MECHANISM OF TOXICITY OF MONILIFORMIN

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I Introduction

Moniliformin is a water soluble mycotoxin isolated from Fusarium moniliforme by Cole, et al in 1973 (ref.1). It is highly toxic to ducklings ($LD_{50}=3.68\text{mg/kg}$) and rats (LD_{50} for female = 41.57mg/kg ; for male= 50.0mg/kg). Autopsy of the rats showed acute congestive heart failure and histological lesions (ref.2). It selectively inhibits the mitochondrial pyruvate and ketoglutarate oxidations (ref.3). There was evidence to suggest that moniliformin may be the causal agent of Keshan disease, a serious local heart disease in some regions of China, especially in the mountainous regions and marshlands, whose causal agent has been unknown for a long time. Hence, we studied the mechanism of toxicity of this toxin(ref.4).

II Extraction and Purification of the toxin

The toxin was extracted from a culture of Fusarium moniliforme var. subglutinans which was isolated from mouldy corn seeds harvested in a serious Keshan disease region in Shanxi Province of China. The purification procedure involved water extraction, anion exchange chromatography, desalination and crystallization. The yield was about 1g/kg of solid culture. It was a needle-like crystal with brownish color under the light microscope and identified as moniliformin by UV, IR and NMR analysis.

III. Toxicity of moniliformin

(a) Alteration of Beijing duckling in situ.

The electrocardiogram(ECG) of the ducklings changed immediately after being fed with moniliformin. The most evident feature was that T shape waves went up.

(b)Damage to heart tissue culture.

The hearts of Beijing duck embryos incubated for 19 days were taken for tissue culture. The toxicity of moniliformin and the relationship between moniliformin and selenium were tested on the fifth day of heart tissue culture. The results were: (1) $3.18 \times 10^{-7} \text{ mM H}_2\text{SeO}_4$ stimulated the beating of the heart tissue in culture. (2) 2.75mM of moniliformin stopped the beating completely in a short time and could not be recovered by washing with fresh culture medium. (3) The pulse rate of the heart tissue was reduced to 50% by adding 0.275 mM moniliformin into the culture. (4) The toxicity of

moniliformin was decreased to some extent by adding 3.18×10^{-7} mM of H_2SeO_4 after treating with moniliformin. (5) The toxicity of moniliformin could be decreased by applying 0.6 mM ATP after treating with the toxin.

(c) Effect of moniliformin on the cardiac muscle cell membrane

Sarcolemmal membrane injury was tested in vivo by using the extracellular macromolecular tracer horseradish peroxidase (HRP). Moniliformin was administered in intravenous infusion in a dose of 21 mg per kilogram of body weight for 30 minutes. HRP was injected intravenously and localized in the heart following 6 minutes of circulation time. Selective deposition of the tracer on normal and altered myofilaments was noted. The result indicated that the sarcolemmal membrane permeability alteration is an early event in moniliformin-induced cardiac muscle injury.

IV Discussion

By our experiments, we consider that moniliformin may be the real agent of Keshan disease. Moniliformin produced by the fungus in soil dissolves in rain water and permeates into ground water. People who drink this kind of water and eat mouldy corn will probably develop Keshan disease. The relationship between moniliformin and Keshan disease is currently under further investigation.

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