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The mechanism of Ochratoxin A neurotoxicity in vitro

Научный руководитель – Бабаян Нелли Самвеловна

Гезалян Мери Артуровна

Студент (магистр)

Ереванский государственный университет, Факультет биологии, Ереван, Армения

E-mail: gyozalyanmeri@gmail.com

Mycotoxins cause neuropsychological impairment or mental and emotional disorders but the mechanism of neurotoxicity of certain mycotoxin remains unknown. Lately it was hypothesized that Ochratoxin A (OTA) is unlikely to act through a single, well-defined mechanism of action, but a network of interacting epigenetic mechanisms is involved in its toxicity [2]. However, the correct model for risk assessment of mycotoxin neurotoxicity, including predictive test-systems, appropriate endpoints, extrapolation models from *in vitro/in vivo* data to human are not clearly identified, that hinder the comprehensive characterization of mycotoxins' hazard to humans. Regardless of endpoints it has been suggested that *in vitro* screens should include human neural cells to allow evaluation of interspecies differences. The reversible/irreversible effects should be also considered in evaluating of neurotoxicity [1]. **The aim of the work** was the delineation of epigenetic, reversible/irreversible neurotoxic effects of OTA in neuronal cell lines derived from human or mouse organisms.

The human SH-SY5Y and mouse HT22 cell lines were selected as test-models. The epigenetic effect of OTA was assessed using methylation sensitive comet assay; the genotoxicity of OTA was tested using CBMN assay. The DHE assay and FPG-comet assays were used to study the OTA induced oxidative stress.

It was shown, that OTA does not induce DNA-damage at highest tested concentrations (10-30 μM) in both human (SHSY5Y) and mouse (HT22) neuronal cell lines. The cell viability tested in parallel experiment was 85-98% (SHSY5Y) and 95-99% (HT22). At the concentrations of 2.5-10 μM OTA induces epigenetic changes in mouse HT22 neuronal cells which bring to the increased level (up to 45%) of unmethylated CpG islands in DNA. Those epigenetic changes may affect genes responsible for oxidative stress, while the increased level of reactive oxygen species and oxidized purines were detected. All observed processes were reversible after single-dose treatment, but can be retained in a case of chronic exposure. OTA induced epigenetic changes were not revealed in human SH-SY5Y neuronal cells, but the low level and reversible oxidative stress was observed after single-dose treatment with OTA. So, human and animal neuronal cells have different sensitivity against mycotoxin-induced toxicity and careful data extrapolation should be performed when use only animal data.

Источники и литература

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