proteinspotlight
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Issue 56, March 2005

www.proteinspotlight.org

Forbidden fruit

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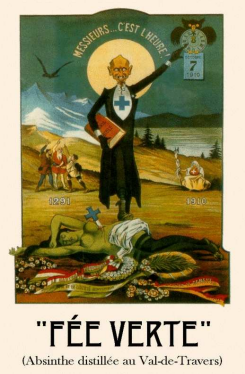
After a century's ban, Switzerland has legalised the production of absinthe – the emerald-green liquor which was said to have caused the madness of many throughout the 1900s, one of whom was the Dutch artist Vincent van Gogh. The beverage is prepared by macerating a cornucopia of spices and herbs such as aniseed, fennel, hyssop, lemon balm, angelica, star anise, dittany, juniper, nutmeg, veronica and wormwood oil in alcohol. It is hardly surprising that, upon abuse and on a long-term basis, such a mixture of chemicals should have an undesirable effect on our system. Nevertheless, at the dawn of the 21st century, a greater understanding of absinthe's claimed toxicity is surfacing and fingers are pointing at thujone, a terpenoid found in wormwood oil. Besides lending absinthe its particular flavour, thujone has the ability to bind to receptors in our brain – gamma-aminobutyric acid A receptors or $GABA_A$ receptors – which can bring on a number of brain disorders.



The ban of absinthe

Towards the end of the 18th century, Switzerland was the major producer of absinthe but its abuse spread fast around the rest of Europe and North America. Like opium, it became popular amongst artists and writers probably because of its antidepressant qualities and its ability to provoke hallucinations, besides the popular misbelief that the concoction had aphrodisiac attributes. The beverage became an icon of the Bohemian style of life and, in Paris, the end of afternoon apéritif was commonly known as *l'heure verte*. Strangely enough, though absinthe was dubbed *la fée verte*, in Switzerland it was – and still is – called *la bleue*. By the end of the 19th century, hoards of criminal acts and psychic disorders were blamed on the abusive intake of absinthe and, by 1910, it was banned altogether in most European countries and America. Despite this, Switzerland has continued to produce the liquor illegally and it has always been possible to find some through the friend of a friend of someone who knows of a hidden distillery.

The symptoms brought on by an exaggerated consumption of absinthe came to be known as 'absinthism', which may not be so far removed from its cousin 'alcoholism'. Absinthism was associated with gastrointestinal problems, auditory and visual hallucinations, epilepsy, brain damage, an increased risk of psychiatric illnesses and suicide. However, in time it has become apparent that the effects of ethanol – found in greater quantities than wormwood oil in absinthe – are just as damaging and that no doubt the combination of wormwood oil, or its toxic component thujone, coupled with ethanol is to blame.

What is it that makes thujone toxic to our system? $GABA_A$ receptors are scattered all over our brain on the surface of postsynaptic neurons. Their ligands – the GABA neurotransmitters – are natural inhibitors of nerve impulses; without them neurons go haywire and signals are fired off unhindered. When GABA binds to its receptor, what it does is trigger off an electric signal which is relayed down the length of the neuron. If any thujone is present however, it will bind to the $GABA_A$ receptor and stop transmission, causing convulsions. In fact, it is now known that many natural or synthetic convulsive agents block GABA-mediated inhibition.

How is this electric signal relayed? $GABA_A$ receptors are pentamers of three kinds of subunits: two alphas, two betas and a gamma, and besides playing the role of receptor, they are also ion channels. Each subunit has an

extracellular domain that carries a number of loops which form the $GABA_A$ receptor site. Further down are the transmembrane regions which are arranged as alpha helical rods. The binding of GABA to the receptor site results in a rearrangement of the alpha helical rods which open up to form a channel through which ions can pass.

How this conformational change occurs is not clear yet, but researchers think that when GABA binds to the loops, these take on a slightly different structure causing them to bend over and couple with specific domains in the transmembrane region. In turn, this particular coupling brings on structural changes to the alpha helices which open out to form a pore. Such a mechanistic interpretation of neurotransmission seems sensible from an energy point of view since the process is fast and reversible. Any greater structure movement would be too demanding.

GABA opens up the channel. What does thujone do? The opening of the channel is probably prevented so that the ions cannot flow through. Hence the message is not sent off and nerve impulse transmission is not constrained.

Wormwood oil has been used for millennia as a means of alleviating digestive pains caused by gastrointestinal worms. It is also used as an insect repellent. How does it work? There are great chances that the active ingredient of wormwood oil – thujone – is toxic in the same way to insects and worms as it is to humans, and that they too are subjected to convulsive fits when thujone binds to the brain GABA receptors. A number of inherited mutations within the GABA receptors are associated with human diseases and, not surprisingly, GABA receptors are the site of action of many drugs of current clinical importance. So a keener understanding of their function is essential. We already know that the alpha and beta subunits are essential for ligand binding, and the beta subunit is not only important for ligand recognition but also has a role in the 'loop-transmembrane' coupling process.

Regrettably, perhaps, as the ban on absinthe is being raised and the accusative finger on its toxicity lowered, some historians believe that a nation's folklore will suffer. In the past 100 years – like anything banned – absinthe had become a forbidden fruit and many tales were told around the dinner table as one sipped an illegal '*bleue*'. And a forbidden fruit you pluck from a tree is far tastier than the one you pick from a bowl.

Cross-references to Swiss-Prot

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Gamma-aminobutyric-acid receptor beta-1,2 and 3 subunits, *Homo sapiens* (human) :
P18505, P47870, P28472 resp.
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Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).