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Nature's junkie

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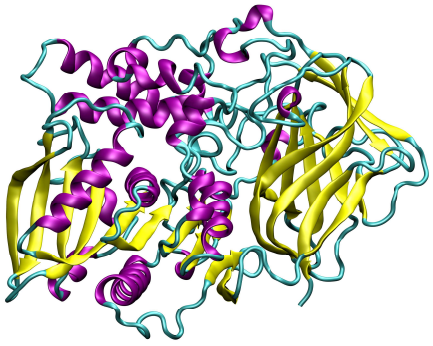
Humans are not the only mammals to indulge in cocaine. A particular strain of the bacterium *Rhodococcus* does too. In fact, it thrives on it. Not for the same reasons however. For this drug-consuming *Rhodococcus*, cocaine is the sole source of carbon and nitrogen. Scientists were led to it whilst rummaging in the soil, which surrounded the roots of coca plants, in their pursuit for a subtle drug detector. The bacterium revealed an enzyme – cocaine esterase – which is at the heart of cocaine metabolism. Cocaine esterase may well offer cocaine trackers a very fine drug sensor and could be used in emergency cases for cocaine overdose.

Cocaine is found in the leaves of the coca plant, *Erythroxylum*. South Americans have been chewing on this leaf for thousands of years, benefiting from the stimulatory effects of its juices which relieve altitude sickness, hunger and fatigue. Chewing on coca leaves became such a natural part of South American behaviour that 'a chew' actually became a measure of time and distance; the distance between A and B was given in so many coca leaf chews. When the Spaniards stepped onto South American soil, they chose to banish the traditional diet of coca leaves though it was given to their slaves – who worked in the precious metal mines – to increase productivity. Coca leaves crossed the Atlantic in the 16th century but the active alkaloid, cocaine, did not become really popular in Western Europe until the end of the 19th century.

Cocaine is a natural insecticide for the coca plant and is a tropane alkaloid. For *Rhodococcus*, cocaine is food. Thanks to its cocaine esterase, *Rhodococcus* splits the alkaloid to produce two metabolites – ecgonine methyl ester and benzoic acid – from which the bacterium ultimately extracts carbon and nitrogen. Cocaine esterase is a globular enzyme of roughly 600 amino acids. Typically it is characterised by three different structural domains: a canonical alpha/beta hydrolase fold (DOM1), an alpha helical fold (DOM2) and a 'Swiss-roll like' beta fold (DOM3) which hugs the two other domains. The 'Swiss-roll' domain, which interacts generously with the two other domains, may act as a kind of scaffolding for the overall 3D structure of cocaine esterase. The point at which all three domains interact is the actual active site. Here a small cleft is formed where the benzoyl moiety of cocaine is lodged and then cleaved to form the cocain metabolites: ecgonine methyl ester and benzoic acid.



Cocaine esterase

Courtesy of Fabrice David, SIB Geneva

The active alkaloid was isolated in the 1850s by a German chemist, Albert Niemann. In the 1880s, the Austrian psychoanalyst Sigmund Freud (1856-1939) took a growing interest in it and drew attention to its manifold merits. Amongst these was the use of cocaine as a mental stimulant or local anaesthetic, or as a treatment against digestive disorders or even morphine and alcohol addiction. It did not take long for cocaine to become the new panacea and

to replace its contemporary – Venice treacle or Theriaca – a potion of over 70 drugs, pulverised and mixed together with honey.

Colossal fortunes were made. The Corsican entrepreneur Angelo Mariani (1838-1914) added cocaine to a Bordeaux; Vin Mariani was a huge success. It became particularly popular amongst artists: Jules Verne, Sarah Bernhardt and Robert Louis Stevenson to name but three. In the United States of America, the pharmacist John Styth Pemberton (1832-1888) concocted his own version of Vin Mariani and called it 'Pemberton's French wine coca'. Under the alcohol Prohibition in 1886, Pemberton was forced to leave out the wine and renamed his concoction Coca-Cola.

It did not take long before cocaine was discovered to be addictive and even fatal. And Western society has been fighting against drug dealers and the consumption of cocaine for decades. The discovery of *Rhodococcus* cocaine esterase could be a major breakthrough in this field. The need for a highly sensitive biosensor is crucial and *Rhodococcus* cocaine esterase could be just that. Coupled with bioluminescent technology, the enzyme could be used to detect minute quantities of cocaine on people or equipment who are suspected to be involved in dealing.

Cocaine esterase could also be used in instances of cocaine overdose. *Rhodococcus* cocaine esterase is a Ferrari: it can break down cocaine 1000 times faster than any other cocaine esterase. This could make it invaluable in an emergency ward. Injected intravenously, the esterase could clear cocaine from the bloodstream before it reaches the brain. For this, two important issues have to be addressed: cocaine esterase toxicity and life span in the human body. And last but not least, the enzyme also has to shun any immune reaction... For all these reasons, the three-dimensional structure of *Rhodococcus* cocaine esterase needs to be studied closely and it could become a model candidate in drug design.

Cross-references to Swiss-Prot

Cocaine esterase, *Rhodococcus sp.* : Q9L9D7

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