The jumping Frenchmen of Maine and the ineluctable requirement of molybdenum

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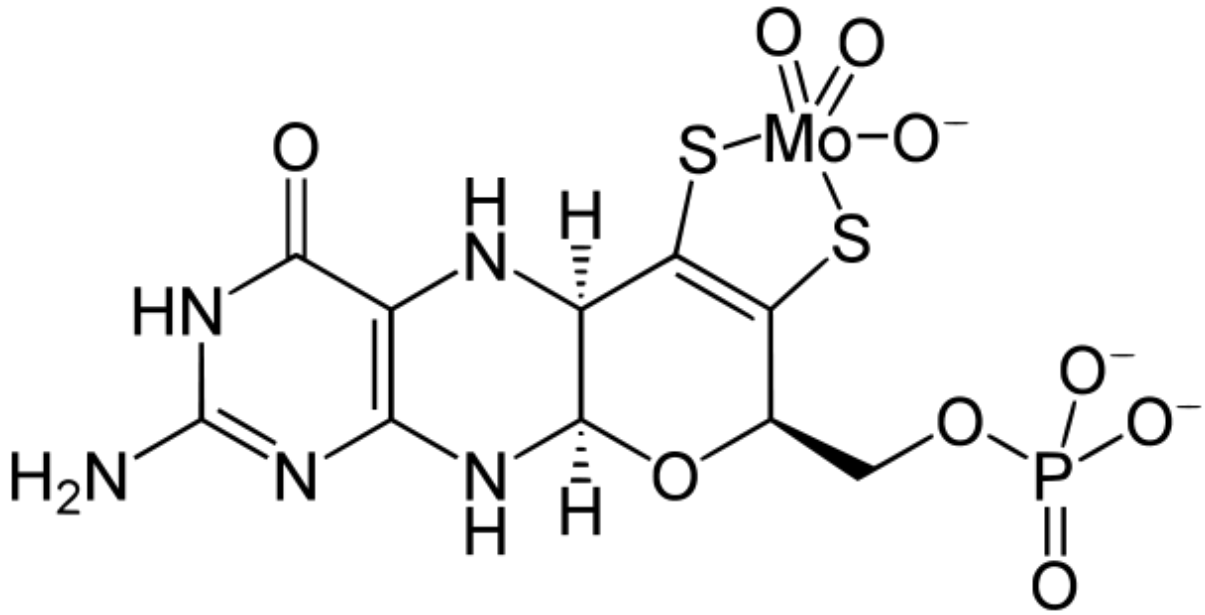

One form of MoCo cofactor: the molybdopterin ring structure with its Mo ion

(Phys.org)—The *Jumping Frenchmen of Maine* is a puzzling neurological syndrome named after a few peculiar 19th-century lumberjacks. Their defining symptom was an unnaturally exaggerated jumping reflex when startled. Georges Gilles de la Tourette included the disorder in his famous 1878 description of convulsive tic disorder, but to this day, its exact cause remains unknown. Among the many informative anecdotes associated with these particular French Canadians from Moosehead

Lake, was that they could be inexplicably made to strike a dear loved one provided their agitator commanded it loudly enough.

This insufficient or otherwise laggy inhibition of behavior has been linked to genetic alterations in various components of inhibitory neural transmission. One protein implicated here is known as gephyrin, which comes from Greek for the word 'bridge'. It's presumed occupation in synapses is to cluster gaba and glycine receptors to each other, and to the cytoskeleton. A curious thing about gephyrin is that it moonlights in another critical, if sometimes enigmatic role: it sits at the apex of a complex molybdenum cofactor synthesis chain, and pops a single Mo ion into the molybdopterin backbone ultimately used in least four human enzymes.

Lurking beneath this ostensibly more ancient Mo insertion skill of gephyrin is a more sweeping Mo culture that has only recently been uncovered. According to Michael Russell from NASA's Jet Propulsion Lab, there may likely have been an 'ineluctable requirement' for this second-row transition metal, and perhaps its column VI tablemate tungsten, at the origin of life itself. As Mo is the heaviest essential element we require (significantly heavier than Fe), it isn't bred in standard stellar fusion reactions. The nucleosynthesis of Mo occurs at much higher energies in rapidly spinning gas giants and supernova explosions. It may therefore be the case that not just the birth of our solar system, but life on Earth required the eclectic services that local supernova provide.

But this noble birth isn't what makes Mo crucial to life. To understand why our sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime reductase keep Mo on retainer to this day, we need to take a brief foray into the world of metallochemistry, electron bifurcation, and redox potentials. The main task is to identify what functions, if any, which Mo can perform that no other biometal can. But

before that it is necessary to show that Mo was available to life at its origin.

In the bacterial world, Mo, vanadium, and tungsten enjoy some limited degree of interoperability as cofactors. There are over 40 Mo enzymes in prokaryotes, many times more than the few used in us. Workhorses like the nitrogenases, which handle nearly all the global cycling of nitrogen through the biosphere use a special iron-molbdenum cofactor to fix dinitrogen gas. The Complex-Iron-Sulfur-Molybdoenzyme (CISM) superfamily members, which include such dignitaries as the primordial ferredoxins, have ubiquitous, if varied roles among prokaryotes.

While tungsten is rare, it would have been available to early life in both acid and alkaline solutions. Mo, although it is roughly 100 times more abundant, presents more of a challenge due to its insolubility in reduced and neutral waters. As with copper enzymes, geochemists have tended to assume that Mo (and its molybdate oxide anions) would not have been available, or at least soluble until oxygen-creating photosynthesis came on the scene some 2.5 billion years ago. The question of Cu availability raises an interesting point which I asked Russell about. Namely, in order to crown the molydopterin cofactor with its Mo, how did it come to be that gephyrin needs to replace a Cu atom that was pre-bound at an earlier synthesis step?

It is widely accepted that the primitive atmosphere, and by implication the primitive ocean, were strongly reducing due to abundant H2, CH4, and H2S. Russell's solution to the Mo availability problem is that the founding 'cradle-of-life' CISM-catalyzed reactions mentioned above were supplied with Mo by alkaline hydrothermal vents. He and his colleagues were able to reconstruct an enzyme phylogeny using multiple 3D structural alignments to show a likely CISM superfamily origin well before the divergence of LUCA, the presumed last universal common ancestor.

But what is it exactly, that Mo offers? Part of the versatility of the elements Mo and tungsten comes from the fact that they are 2-electron redox compounds—they can shuttle between the +4/+5 and the +5/+6 redox couples. In other words, they can perform diverse and energetically challenging redox reactions. Practically speaking, this means that they can act as an electron sink or source at low redox potential. Furthermore, they seem to be the only elements that can effectively transfer oxygen and sulfur atoms during reactions taking place at low potential.

Recall that redox potential is simply a measure, typically in millivolts, of the tendency of chemical species to acquire electrons and thereby be reduced. A high positive redox potential electron acceptor accepts electrons more readily than one of low potential. Some CISM enzymes can participate in 'crossed-over' redox transitions, which were likely critical in early and energetically challenging reactions. These so-called 'electron bifurcation' phenomena (which we will delve into in more detail in the next post), are now known to play a central role in a wide range of metabolisms, not least being the Q cycle component of the electron transport chain in mitochondria.

A recent paper in *Current Opinion in Chemical Biology* by Guenter Schwarz describes some of the more practical, modern day incidentals of the Mo world. Of note he has been looking for a way to address problems in sulfite oxidase deficiency. Normally this enzyme transforms undesirable sulfite to sulfate by passing electrons from sulfite sequentially to its MoCo (Mo cofactor), then to its haem cofactor, and then ultimately to its terminal acceptor, cytochrome c. For a patient that might have a malformed or ill-placed oxidase, Schwarz is working on a replacement enzyme which lacks the haem. In this case, the enzyme behaves like the plant version and passes its electron to a terminal molecular oxygen.

It's not just in normal metabolism of sulfur-containing amino acids like methionine and cysteine that sulfite oxidase is critical. The current use of sulfur dioxide in food preservation and winemaking persists today in an unbroken tradition dating back to the early Egyptians and Romans who used fumes from burning sulfur as a sanitizing agent. The uptake and transport proteins our bodies use to bring in Mo from the environment, and distribute to various compartments within the cell does a fair job of discriminating between the similar sized sulfate and molybdate ions. Without proper handling, excess sulfite can lead to severe reaction.

Similarly, problems with the xanthine oxidase system (or its MoCo units), can disrupt the normal metabolism of certain nucleotides into uric acid. One interesting part of MoCo synthesis is that it all begins in the mitochondria using the nucleotide GTP. Various enzymes 'cycle' the GTP, transforming its ribose into part of the canonical pterin ring structure that is so ubiquitous to the cofactors favored by early metabolisms. Pterins, named for the Greek word 'pteron', meaning wing, were first discovered in the bright pigments of butterfly wings.

As for the gephyrin problems we originally mentioned, and the 'stiff man' and related symptoms which can result, the jury is still out. It may seem now that the issue is entirely due to the synaptic functions; a result of errors in the various exon cassettes used to construct and target gephyrin to receptors, or to antibodies subsequently made against the protein. MoCo units don't even seem to be made in neurons—culture studies show their synthesis only occurs in astrocytes. However, the story of how the MoCo protein that sits atop the synthetic pipeline came into its critical new synaptic organization role likely holds a few more secrets.

More information: Guenter Schwarz, Molybdenum cofactor and human disease, *Current Opinion in Chemical Biology* (2016). DOI: 10.1016/j.cbpa.2016.03.016

Abstract

Four molybdenum-dependent enzymes are known in humans, each harboring a pterin-based molybdenum cofactor (Moco) in the active site. They catalyze redox reactions using water as oxygen acceptor or donator. Moco is synthesized by a conserved biosynthetic pathway. Moco deficiency results in a severe inborn error of metabolism causing often early childhood death. Disease-causing symptoms mainly go back to the lack of sulfite oxidase (SO) activity, an enzyme in cysteine catabolism. Besides their name-giving functions, Mo-enzymes have been recognized to catalyze novel reactions, including the reduction of nitrite to nitric oxide. In this review we cover the biosynthesis of Moco, key features of Moco-enzymes and focus on their deficiency. Underlying disease mechanisms as well as treatment options will be discussed.