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H_2S Induced Animation/hibernation–the Existence of Two Eukaryotic Metabolic States.

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Hibernation is a common metabolic state among many different groups of mammalians characterized by slow heart rate, decreased body temperature and reduced metabolic rate. However, similar states are also observed in insects, amphibians and fish during hot or dry periods, including for the deeply branching lung fish (lung fish are thought to be related to the first fish that went ashore from the primordial ocean as ancestor(s) to mammals, birds, amphibians and reptiles). Indeed, plant seeds and fungi spores might be considered dormant stages of these organisms that are similar to hibernation.

Interestingly, studies have shown that a hibernation/animation like state can be induced in mice and rats, by exposing them to either H_2S gas or by injection of a compound that is converted into the gas H_2S by cellular enzymes (H_2S is the gas that we associate with the smell of rotten eggs, and can at high concentrations be lethal) (1,2). These cellular enzymes also normally function to produce low but steady state levels of H_2Sin some tissues,mainly by using the amino-acid cysteine as a substrate.In these two studies, a similar reduction in hart-rate, drop in body temperature and metabolic ratewas observed as is observedas during hibernation.

Another interesting study of blood vessels has shown that hypoxia and H_2S produce temporally, quantitatively identically (variation between species but not with regard to the hypoxia and H_2S responses) and competitive responses in all vertebrate classes, suggesting that the hypoxia/H_2S response is a primordial feature of the earliest vertebrate vessels (3, 4).Also, Searcy (ref 4) notes that H_2S is the energy source of cren-archaeotathat eukaryotes originated from. archaeota; one of the ancestral prokaryotic organisms that eukaryotes originated from."

Indeed, combined these observations and results are consistent with that there for eukaryotic cells, including mammalian cells, exist two metabolic states that reflect our deepest evolutionary origin-when eukaryotes were formed as a fusion between a cren-archaeal cell and a purple bacteria (the latter evolved into the mitochondria). This ancestral cell was the ancestor of all the three phylogenetic kingdoms; plants, fungi and animals.

Importantly, cren-archaeal organisms live in, and originate from, H2S rich environments (volcanic springs); a type of environment also present during the early periods of the evolution of life on earth.".As mentioned above, H_2S is the molecule that cren-archael cells utilize for energy (ATP) production. Later, with the evolution of photosynthesis and plants, the earth atmosphere changed as O_2 concentrations increased, allowing respiring organisms, such as mammals, to evolve and thrive. However, the ancestral metabolic state of the cren-archaeal cell with the capacity to utilize H_2S as an energy source and function in an environment with low O_2 levels might be the explanation for hibernation and potentially underlie many cellular processes in our body. Many of our cells and tissues experience hypoxic environments, either intermittent or more permanently, and have to respond and survive accordingly. Eukaryotic cells are chemical systems with dissolved gasses (CO, H_2S, CO_2, NO, O_2) and the interplay between H_2S and O_2 may play an important role in regulating the shift between the proposed cren-archaeal metabolic state and the aerobic (normoxic) state. While O_2 is absorbed from the air we breathe, H_2S is generated by the cells. However, both O_2 and H_2S can diffuse freely within the tissues. Furthermore, both gasses can in the mitochondria act as substrate for cytochrome C, involved in the generation of ATP (5-8). Most likely, at high O_2 concentrations, a high-energy state is present that is characterized by a high metabolic rate, but also with associated oxidative damage due to the high redox potential of O_2. However at low O_2 concentrations, the H_2S present, will pull down the redox potential of the system, reducing the metabolic rate as well as the oxidative damage,

while acting as the electron donor for cytochrome C. Potentially, the tissue damage that we know occur at reduced levels of oxygen, could be due to that the cells experience a concentration of O_2 between the two metabolic states. This could be dangerous for the cells, as both "metabolic states" will be active/inactive.

Furthermore, the low metabolic state induced by the cellular H_2S generation might play central role during differentiation and development; damaged tissues have poor blood supply and healing involves cellular differentiation including angiogenesis; similarly in the developing fetus, the supply of O_2 in newly formed tissues is low as blood vessels develop subsequently.

An interesting question is of course whether it is possible to induce hibernation in humans (in animals hibernation might be induced by the carotid body in the brain). The potential health advantage of this could be significant. The reduced heart rate could limit blood loss in case of injury; brain damage due to stroke could be limited; heart attach victims chances of survival could potentially increase; hibernation could potentially be used as a form for anesthesia during operations, as well as, during the initial subsequent healing process. Indeed, hibernation might even be used to treat some cancers. Cancer is due to cells dividing uncontrolled, and involves the cells being in a high metabolic stage; one piece of evidence that support this is that inhibiting angiogenesis (oxygen supply) within tumors prevents tumor growth and spreading. Potentially, by inducing the low metabolic state of hibernation, tumor cells will be unable to adapt and die.

It is still early days for this research field, and many questions have to be answered, but the potential for human health is breathtaking.

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