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> ONE MONTH, ONE PROTEIN <

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why dung?

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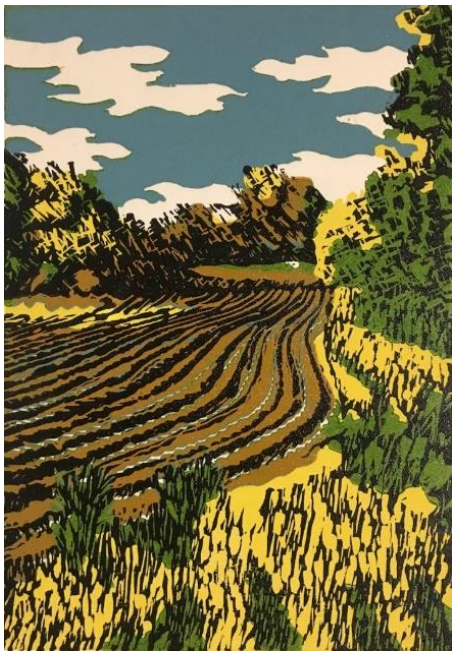
Who hasn't gone out for some fresh air and been incommoded by the pungent smell of manure? Why have farmers been flinging dung on their ploughed fields for thousands of years? The answer is nitrogen. Though our ancestors were unaware of the chemistry involved in their actions, they did realise that what livestock excreted – urine and faeces – was good for their crops. This is because animal urine is full of urea, which is full of nitrogen. When livestock faeces and urine is mixed, the faecal enzyme urease breaks down the urea to release carbon dioxide and the nitric compound ammonia, which is volatile. That's the stench. Ammonia is fixed by plants, which then use it to form compounds as fundamental as DNA, RNA, ATP and amino acids. In animals, or humans for that matter, ammonia is actually a waste product and can be toxic at high levels. Our liver deals with this toxicity by transforming ammonia into urea. But it is not the only way to deal with this compound. Scientists discovered that the enzyme glutamine synthetase can also render ammonia harmless by transforming it into glutamine.



PLOUGHED FIELD, NORTH NORFOLK

Jeremy Bevan
courtesy of the artist

Nitrogen is the most abundant element in the Earth's atmosphere, forming over 75% of it. So it comes as no surprise that, with several other elements too, life on this planet is based upon it. DNA, RNA, ATP and proteins all rely on nitrogen in different forms: namely nucleic acids and amino acids. Without these fundamental molecules, life would have no way of existing. And thanks to them, life has been able to keep going for the best part of 4 billion years. That's a very successful achievement. Some nitrogen is found in the Earth's crust where it is far less abundant, however. The nitric compounds commonly known as smelling salts (ammonium nitrate) and saltpetre (potassium nitrate) were mined until the industrial revolution. Today, both nitrates are produced industrially. Potassium nitrate changed the course of human society as it became the major component of gunpowder and hence explosives. Today, it is still used in fertilisers and for fireworks but also for quarrying and demolition for example.

Discovered by the Scottish physician Daniel Rutherford in 1772, nitrogen was first called '*noxious air*'. The French chemist Antoine Lavoisier preferred to refer to it as '*azote*', from the Greek meaning 'no life'. Towards the very end of the 18th century, the French chemist Jean-Antoine Chaptal suggested '*nitrogène*', meaning 'producing potassium nitrate'. Funnily enough, nitrogen stuck in the English language while '*azote*' continues to be used in French. Animals and humans alike do not use atmospheric nitrogen because it comes in the form of N_2 which is particularly difficult to split and we lack the metabolism to do that. So we get it from the food we eat. As our organism digests the nucleic acids and proteins our meals provide, ammonia builds up. Just like livestock, our liver transforms the toxic ammonia into urea which is excreted in our urine. But something else

is also helping to detoxify ammonia: glutamine synthetase.

Also sometimes called glutamate ammonia ligase, glutamine synthetase is found in the human liver but also in the human brain and muscle as well as the male reproductive organs. It seems that, depending on the pH, the liver can switch from the urea cycle to the glutamine synthesis pathway to detoxify ammonia, thereby clearing about two-thirds of the body's ammonia. However, outside the liver, our body can only count on glutamine synthetase to keep ammonia levels low. This has proved to be vital since defects of the urea cycle but also of glutamine synthetase bring about serious conditions such as organ failure, severe brain malformations and skin abnormalities in non-viable embryos for instance. While in adults, too much ammonia can lead to neurological disorders. Why? Because the glutamine synthetase metabolism is intimately linked to that of the brain's neurotransmitters.

Brain neurotransmitters are chemical messengers our brain uses to tell our body to do the hundreds, if not thousands, of things it does on a daily basis – many of which we are barely aware: move, breathe, sleep, remember, smell, see, eat. Neurotransmitters keep our heart beating, our lungs breathing, our thoughts conscious, our feelings alert. As the precursor of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter gamma aminobutyric acid (GABA), glutamine is abundant in the central nervous system. It enters neurons by way of glutamine transporters, where it is converted into glutamate – which can be converted further into GABA. But what does this have to do with ammonia? Glutamine synthetase uses ammonia and glutamate – and a dab of ATP – to form the GABA precursor glutamine. In so doing, it keeps the level of ammonia low in the brain.

Human glutamine synthetase is thought to act as a homodecamer – where five identical subunits bind to form a ring similar in structure to a doughnut, and then two rings are stacked one upon the other. The interface created between two adjacent subunits is expected to harbour one catalytic site. In this way, one glutamine synthetase homodecamer sports no less than 10 identical catalytic sites! Glutamine synthesis and ammonia detoxification seem to occur in a two-step fashion. ATP is thought to bind to the catalytic site first, where it induces conformational changes needed to bind glutamate. Once ATP and glutamate are in place, the terminal phosphate (P) group of ATP is handed over to glutamate. This yields ADP and ɣ-glutamyl phosphate (GGP). Ammonia than attacks GGP – and glutamine, ADP and P are released.

It is not difficult to grasp, then, that if glutamine synthetase is deficient, not only will the brain be lacking in vital neurotransmitters, but the level of ammonia will become toxic leading to yet further complications. This explains neurological disorders in adults suffering from hyperammonemia, which can also arise from liver dysfunction (though it is thought that the brain is affected in different ways). Certainly, glutamine synthesis and ammonia detoxification are intimately bound to one another – both in the liver (where the urea cycle also steps in) and in tissues outside the liver. A greater understanding of glutamine synthesis as a whole could well help to find novel drug targets for patients suffering from body levels of ammonia that are too high.

Cross-references to UniProt

Glutamine synthetase**,** *Homo sapiens* (Human) : P15104
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