Working together to eliminate cyanide poisoning, konzo, tropical ataxic neuropathy (TAN) and neurolathyrism.

CCDN News

Cassava Cyanide Diseases & Neurolathyrism Network

Issue Number 15, June 2010

Contents

CCDN Coordinator:
Dr. J. Howard Bradbury
EEG, Research School of Biology,
Australian National University
Canberra ACT 0200, Australia
Phone: +61-2-6125 0775
E-mail: howard.bradbury@anu.edu.au

Website:
www.anu.edu.au/BoZo/CCDN

Brain glutathione as a target for aetiological factors in neurolathyrism and konzo

Both neurolathyrism and konzo are associated with the nutritional dependence of human populations on a single plant food. These diseases express themselves as chronic disorders of upper motor neurones, leading to signs and symptoms that are characteristic of motor neurone disease. The plant food associated with neurolathyrism is grass pea, which contains the neurotoxic-N-oxalyl-α,β diaminopropionic acid (β-ODAP). The plant food associated with konzo is cassava, which may contain significant concentrations of cyanogenic glycosides and their degradation products. A monotonous diet of grass pea is likely to generate nutritional deficiencies; it is proposed that one of these, plasma methionine deficiency, may predispose neurones to the neurotoxic effects of β-ODAP. Subjects suffering from konzo also have low concentrations of plasma methionine as a result of a dietary deficiency of this amino acid. However, the plasma cystine concentration is also compromised because cyanide released from cyanogenic glycosides in cassava probably reacts with plasma cystine non-enzymatically. The product of this reaction is the neurotoxin 2-imino-4-thiazolidine carboxylic acid. Since both plasma methionine and cystine are used for glutathione synthesis it seems likely that one common feature that leads to motor neurone death in neurolathyrism and konzo is the depletion of brain glutathione. That deficiencies in dietary sulphur amino acids are significant in neurolathyrism was first proposed by Rudra and Chowdhury[1] and in konzo by Cliff et al.[2]

It is pertinent to revisit, in the diamond jubilee year of its publication, the concept advanced by Rudra and Chowdhury.[1] These authors thought that methionine deficiency formed the backdrop to neurolathyrism and that another factor then precipitated neurodegeneration. If sulphur amino acid deficiency predisposes subjects to the neuropathology observed in both neurolathyrism and konzo, mechanistic research on the toxins contained in grass pea and cassava continues to be justified to determine the major features that constitiute the 'second attack' on human upper motor neurones in these disorders. β-ODAP interacts with many cellular processes; e.g., it is an excitotoxin; it affects mitochondrial function and generates free radicals, which inhibit cystathionine lyase. β-ODAP inhibits the cystine/glutamate x_c^- transporter and is itself transported by the same system; it perturbs intracellular Ca^{2+} homeostasis. Examples of the biological activities of cyanide, include its long established role in inhibiting mitochondrial electron transport, its reaction with cystine to yield 2-imino-4-thiazolidine carboxylic acid, and its role in increasing cytosolic free Ca^{2+} concentrations. In sulphur amino acid deficiency cyanide is metabolised to neurotoxic cyanate, which inhibits glutathione reductase and depletes intracellular reduced glutathione.

With these and other mechanisms affected by β-ODAP and cyanide we still have no clear idea of the likely sequence of events that precipitates the death of motor neurones in neurolathyrism and konzo. It has

been proposed that the mechanism by which plasma methionine concentrations are depressed in human populations stems from the normal physiological response to feeding protein which is deficient in an essential amino acid. If this mechanism is correct, the prevention of neurolathyrism and konzo lies in nutritional supplementation with methionine. Rudra and Chowdhury's own data suggest that, where available, rice supplements would be ideal.[3] Unfortunately, it is unlikely that subjects already chronically affected would benefit from this intervention.

References

[1] Rudra MN, Chowdhury LM, (1950) Methionine content of cereals and legumes. Nat. 166, 568.

[2] Cliff J. Lundquist P. Martennson J. Rosling H, Sorbo B. (1985) Association of high cyanide and low sulphur intake in cassava-induced spastic paraparesis. Lancet ii, 1211-1213.

[3] Nunn PB, Lyddiard JRA, Perera KPWC, (2010) Brain glutathione as a target for aetiological factors in neurolathyrism and konzo. Food Chem. Toxicol., in press

Peter B. Nunn
School of Pharmacy and Biomedical Sciences,
University of Portsmouth, Portsmouth U.K.
shoeman_r@yahoo.co.uk

Predicting cyanogen levels in cassava under future emission scenarios

The concentration of carbon dioxide (CO_2) is increasing in the atmosphere as a result of burning fossil fuels and land clearing. In the past 50 years the concentration has increased from about 340 ppm to 380 ppm, and given the current high levels of CO_2 emissions, is expected to reach 700 ppm by the middle of this century. Because CO_2 is a greenhouse gas, rising CO_2 is usually discussed as one of the forcing agents of climate change. Another important consequence is the direct effect of CO_2 on plants through the process of photosynthesis which in turn affects the nutritional value of plants.[1]

Photosynthesis is the process whereby plants convert CO_2 to carbohydrates using sunlight and water. The enzyme that drives this conversion, Rubisco (Ru), combines the substrate RuBP (a sugar) with either CO_2 (to make carbohydrates), or oxygen (O_2) in an energy consuming process called photorespiration. Rubisco is the most abundant protein on the planet and makes up to 50% of the protein and 25% of the nitrogen in the leaf. If there is more CO_2 in the atmosphere (or less O_2) the production of carbohydrates becomes more efficient and less energy is lost in photorespiration. When an established plant is transferred to an atmosphere that is high in CO_2, the production of carbohydrates and the growth rate increases. This is sometimes called the "CO_2 – fertilisation" effect. However, when plants are established and grown in an atmosphere with enhanced CO_2, they acclimatise to it so that the fertilisation effect is significantly less than was predicted by the short term experiments. The main reason for this seems to be that plants grown at high CO_2 make less Rubisco, reducing the demand for nitrogen fertiliser and allowing the plants resources to be reallocated to other processes.

The immediate consequence for human nutrition from CO_2-acclimation is that leaves and grains of plants using the normal C3 photosynthetic system have 15-20% less protein when grown at about 720 ppm, about twice the amount of CO_2 in today's air. Plants such as maize and sorghum use a different photosynthetic system (C4) and the reduction in protein is about half that. Another less appreciated consequence of the lower protein concentrations is the flow on effect to other herbivore defence compounds such as cyanogenic glycosides.

We grew cassava (MCol 1468) in air with today's concentration of CO_2 (360 ppm), and air containing one and a half times and twice the concentration of CO_2 (550 ppm and 710 ppm).[2] Surprisingly, total leaf nitrogen, used here as a proxy for leaf protein, was actually higher in plants grown in the elevated CO_2 treatments. Leaves of cassava grown at 1.5 times the CO_2 showed only a small, significant increase in cyanogens, but those grown at twice-ambient CO_2 contained two to three times the concentrations of cyanogens, compared with control plants (depending on the type of fertiliser). This means that in the future cassava leaves will be more toxic as the cyanogen: protein ratio almost doubled. The peel also had similar levels of cyanogens and total nitrogen, in plants grown in the future emission scenarios.

The good news is that the tubers had the same concentration of cyanogens, no matter what atmospheric conditions they were grown under. The danger to humans may come from the decrease in protein from other foods such as grains, increasing the overall cyanogen: protein ratio in the diet overall. One serious unexpected finding in our experiment was that the size and number of tubers was much less in the plants grown at elevated CO_2. Those grown at 720 ppm had an 80% reduction in yield overall. Unpublished data for other cultivars supports these results. We do not have a good explanation for this and further experiments are underway. We also do not know what effects temperature and drought will have.

What our research does show is that higher levels of CO_2 in the atmosphere are not necessarily good for plants, and that there may be unexpected consequences for major staple crops. Certainly cassava is not behaving in a way that was predicted by the models developed for other crop plants. It is important that plant breeders continue to monitor the cyanogen levels of their cultivars as well as the yield. as the composition of the atmosphere changes. Equally important is that end users continue to process cassava products thoroughly to reduce the amount of cyanogens in the overall diet.

References

[1] Gleadow RM (2010) Food security in a warming world. *Australasian Science* Jan/Feb 2010, 33-35.

[2] Gleadow RM, Evans JR, McCaffrey S, and Cavagnaro TR, (2009). Growth and nutritive value of cassava (*Manihot esculenta* Cranz.) are reduced when grown at elevated CO_2. *Plant Biology* 11, (Suppl. 1) 76–82.

Ros Gleadow
School of Biological Sciences,
Monash University, Victoria., Australia
ros.gleadow@monash.edu

Correct and incorrect ways to process cassava leaves – A Warning

Processed cassava leaves are used widely in Africa[1,2] as a good source of proteins,vitamins and minerals. However the leaf protein is of poor quality, being short of essential S-containing amino acids.[3] Cassava leaves contain 500-2000 ppm[4] of cyanogenic glucosides (linamarin and a small amount of lotautralin) which are very poisonous to humans. The enzyme linamarase catalyses the breakdown of linamarin to glucose and acetone

cyanohydrin and hydroxynitrile lyase (HNL) catalyses its further decomposition to hydrogen cyanide (HCN) and acetone.

Bokanga[2] found that pounding cassava leaves containing 900-1200 ppm of total cyanide for 15 min reduced the cyanide by 62-72% and their subsequent boiling in water for 15 minutes reduced the cyanide content to < 1%. We found that pounding for 15 min of young leaves from four varieties of sweet cassava containing about 500 ppm total cyanide, reduced the cyanide to 10% and subsequent boiling for 15 min reduced the cyanide content to 0.4%. These results confirm earlier work[2,5] that pounding of cassava leaves followed by boiling is a very good method of removing cyanide from them.

Like virtually all enzymes, linamarase and HNL are inactivated on boiling in water. Thus, if the intact leaves are placed in boiling water these enzymes are inactivated and hence are unable to catalyse the break down of linamarin to HCN. We found that using the same sample of young leaves as above, 25-30% of total cyanide (125-150 ppm) remained after boiling leaves in water for 15 min. Loss of linamarin was due to its solubility in water. There was no further loss of cyanide on subsequently pounding the leaves for 15 min. Clearly, boiling cassava leaves is a very poor method of processing, because dangerous amounts of cyanide (>100 ppm) remain in the leaves. (The World Health Organization safe level for total cyanide in cassava flour is 10 ppm.[6]) This dangerous method of processing cassava leaves is used in the Democratic Republic of Congo and recommended on the internet in many sites.

Based on these studies we issue the following warnings:

1. Under no circumstances should fresh young cassava leaves be eaten without processing, because they contain highly dangerous levels of cyanide (500-2000 ppm).
2. Processing of cassava leaves should be carried out by pounding for 15 min followed by boiling in water for 15 min.[2] Never boil the **intact** leaves in water first, because boiling inactivates the enzymes and dangerous amounts of cyanide are retained in the leaves, which can cause cyanide poisoning and possible death.

References

[1] Achidt AU, Ajayi OA, Bokanga M, Maziya-Dixon B (2005) The use of cassava leaves as food in Africa, Ecol. Food Nutr. 44, 423-435.

[2] Bokanga, M. (1994) Processing of cassava leaves for human consumption. Acta Hort. 375, 203-207.

[3] Ngudi, D.D., Kuo, Y.H. and Lambein, F. (2003) Amino acid profiles and protein quality of cooked cassava leaves or 'saka-saka'. J Sci Food Agric 83, 529-534.

[4] Cardoso, A.P., Mirione, E., Ernesto, M., Massaza, F. Cliff, J. Haque, M.R. and Bradbury, J.H.(2005) Processing of cassava roots to remove cyanogens, J Food Comp Anal. 18, 451-460.

[5] Ngudi, D.D., Kuo, Y.H. and Lambein, F. (2003) Cassava cyanogens and free amino acids in raw and cooked leaves. Food Chem Toxicol. 41, 1193-1197.

[6] FAO/WHO (1991) Joint FAO/WHO Food Standards Programme, Codex Alimentarias Commission XII, Supplement 4, FAO, Rome.

J. Howard Bradbury and Ian C. Denton
Howard.Bradbury@anu.edu.au

Can we meet the first Millenium Development Goal in konzo and lathyrism settings by 2015?

Tens of thousands of people are affected by konzo and lathyrism, two toxico-nutritional neuro-degenerative diseases which persist exclusively among the poorest and most marginalized communities.

Konzo and (neuro-) lathyrism are clinically similar with spastic paraparesis of the legs as a common picture. As of now, there is no geographical overlap in the cultivation and consumption of cassava (*Manihot esculenta*, the causative agent of konzo) and grass pea (*Lathyrus sativus*, the causative agent of lathyrism) and in the occurrence of those two diseases, caused by their prolonged overconsumption. Konzo is only reported in sub-Saharan Africa whereas lathyrism occurs in Ethiopia and the Indian Subcontinent. Lathyrism is now eradicated from Europe where several countries (Spain, Greece, Poland, Ukraine) were affected in the past century.[1,2] Epidemics of konzo and lathyrism usually appear when environmental conditions result in heavy dietary reliance on cassava or on grass pea, respectively. These two crops are high-yielding with relative resistance to abiotic stress such as drought or low fertility of the soil, or to entomological and phytopathological attacks. However, adverse environmental conditions such as drought, demographic pressure, climate change or war forced the poorest populations to live on subsistence farming and to rely almost exclusively on products derived from those two resistant crops and the consequences of this are outbreaks of those two diseases.[2] Both konzo and lathyrism occur almost exclusively among subsistence farmers who consume virtually only the produce of their often marginal land.

These diseases do not travel easily. They are mostly concentrated in settings of extreme poverty and in remote rural areas with a high proportion of people whose income is less than 1 US $ a day at purchasing power parities (PPP) values. The 1 US $ a day at PPP prices is an international poverty line extensively used and computed by the World Bank. This poverty line is supposed to define the inability to pay for food needs.[3] The low commercial value of the products of these subsistence famers has contributed to this phenomenon.

The affected households are poor and often illiterate and have little or no political voice. The proportion of illiterate people is high and these diseases thrive in places with unsafe water, poor sanitation, and limited access to basic health care. These factors also contribute to the underreporting of konzo and lathyrism.

In September 2000, the world's leaders agreed on the Millennium Development Goals (MDGs), committing their countries to exert stronger efforts to reduce poverty, improve education and health levels, achieve gender equality, and environmental sustainability. The first general MDG is to "eradicate extreme poverty and hunger". In particular, target 1 states the goal of halving poverty between 1990 and 2015, the proportion of people whose income is less than 1 US $ a day at purchasing power parities (PPP) values.[4]

Improving conditions to prevent konzo and lathyrism is possible but many countries remain far from reaching the first (UN) millennium development goal (MDG) by 2015, and much of the progress is being eroded by the recent global food price and economic crises.[5] Increasing the commercial value of products from those subsistence farmers could help them to better access more varied and thus healthier diets, and would certainly contribute to the achievement of the UN Millennium Development Goals.

References

[1] Tshala-Katumbay D. and Spencer P.S. (*2007).* Toxic disorders of the upper motor neuron system. In: Eisen A. & Shaw P. (Eds), Handbook of Clinical Neurology, Motor Neuron and Related Diseases. Elsevier, Edinburgh, pp 353-74.

[2] Lambein, F., Diasolua Ngudi, D. and Kuo, Y.H. (2010). Progress in prevention of toxico - nutritional neuro-degenerations. ATDF J. 6, 60-65. <http://www.atdforum.org/spip.php?article351>

[3] Chen, S. and Ravallion., M. (2001). How did the world's poorest fare in the 1990s? World Bank working paper.

[4] Cicowiez, L.G.M. (2005). Meeting the poverty reduction MDG in the southern cone. CEDLAS, document de Trabajo No 23

[5] Fanzo, J and Pronyk, P. (2010) An Evaluation of Progress Toward the Millennium Development Goal One Hunger Target: A country-level, food and nutrition security perspective. World Food Program report

Delphin Diasolua Ngudi ddiasolu@yahoo.com
and Fernand Lambein
Fernand.Lambein@ugent.be
IPBO – Ghent University, Ghent, Belgium

The burden of cassava cyanide-induced disease: estimates for the World Health Organization

The Foodborne Epidemiology Reference Group (FERG) was established by the World Health Organization (WHO) under the leadership of WHO's Department of Food Safety, Zoonoses, and Foodborne Diseases. The purpose of the Group is to estimate the global burden of disease from foodborne illness, including cyanide from cassava.

To estimate the burden of disease induced by cyanide in cassava, initial estimates of the incidence and prevalence of the different diseases (in particular konzo, tropical ataxic neuropathy and endemic goiter and cretinism) are needed.

I am currently working on these estimates, and will be contacting members of the CCDN network to request further information. If you have any information that you think will be useful for the exercise, please contact me at: julie.cliff@gmail.com.

Please feel free to contact me with any queries.

Konzo count

The total number of reported konzo cases was first estimated by Tylleskar[1] in his doctoral thesis. He gave a total of 3711 cases up to 1993. In this article, I update the count with more recent data (see References).I searched for numbers of reported cases in published articles, doctoral theses, the grey literature and in the proceedings of the workshop on Toxico-nutritional Degenerations Konzo and Lathyrism, Ghent, 2009, see CCDN News 14. For Mozambique, I used a database of reported cases.

Table 1 shows that the total number of reported cases up to the end of 2009 came to 6788. Reported cases considerably underestimate the true number, given that konzo often occurs during times of crisis and in isolated areas.

I also found references to other reports that I have not included. For example, in the Democratic Republic of Congo (DRC), Diasolua Ngudi[2] reported that the Ministry of Health estimated that there were 100,000 cases in 2000. Medecins du Monde have also reported cases from Muetshi in Kasai Occidental Province[3], and Lantum[4] reported cases from Cameroon in 1998, with a prevalence of 18/1000.

Please send corrections, updates and further information to CCDN News or julie.cliff@gmail.com

References

[1]Tylleskar, T (1994). The causation of konzo. Studies on a paralytic disease in Africa. *International Child Health Unit, Uppsala University and Department of Epidemiology and Public Health, Umea University*. Uppsala University, pp. 108.

[2] Diasolua Ngudi D (2004). Konzo and cassava toxicity: a study of associated nutritional factors in the Popokabaka District, Democratic Republic of Congo. *Faculty of Bioscience Engineering*. Ghent, 2004-5 pp. 162.

[3] Medecins du Monde, Lutte contre la malnutrition. www.medecinsdumonde.be/Urgence-nutritionnelle-a-Mwetshi.html

[4] Lantum, H.(1998) Spastic paraparesis. konzo - in the Garoua Boulai Health District, East Province- Cameroun. A hidden endemic disease.Yaounde, pp. 85.

[5] Tshala-Katumbay, D (2001). On the site of the lesion in konzo. *Faculty of Medicine*. Uppsala, Acta Universitatis Upsaliensis. Comprehensive summaries of Uppsala dissertations,1092,p.72.

[6] Banea, M. et al.(1997) Konzo and Ebola in Bandundu region of Zaire. *Lancet. 349* (9052): 621.

[7] Bonmarin, I. et al.(2002) Konzo outbreak, in the south-west of the Democratic Republic of Congo, 1996. *J. Trop Pediatr. 48* (4): 234-8 .

[8] Banea-Mayambu, J.P. et al.(2009) Bitter cassava consumption and konzo in Kahemba Territory, Bandundu Province, DRC. In: *Toxico-nutritional degenerations Konzo and Lathyrism, Ghent,*. CCDN News vol. 14, p. 5-6.

[9] Chabwine, J.N., et al.(2009). Spastic paraparesis in Burhinyi: evidence for the first outbreak of konzo in eastern DRC. In: *Toxico-nutritional degenerations Konzo and Lathyrism.Ghent,*. CCDN News, vol. 14, pp. 6.

[10] Howlett, W., Brubaker G, Mlingi N, Rosling H. (1992) A geographical cluster of konzo in Tanzania. *J. Trop. Geogr. Neurol.. 2*: 102-8.

[11]Mbelesso, P. et al. (2009) Outbreak of konzo disease in health region No. 2 of the Central African Republic. *Rev Neurol (Paris). 165* (5): 466-70..

[12] Ciglenecki, I. et al. (2010) Konzo outbreak among refugees from Central African Republic in Eastern region, Cameroon. *Food Chem Toxicol*. Early online publication.

Total number of konzo cases reported up to 2009

	Prior to 1975[1]	1975-1993[1]	1975-1993 Corrected	1994-2009	Total up to 2009
DRC				12[5]	
				22[2]	
				14[6]	
				167[7]	
				1047[8]	
				41[9]	
Total	1237	919	919	1303	3459
Mozambique		1420	2123*	281	2404
Tanzania		119	121[10]**	238	359
Central African Republic		16	16	81[11]	97
Cameroon				469[12]	469
Total	1237	2474	3179	2372	6788

* Corrected with currently available data

** Two reported deaths added

CCDN News is the Newsletter of the Cassava Cyanide Diseases and Neurolathyrism Network (CCDNN). The CCDNN is a free, worldwide network commenced in June 2001, which is working towards the elimination of konzo, TAN and other cassava cyanide diseases.

CCDN News will consider for publication short articles and letters (1-3 pages A 4 double spaced) written in English

Because CCDN News is a newsletter, full-size original papers or reviews cannot be considered for publication. Please send all correspondence to the CCDNN Coordinator, Dr J Howard Bradbury, Evolution, Ecology and Genetics, Research School of Biology, Australian National University, Canberra, ACT 0200, Australia.