

PROBING MECHANISMS OF CYANOGEN NEUROTOXICITY: RELEVANCE TO THE PATHOGENESIS OF KONZO, A MOTOR NEURON DISEASE HIGHLY PREVALENT IN SUB-SAHARAN AFRICA

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Background: Cassava dietary dependency is associated with deficiency in essential sulfur amino acids (SAA) cysteine and methionine needed for the detoxification of cyanide, a by-product of the main cassava cyanogenic glucoside, and outbreaks of konzo.

Objective: Elucidate nervous system (CNS) targets of cassava cyanogen analogs, notably sodium cyanide (NaCN) and sodium cyanate (NaOCN), under conditions of balanced vs. SAA amino acid diets.

Methods: Young adult rats were treated with 2.5 mg/kg NaCN, 50-200 mg/kg NaOCN, or saline; and fed normal (AAA) or 75% SAA-deficient diet. Activity of SAA-dependent CN-detoxifying rhodanese was assessed in plasma and CNS. Proteomic studies elucidated changes associated with the neurotoxicity of NaCN or NaOCN.

Results: NaCN induced seizures under SAA-deficient diet while NaOCN induced motor weakness. Rhodanese activity was higher in CNS vs. plasma, however, with no differences across treatments and diets. Proteomic analyses revealed differential patterns of (neuro)protein-carbamoylation. Proteins involved in redox and protein folding mechanisms, and maintenance of neuronal integrity, appeared to be targeted.

Conclusion: Our studies revealed molecular targets of cassava cyanogen analogs under conditions of balanced vs. SAA-deficient diet. The lack of rhodanese response to SAA dietary-deficiency suggests that (1) chronic SAA-deficiency may be needed to impair the detoxification of cyanide, (2) other thiol-donors may compensate for the SAA-dietary deficiency, and (3) in concert with our proteomic findings, the putative role of SAA deficiency in konzo may need to be revisited with a focus placed on its role on redox and protein folding mechanisms