the cell and communicated to the nervous system, which then takes action.



One of these defensive actions is Insulin Resistance:

It can be physiological:

eg. Hibernating animals, animals living in cold environments- there is also evidence of seasonal as well as diurnal variation in IR - to supply the high energy consuming areas of the body - brain and heart - with the glucose they need when it is in short supply.

Also Gestational diabetes ensures the placenta receives sufficient glucose.

However, it can also be pathological.

Most notably in type 2 DM and heart disease and possibly Alzheimer's dementia.

This is an adaptive response to overnutrition.

Eating too much food, be it fats or carbohydrates creates increased cellular stress in the form of Reactive Oxidant Species ROS, in the mitochondria and ROS is a signal for inflammation.

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

In order to understand how and why Insulin Resistance can be viewed as a protective mechanism, let us take a closer look at obesity - one of the major risk factors for SARS-CoV2.

Most people understand this as a metabolic problem, however, this is another 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”!

Of course this has been an abject failure and has seen obesity numbers soaring and life expectancies falling for the first time in a hundred years.

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 - (I would also add the Microbiome to this list, but will save that for another day).

Back then to a stressed out fat cell - An increase in ROS due to overeating creates hypoxic/pseudohypoxic conditions inside the cell, 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).

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

Now, you can begin to understand why insulin makes people fat and why in type 2 DM, it actually makes the environment inside the cell worse, more overcrowded, more hypoxic, and even more inflamed, and the only way for the fat cells to cope is either to get bigger or increase their numbers.

This inflammation requires the involvement of the immune system and is associated with all of these chronic diseases.

However, as well as being energy draining, it also leads to a dysfunction in one of the most important cells involved in the removal of viral infections and a key player in your innate immune system - Natural Killer cells or NK for short - when these aren't working properly you are more vulnerable to a viral infection.

In conditions like, obesity and type 2 DM, you are effectively immune compromised

Why?

Because, NK cell function is intrinsically dependent on cellular metabolism, with several studies highlighting the absolute requirement of NK cells to engage in glycolysis and oxidative phosphorylation.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6521109/#B42-cancers-11-00573>

We must also remember the role of the nervous system in how this pans out!

So, let us bring onto the field of play - Leptin - The “Master Hormone” of the brain.

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

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6521109/#B79-cancers-11-00573>

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.

Leptin Resistance can be viewed as another defensive tactic by the body to ensure energy is directed to where it is most needed, to deal with a stressor.

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.

And lo and behold, 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>

If somehow a Virus can activate these HIF-1 pathways, then it has access to the energy and nutrients it needs for replication - this is thought to be the most likely pathway by which some viruses cause cancer eg HPV (viral oncogenesis).

For example, a common upper respiratory infection common in infants - respiratory syncytial virus (RSV) induces HIF-1 in bronchial epithelial cells via a NO-dependent pathway.

The increased levels of HIF-1 in turn stimulate VEGF production, enhancing monolayer permeability, which may play a role in the airway oedema of acute RSV infection.

<https://link.springer.com/article/10.1007%2Fs10753-004-6047-y>

Oxygen is the Molecule of Life (and Death)!

TL:DR

Hypoxia — ↑ Stress — ↑ SNS — ↑ Metabolism — ↑ ↓ Immune System

Hypoxia — ↑ HIF-1 — ↑ Cytokines — ↑ Inflammation — ↑ Energy consumed

You can survive months without food, days without water, but, only a few minutes without oxygen!

In a system that relies so much on oxygen for energy/survival, it is hardly surprising feedback systems involving the SNS, immune system and metabolism are in place to respond to such crises.

Indeed, even though oxygen is invisible and odourless, there is emerging evidence that the body can actually smell it and perhaps even see and taste it.

There is a reason why the Olfactory nerve takes pride of place, at number one in the Cranial nerve charts.

<https://www.mpg.de/10843354/mice-can-smell-oxygen>

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 addicted to glucose for growth and survival. (Warburg effect)

In the Nervous System - Carotid Bodies detect oxygen levels this is linked to the glossopharyngeal nerve (taste).

When acute hypoxia is detected by the nervous system this increases breathing, heart rate, and restlessness - low co₂.

Whereas, chronic hypoxia in the lungs has the opposite effect - hypoventilation and increased co₂.

We also see that HIF has time related effects:

During acute hypoxia - Survival/Protective mechanisms are activated. eg vasoconstriction, innate immune system, respiration without oxygen.

However, with chronic hypoxia - long term measures to protect the body are made - this involves epigenetic changes related to metabolism, proliferation, survival, and angiogenesis, which help to protect the essential organs eg heart and brain, which require the most energy.

After reviewing all the evidence connecting hypoxia/pseudo hypoxia and HIF with the Nervous system, immune system and metabolism, I now firmly believe this energy stress is the “Root Cause” of the majority of chronic diseases if not all!

HIF-1 Summary

Hypoxia — HIF-1 — Cytokines — Inflammation — Energy used —
Cytokine Storm —  Energy

Hypoxia — HIF-1 — GLUT1 — Glucose uptake — Glycolysis — Viral
replication —  Energy

Hypoxia —  HIF-1 —  Insulin — Anabolic —  Apelin — 
Angiogenesis

Hypoxia —  HIF-1 —  IGF-1 — Anabolic —  Angiogenesis
—  chronic diseases

Hypoxia —  HIF-1 —  PDGF —  Angiogenesis —  chronic
diseases

Hypoxia — ↑ HIF-1 — ↑ Ang 2 — ↑ Vasoconstriction — ↑ BP

Hypoxia — ↑ HIF-1 — ↑ Leptin — Immune system + Nervous system + Metabolic effects

Hypoxia — ↑ HIF-1 — ↑ LPS — ↑ TLR (4) — ↑ Innate immunity — Cytokine storm

Hypoxia — ↑ Endothelin — ↑ Vasoconstriction — HIF1 — Positive feedback Loop — ↑ BP

Hypoxia — ↑ Thrombin — ↑ Clot — ↑ HIF-1 — ↑ IHD

Hypoxia — ↑ VLDL — ↑ VLDL + ↑ LDL — ↑ Lipid Droplet — ↑ IHD

https://www.researchgate.net/profile/Ming_Tai_Chen/publication/51692879_Hypoxia-inducible-factor-1_HIF-1_promotes_LDL_and_VLDL_uptake_through_inducing_VLDLR_under_hypoxia/links/557186a908ae6d917bc4e325/Hypoxia-inducible-factor-1-HIF-1-promotes-LDL-and-VLDL-uptake-through-inducing-VLDLR-under-hypoxia.pdf

Hypoxia in Lungs.

Hypoxia — ↑ HIF-1 — Short term ↑ ACE2

Hypoxia — ↑ HIF-1 — Long Term ↓ ACE2

Hypoxia — ↑ HIF-1 — ↑ ACE1 — Hypoxic Pulmonary Hypertension

Heart	Acute	Ischemic preconditioning	↑HIF1A	↑CD73 ²⁰
			↑HIF1A	↑ADORA2B ²¹
			↑HIF2A	↓KCNMB1 ²²
	Ischemia/reperfusion	↑HIF1A	↑iNOS ¹⁸	
		↑HIF1A	↑HO-1 ¹⁹	
		↑HIF2A	↑AREG ²⁴	
Chronic	Aorta-caval shunt	↑HIF1A	↑VEGF ²⁸	
	Transverse aortic constriction	↑HIF1A	↑SF3B1, ↑KHK-C ³⁰	
Lung	Acute	Ventilator-induced lung injury	↑HIF1A	↑ADORA2B ³⁹
		CLP-induced lung injury	↑HIF2A	↑VE-PTP ⁴³
	Chronic	Chronic hypoxia	↑HIF2A	↑ET1 ⁴⁶
			↑HIF2A	↑SNAI1/2 ⁴⁸
		Bleomycin-induced pulmonary fibrosis	↑HIF1A	↑PDK1 ⁵³
		Cigarette smoke-induced pulmonary injury	↑HIF1A	↑MUC5AC ⁵⁸
Liver	Acute	TAA-induced liver injury	↑HIF1A	↑CD73 ⁶¹
		APAP-induced liver injury	↑HIF1A	↑Cleavage of hemojuvelin, ↓Hepcidin
		Ischemia/reperfusion	↑HIF1A	↑HO-1 ⁶⁷
	↑HIF1A		↑CD73 ^{72,73,74}	
	Chronic	Bile duct ligation	↑HIF1A	↑PDGF, ↑FGF ⁷⁷

Black Swans!

One should always take a look at the Black Swans, in order to understand a problem.

Smoking

When I first looked at the early data from China, published in the Lancet, it was striking and surprising how few smokers actually contracted the virus or died from it.

Characteristics of patients dying from SARS-CoV from early studies:

<https://www.bmj.com/content/bmj/368/bmj.m1091.full.pdf>

“Few patients had a current or former cigarette smoking history of at least 30 pack years”

“total carbon dioxide concentration were markedly lower in deceased patients than in recovered patients.”

In one study involving 191 cases only 11 (6%) were smokers, in a population heavily addicted to cigarettes with 27.7% of adults regular smokers of which 52.1% are men - which makes it particularly relevant given the higher prevalence of mortality in men.

It would appear smoking counterintuitively confers some kind of protection, despite the fact this virus attacks the lungs and causes SARS (severe acute respiratory syndrome).

Which begs the question - why might that be?

I suspect the answer is twofold - Nicotine - down regulates the number of ACE2 receptors so there are less doors available for the virus to enter and chronic mild hypoxia also dampens down the immune response and decreases inflammation via HIF-2.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6295500/>

This does pose the question as to whether chewing nicotine gum could offer some sort of protection to SARS-CoV2 since it effectively reduces the entry points for the virus. Though I suspect the answer to that question would be frowned upon.

In respect of HIF-2 - it is a subunit of HIF and plays a slightly different game to HIF-1.

In the case of chronic lung hypoxia/damage you find with air pollution or smoking, HIF-2 has a protective anti-inflammatory role.

It increases the number of Club cells in the lungs which protect the airway cells (alveoli) from further stress (ROS and inflammation).

Club cells engulf airborne toxins and break them down via cytochrome p450 enzymes - I suspect this is why smokers are not being hit as hard as you might expect from covid-19.

It also appears that HIF-1 may be triggered by more severe hypoxia than HIF-2

<https://www.nature.com/articles/srep25357>

It is therefore conceivable that HIF-2 activation (protective) in the lungs requires milder hypoxic oxygen tensions than HIF-1.

Thus it could be hypothesised that a mild hypoxia is actually beneficial to survival, and that using high flow oxygen in the setting of high temperature (Bohr effect) could be creating even more ROS and inflammation (cytokine storm) in the cardiovascular system.

Raising the possibility of using - Hypothermia - to reduce metabolism/ROS/Cytokine storm.

Hypothermia is currently used to reduce damage to the brain in head trauma and also during some cardiac surgery.

<http://eknygos.lsmuni.lt/springer/26/Part%206/495-506.pdf>

Hypothermia -  UCP1 in mitochondria “burns off” excess ROS to generate heat - therefore reduces stress in cell.

Cold —  Norepinephrine —  UCP1 —  Heat — 
ROS —  Inflammation

SARS-CoV2 : Oxygen attack!

The Virus makes a 2 pronged attack on oxygen.

1.Exacerbation of pseudo-hypoxia in an already stressed out cell by hijacking anabolic and metabolic apparatus to generate lots of virus particles.

2. Hypoxia in lungs, triggering Nervous system (SNS) and Immune systems, placing extra strain on Metabolism.

When Oxygen levels fall :-

Energy Flow Falls.

The flow of energy is an absolute necessity for life.

From this flow we get 3 things that allow life to develop, and play to continue:

1. Structure.
2. Information.
3. Movement.

In the body, the majority of energy production occurs in the mitochondria and largely requires oxygen.

That is why the Mitochondria are so important to health and disease, because once energy supplies start failing the system begins to unravel and disease develops.

And, in a dynamic bioenergetic system, energy is almost everything - without it you die!

The world's leading expert on mitochondrial disease is Professor Doug Wallace from the children's hospital in Pennsylvania, he estimates that at least 80% of chronic diseases are due to mitochondrial dysfunction,

As with any dynamic energetic system, supply and demand are the two key factors.

When the supply side is struggling, the demand side needs to make adjustments for the system to cope.

Stresses can be viewed as a drain on energy resources.

And there is no bigger stress on an aerobic respiring body or cell, than a lack of Oxygen!

The Laws of Thermodynamics.

The fractal nature of life is often forgotten but, the underlying bioenergetics of any system all follow the same Laws:

The Laws of Thermodynamics (LOT).

It is not my purpose here to go into any great mathematical detail on how these apply to the human body - suffice to say:

Einstein described them as; “the only physical theory of universal content” that “would never be overthrown.”

What we are witnessing in the world right now is the 2nd LOT in action.

This law is often called the law of increasing entropy, a world in which chaos rules supreme.

According to this law:

When work is done to create order it should (almost) always lead to an increase in entropy - and with SARS-CoV2- it does this in spades!

Put in simple terms, the human body can only generate so much energy in its relatively short lifespan, and when inevitably that energy runs out and chaos ensues, in the inimitable words of Woody Allen; “sooner or later everything turns to shit!”

There are many stresses and strains in modern environments right now, both inside and outside; emotional, physical, financial, atmospheric, metabolic, oxidative, it’s a pretty long list that just goes on and on.

Each one of these stresses is effectively a drain on energy resources.

And, since the key to a long and healthy life, is having enough oxygen and therefore energy to deal with these stresses, it is vitally important to ensure both the outside environment and the inside environment are well supplied.

Game Plan for Covid-19:

TL:DR

Reduce environmental stressors.

Reduce cellular stressors

Relax as much as possible.

Get plenty of Sleep.

Two parts: Environmental and Team (Host) - Inside & Out!

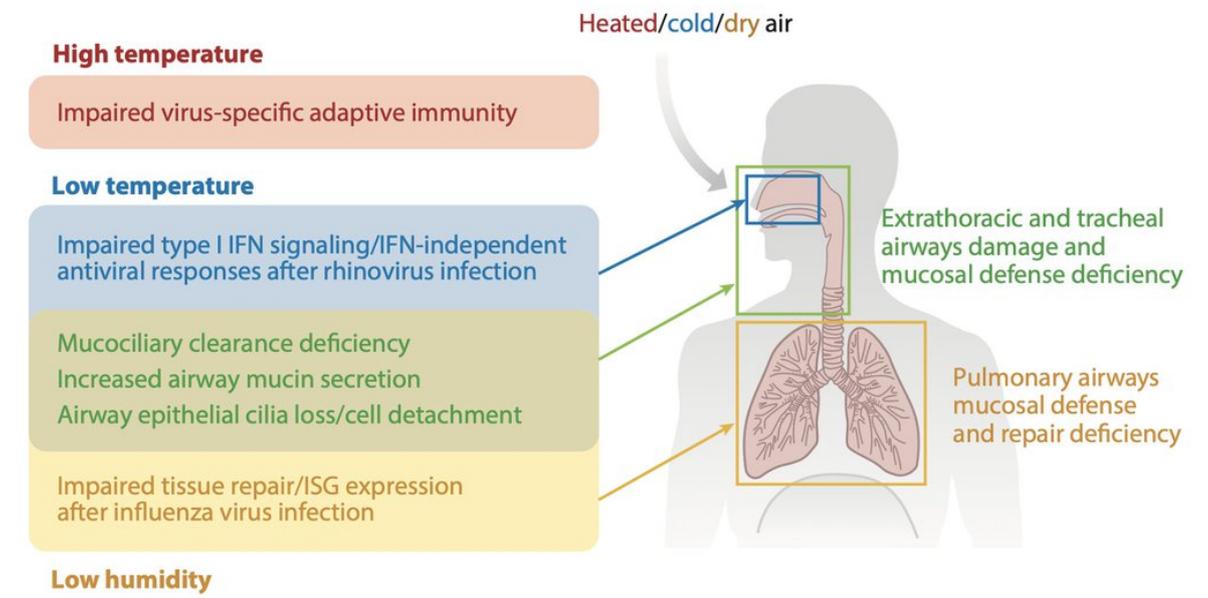
Outside Environment:

Environmental factors effect us all, and have relatively simple, all be it, economically costly solutions:

And yet, the World Health Organisation estimates that globally, 4.5 million people a year die prematurely because of air pollution.

Policies for Cleaner Air. More trees, less traffic, cleaner fuels etc
Reduce environmental pollutants.

Ensure humidity in room is high - 40-50% relative humidity helps to maintain good airway hydration and defend against viruses.



Low humidity (20-35%) increases infection rates.

Good ventilation in rooms - open windows.

Switch off WiFi at night.

Reduction in ALAN (artificial light at night).

Reduction in screen time.

Inside Environment (Cellular)

There are three strategies the individual can use to protect themselves against a novel virus.

1. Avoidance. - Effective self isolation. Masks, Cleaning, No physical contact.
2. Resistance - A robust innate immune system to stop the virus quickly, before it gets into your cells.
3. Tolerance. - Enough energy to deal with the virus if it does infect your cells.

Strategy 1 - Avoidance. This is the response of an intelligent system aware of its vulnerabilities and priorities.

Wear face masks whenever outside - there is now good evidence that the virus is airborne - it's in the air we breathe!

Ensure effective self isolation - especially vulnerable groups - there are many asymptomatic potential "super spreaders."
Especially in the younger age groups.

Wash hands after handling post and parcels - potential viral contamination.

Clean surfaces that may have been contaminated eg door handles, desk tops,

Avoid public toilets as evidence of faecal-oral route of spread

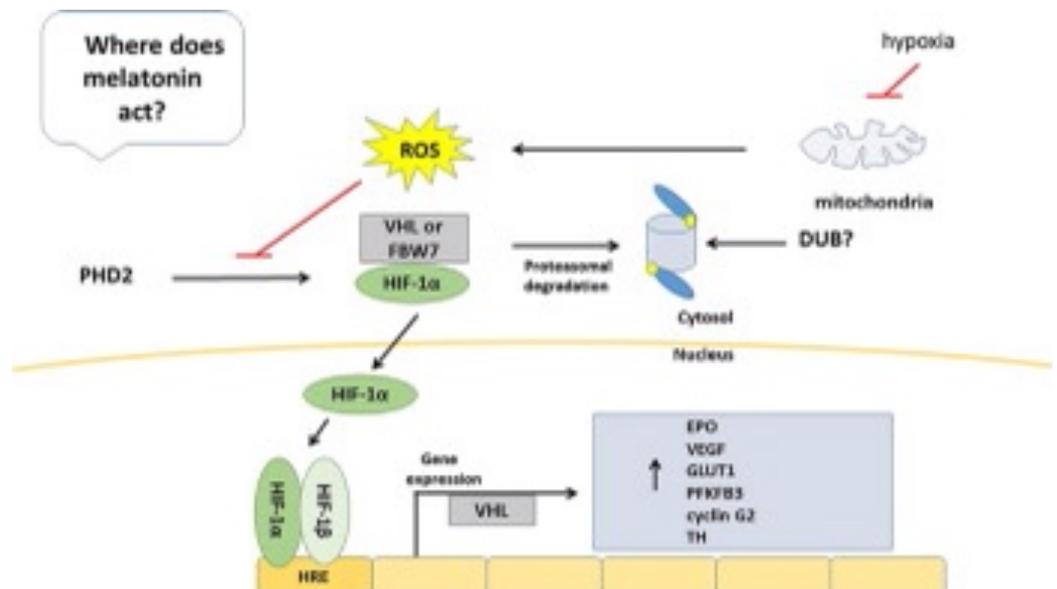
Stringent and repetitive testing of all those who have contact with vulnerable groups - medics, paramedics and carers etc.

Strategy 2 - Resistance - This is a characteristic of a strong responsive system - quick to react in a timely and appropriate manner.

**** Prioritise Sleep ****

Melatonin - The body's natural sleep hormone is also a very powerful antioxidant and crucially acts to down regulate HIF-1

Melatonin
<https://>



www.sciencedirect.com/science/article/abs/pii/S0304419X16300208

👉 Melatonin — 📉 ROS — 📉 Oxidative/Stress — 📉 HIF-1 👉

Equally as important, Melatonin indirectly regulates the ACE2 receptor, so low melatonin = more viral risk, conversely high melatonin = lower viral risk.

😴 Melatonin — Activates ACE2 receptor — Prevents viral entry! 😴

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6017142/>

Melatonin ace2: <https://www.nature.com/articles/s41421-020-0153-3>

<https://pubmed.ncbi.nlm.nih.gov/24330221/>

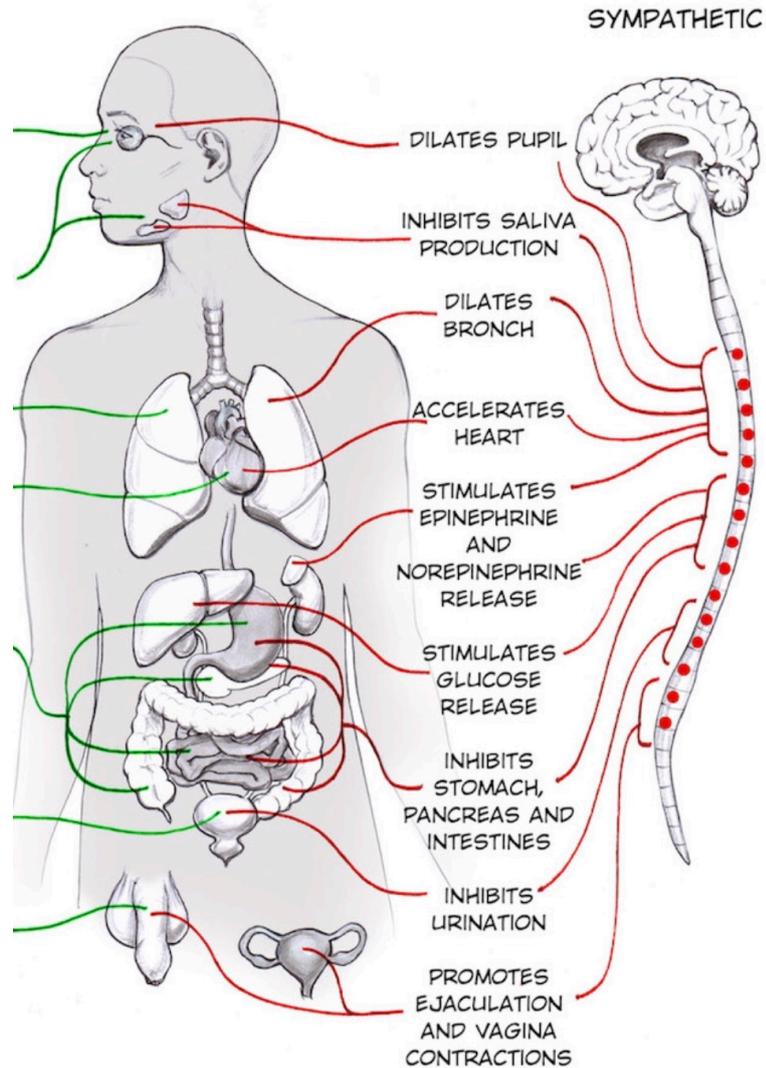
Moreover, lack of sleep reduces your innate immunity via activation of your sympathetic nervous system RAS/SNS.

<https://jasn.asnjournals.org/content/28/5/1350>

💡 Light 💡

The sympathetic nervous system is responsible for priming the body for action, particularly in stressful situations threatening survival - predators or prey, fight and flight, the search for water and food.

From an evolutionary perspective it makes sense that light should activate the SNS in preparation for dealing with the events of the day. By dilating the pupil more information from the environment is collected in order to deal with the stressor.



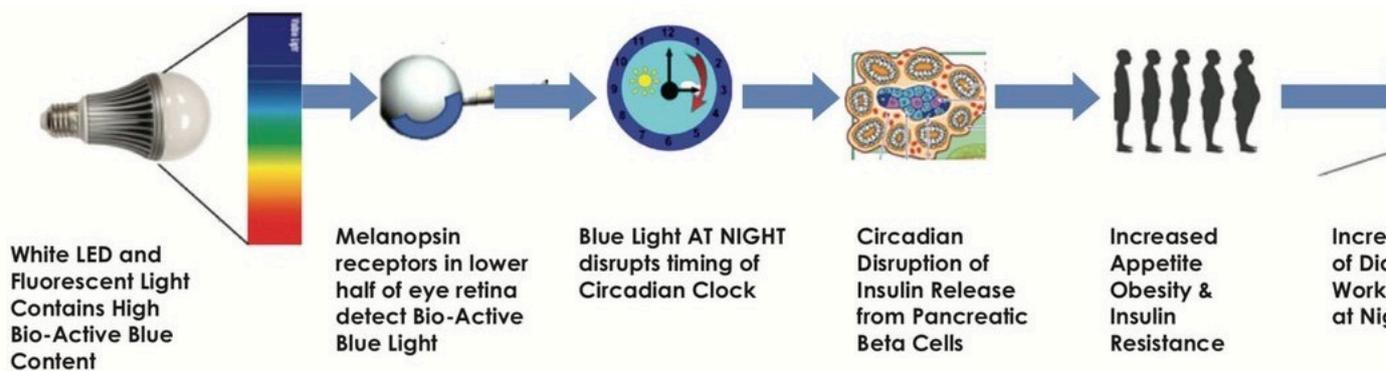
What is not recognised as much is that emotional stress can also dilate the pupil.

Most people understand that bright light causes the pupil to constrict, again as a defensive mechanism to prevent too much light damaging the retinal cells. However, what is often forgotten is that white light is comprised of all the colours of the rainbow and one of these colours is Blue light.

Blue light actually stimulates the SNS via its action on S-cone cells in the retina and so elicits a stress response.

Some cells in the retina contain light sensitive receptors that can specifically detect blue light - these are called melanopsin and they report back to the Master Clock in the brain - the Suprachiasmatic nucleus (SCN) - which essentially tells all the other cells in the body what time it is and sets the circadian rhythms.

NB Melanopsin receptors are also located in fat cells, skin and capillaries.



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

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

<https://www.scientificamerican.com/article/eye-opener-why-do-pupils-dilate/>

[https://www.sciencedirect.com/science/article/abs/pii/
S0014482717301490?via%3Dihub](https://www.sciencedirect.com/science/article/abs/pii/S0014482717301490?via%3Dihub)

↑ Blue — ↓ Melanopsin — SCN (Brain) — ↑ PER2

↔ — ↑ HIF-1 — Met Syn

↑ Blue — ↓ Melanopsin — ↓ Melatonin — ↓ Sleep — ↓

Immune function

Here we have a very interesting evolutionary connection between light and sleep (dark) which links HIF-1 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.

Interestingly, recent studies in chronotherapy have highlighted the benefit of taking certain blood pressure tablets at night time to reduce the risk of heart attacks and strokes (45% reduction).

<https://www.sciencedaily.com/releases/2019/10/191022210216.htm>

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 batteries you need for life.

Furthermore, given that artificial light at night (ALAN) suppresses melatonin production and therefore has an adverse effect on sleep and the immune system, it would make sense to limit your exposure to light at night.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4375362/>

<https://www.forbes.com/sites/fionamcmillan/2018/08/11/how-blue-light-damages-cells-in-your-eyes/#7498ec95384b>

Limit Screen time on; Mobiles, Pads, Computers etc at night - This is a Stress to the system.

High resolution screens give off predominantly blue light, which is what makes them so clear and bright - this signals to the brain via the retinal suprachiasmatic pathway (eye - brain) that the time is midday and not time for sleep, so melatonin production is stopped.

Consider switching to Night time mode on screens.

Or

Blue blocking glasses which filter out the blue light.

Diet.

I am not a fan of supplementation with anti-oxidants, I think that is best left to the body to decide what it needs by giving it a range of nutrient dense unprocessed foods.

Nor do I wish to go into the pros and cons of different diets - we each have individual needs and preferences, making it very difficult to be prescriptive.

That said, there is some limited evidence that a Ketogenic diet can boost T - cell immunity against viral infections, and might be worth considering during this period.

<https://www.newscientist.com/article/2223688-eating-a-keto-diet-may-give-some-protection-against-the-flu/>

Furthermore, in the context of pseudo/hypoxia at a cellular level, eating a higher proportion of healthy fats may help to reduce ROS damage/inflammation by “burning off” more oxygen.

What you don't want to be doing is eating a high calorie, high sugar and fat “Junk” food diet, which feeds the virus.

<https://www.sciencedaily.com/releases/2013/12/131215160856.htm>

Strategy 3 - Tolerance. This is a characteristic of a robust system which has the capabilities to withstand severe stresses.

Direct energy to where it is needed:

AMPK is an important Energy sensor in the cell and helps to ensure energy is directed to where it is needed.

Increasing AMPK could be a key tactic in reducing energy supplies to the virus and preventing replication, because, viruses can only survive and replicate by using the machinery and metabolism of your own cells.

https://www.researchgate.net/publication/304016832_The_role_of_AMPK_in_viral_infection

For a full and comprehensive list of AMPK activators I would recommend reading this:

<https://selfhacked.com/blog/natural-ampk-activators/>

My own tactics include:

Intermittent Fasting /Calorie restriction - reduce glucose and PUFA

Exercise - short bursts of high intensity exercise (5 min max) - don't overtrain or risk injury.

Reduce caffeine consumption - depletes thiamine

No alcoholic binges - depletes thiamine - one or two alcoholic beverages in evening if helps with relaxation - ensure alcohol free days to avoid tolerance and addiction.

Drink lots of high quality water.

Conserve Energy.

This involves relaxation to increase Parasympathetic Nervous System activation as a counterbalance to Stress.

Avoid Negative emotions.

Anxiety, Anger, panic & fear, frustration and sadness etc - All activate the SNS and drain energy.

NB. Watching distressing News items all day long is not going to help!

Focus instead on:

Sleep

Relaxation

Meditation

Diaphragmatic breathing

Yoga

Hypnosis

Mindfulness

Exercise

Laughter

Take a walk in the park.

Lay in the Sun to boost Vit D - important for the immune system.

Anything that helps you to relax.

If you develop mild symptoms do not panic.

Do not take ibuprofen or paracetamol for reasons already outlined.

Rest and relax as much as you can - Keep stresses to a minimum to allow your energy to be focussed on fighting the infection. Do not overeat or consume junk food and get as much sleep as you possibly can in complete darkness.

In Conclusion.

Stress - any stress, causes an increase in glucose, it's part of your body's "fight and flight" response (ACE2 involvement), to ensure energy is available to deal with the problem.

This energy (glucose) is used by the virus to replicate. This is why the most at risk are those under most metabolic stress - hypertensives, diabetics, obese people and frontline medics.

This is a multi-system non linear thermodynamic problem, involving crosstalk and misunderstandings/mistiming, between the nervous system, immune system, metabolic system and microbiome, triggered by the biggest stress of all to an aerobic organism - hypoxia.

And when oxygen is low and stress levels are high, it doesn't take long for the energy to drain and the body to die!

In many ways the solution is as simple as the problem, but it requires a realisation, a willingness, cooperation and a common purpose, which all functional systems and successful teams should possess.

However, when a world is dominated by greed and fear, and where a grotesque fakeness pervades every aspect of modern life, it becomes extremely difficult to see the wood for the trees.

And the truth is, people really care more about how they feel and what they themselves are doing, than what someone else tells them to do.

Any change must first start with the individual, because as Gandhi so eloquently said; " if we could change ourselves, the tendencies in the world would also change. As a man changes his own nature, so does the attitude of the world change towards him."

Moreover, to find the truth we must look as much outside as in, because the environment is always the instigator of any change.

And, if we can show that little extra love and respect to nature's laws and values, then maybe just maybe, it will supply us with the energy we need for a long and productive life!

Chinese Whispers, Deadly Consequences!

Chinese Whispers is a game in which one person whispers a message to the person next to them and the story is then passed around the group, with inaccuracies accumulating as the game goes on, until you end up with a nonsense story that bears little resemblance to the original message.

With Covid-19, the message is the virus, which is getting passed around from person to person and each individual is interpreting it differently, based upon their own immune system and metabolic health.

A healthy immune system would interpret it clearly as a threat, and kill it without passing the message on.

An older immune system doesn't hear it quite so well, and allows it to enter the cell, whereupon a different message is communicated - the one for energy and materials for replication - a veritable hijacking of your metabolic teams.

Once again a healthy flexible metabolic system should be able to block this signal by switching to an alternative source of fuel (fats) and deprive the virus of the oxygen it needs to reproduce - glucose.

Unfortunately, modern lifestyles and polluted environments have left many people metabolically challenged, deficient of the energy they need for a vigorous and vital life.

When energy/oxygen levels are low in the batteries of life (mitochondria), another false memo gets circulated around the body - a stress message called pseudo hypoxia - which dictates that although oxygen levels haven't actually fallen, the body thinks they have, and reacts accordingly.

A mistaken plea for more energy production is then transmitted to certain departments of the body and they start producing more and more glucose in a process known as gluconeogenesis.

Yet again, when this occurs, either for too long or at the wrong time, it triggers another cry for help, this time to the beta cells in the pancreas to start producing more and more insulin and if this persists for any extended period - the next misinterpretation is made.

The muscle cells are informed to shut up shop to conserve valuable energy, which they obligingly do by playing a defensive tactic called insulin resistance.

By cutting down the muscles ability to use up energy stores - the body is ensuring enough glucose is available for more important areas on the pitch - the heart and brain.

We are now left with a game situation in which energy levels are low, immune system functioning is compromised, and the body's ability to defend against an attack is severely weakened, yet energy stores (fat) are abundant and fuel supplies (food) are plentiful!

So what then happens when the virus enters this deadly game of Chinese whispers?

It gets into the lung cells, causes localised damage and reduces oxygen availability (actual hypoxia).

The final message is now loud and clear - This is a full blown emergency - fuel supplies cannot meet demand - we must go to War or die!

This is the signal that the SARS Covid 2 virus makes to a metabolically challenged body - Severe Acute Respiratory Syndrome.

The tragedy being, that what originally started out as a simple message from a novel virus, has ended up creating death and destruction on a Worldwide Scale!

We need to find a better way to listen to what the environment is telling us, because Chinese Whispers is not a game most teams are well equipped to play!

Appendix.

Thoughts on treatment

Azithromycin reduces LPS therefore has anti-inflammatory effects.

Other antibiotics that reduce LPS include tobramycin gentamicin ciprofloxacin

Hypoxia —  HIF-1 —  LPS —  TLR (4) —  Innate immunity — Cytokine storm

SARS-CoV MA15 infection stimulates TLR4, which is classically known as the lipopolysaccharide (LPS) receptor”

This suggests that investigation of anticomplement drugs for treatment of coronavirus infections is worth exploring.

Azithromycin —  LPS —  TLR —  Immune Response —  Damage

<https://www.sciencedirect.com/science/article/pii/S0161589018301986>

<https://www.sciencedirect.com/science/article/pii/S0925443915000721>

Which may be one of the ways hydroxychloroquine has some therapeutic anticomplement along with its anti-thrombotic properties.

https://www.researchgate.net/publication/254259949_Antithrombotic_effects_of_hydroxychloroquine_in_primary_antiphospholipid_syndrome_patients

Heparin is another anti complement anti thrombotic treatment
https://www.researchgate.net/figure/Anticomplement-activity-of-heparin-Antiphospholipid-aPL-antibodies-activate-complement_fig2_6698717

The administration of oral proteins or intravenous amino acids in the awake state is accompanied by an approximately 20% increase in energy expenditure and heat production.

<https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1922558#>

High flow oxygen in the setting of high temperature (Bohr effect) can be creating more ROS and inflammation (cytokine storm) in cardiovascular system.

? Hypothermia - to reduce metabolism/ROS/Cytokine storm.

Hypothermia - UCP1 in mitochondria “burns off” excess ROS to generate heat - therefore reduces stress in cell.

Cold —  Norepinephrine —  UCP1 —  Heat — 
ROS —  Inflammation

It uncouples the electrochemical gradient from ATP synthesis

Vit C —  SVTC1 + SVTC2 receptors —  HIF-1

<https://pubmed.ncbi.nlm.nih.gov/20380593/>

<https://pubmed.ncbi.nlm.nih.gov/17541511/>

Thiamine

Melatonin.