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Foodborne cereulide causes beta cell dysfunction and apoptosis

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From Genes and nutrition, is personalised nutrition the next realistic step?
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Background

Environmental factors play a major role in the rising prevalence of type 1 and type 2 diabetes mellitus. Cereulide is a lipophilic peptide that is often found at low concentrations in starchy food. It is a culprit to consider in this era of prepackaged meals.

Materials and methods

Mouse and rat insulin producing beta cell lines, MIN6 and INS-1E respectively, as well as whole mouse islets, isolated from 2 week old C57Bl/6J mice, were exposed to cereulide concentrations ranging from 0.05ng/ml to 5ng/ml for 24 and 72h. Cell death was evaluated by a Hoechst/Propidium Iodide assay, and compared to cell death in human hepatocellular HepG2 and monkey fibroblast-like COS-1 cells. Subsequently, MIN6 cells were exposed to low concentrations of cereulide (0.15 - 0.5 ng/ml) for 24h and glucose-stimulated insulin secretion was evaluated as well as mechanisms of toxicity by mRNA profiling, electron microscopy and caspase activation and cytochrome c release assay.

Results

Cereulide exposure caused cell death in MIN6, INS-1E and pancreatic islets, but not in HepG2 or COS-1E cells (Table 1). Caspase 3/7 activation confirmed the apoptotic cell death process. Glucose-stimulated insulin secretion decreased from 10.48 ± 3.33 fold to 2.01 ± 0.51 ($P < 0.05$) in MIN6 cells after 24h exposure with 0.25 ng/ml cereulide. Exposure to 0.25ng/ml cereulide induced markers of mitochondrial stress, including PUMA (p53 upregulated modulator of apoptosis; 271 ± 77 % of control; $P < 0.05$) but also markers of ER stress, such as CHOP (CCAAT/-enhancer-binding protein homologous protein; 641 ± 190 % of control; $P < 0.01$). EM revealed swelling and loss of mitochondria, and cytoplasmic cytochrome c release confirmed mitochondrial cell death signalling (360 ± 83 % of control after exposure to 0.5 ng/ml for 24h ($P < 0.05$).

Conclusion

Cereulide, a toxin frequently found in prepackaged or prepared starchy meals, increases levels of mitochondrial and ER stress markers in beta cells of rats and mice, even

Table 1 Apoptosis induced after 24h exposure to cereulide (mean percentage ± SEM).

	MIN6 (n=5)	INS-1E (n=4)	HepG2 (n=3)	COS (n=3)	Islets (n=3)
Medium	7.3 ± 1.3	2.5 ± 0.3	5.8 ± 0.6	1.2 ± 0.6	3.1 ± 1.2
0.05 ng/ml cereulide	5.9 ± 1.0	3.2 ± 0.5	6.6 ± 2.1	1.6 ± 0.4	3.9 ± 1.5
0.25 ng/ml cereulide	31.6 ± 5.8 *	58.1 ± 11.4 *	6.9 ± 1.5	2.9 ± 0.7	8.6 ± 2.4
0.5 ng/ml cereulide	43.6 ± 6.1 *	100.0 ± 0.0 *	11.9 ± 2.5	2.6 ± 0.6	49.2 ± 9.0
5 ng/ml cereulide	100.0 ± 0.0 *	100.0 ± 0.0 *	7.7 ± 2.3	4.3 ± 0.9	96.4 ± 3.5*

* $p \leq 0.05$ vs control

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at low doses. In a dose dependent way, it also leads to impaired beta cell function and apoptosis. Cereulide might thus be involved in the current diabetes.

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