ATLA Alternatives to Laboratory Animals Volume 24, Issue 4, July 1996, Pages 533-540

Aflatoxin B1 Cytotoxicity in Neurons in Culture

Bonsi, P., Palmery, M., Augusti-Tocco, G.

Abstract: Aflatoxin B1 (AFB1), a metabolite produced by Aspergillus flavus and Aspergillus parasiticus, is mainly known for its strong hepatotoxic and hepatocarcinogenic actions. Acute and reversible effects due to exposure to aflatoxin and the presence of aflatoxins in various human tissues and organs have also been reported. In particular, aflatoxin M1 (a metabolite of AFB1) has been identified in human brain tissue, and a syndrome characterised by encephalopathy has been observed in humans poisoned by AFB1. As a first approach to the study of the neurotoxicity of AFB1, we used the human neuronal cell lines, SKNMC and SKNSH. The data reported show clearly that AFB1 is capable of interacting directly with neuronal cells and causing a decrease in cell number following the addition of toxin to the culture. Decrease in cell survival is dependent on the toxin concentration, on time of exposure, and on cell density. The cytotoxic response of these cells has been compared to the effects of AFB1 on hepatoma cells and spinal cord motor neurons. Postmitotic neurons are also susceptible to AFB1 toxicity, although to a lower extent than proliferating cells. A non-proliferating state thus appears to lower, but not destroy, neuron sensitivity to the toxin.

Toxicol Sci. 2000 Jun;55(2):383-91.

Intranasal instillation of aflatoxin B(1) in rats: bioactivation in the nasal mucosa and neuronal transport to the olfactory bulb.

Larsson P1, Tjälve H.

Abstract: Aflatoxin B(1) (AFB(1)) may be present in moldy dust. Inhalation of contaminated dust particles may result in high local exposure of the nasal mucosa. The present study was designed to assess bioactivation and toxicity of AFB(1) in the nasal mucosa after intranasal administration of the mycotoxin in rats and also to examine if translocation of the mycotoxin occurs from the nasal mucosa to the brain along olfactory neurons. Female Sprague-Dawley rats were given (3)H-AFB(1) (0.2, 1 or 20 microg) intranasally and were sacrificed at various intervals (1 h to 20 d). Tissues were examined autoradiographically or histopathologically. Quantitative data were obtained by beta-spectrometry in rats given (3)H-AFB(1) intranasally or orally (for comparison). The data indicated that intranasal administration of AFB(1) resulted in formation of tissue-bound metabolites in sustentacular cells, in some cells of Bowman's glands, and in a population of neuronal cells in the olfactory mucosa, whereas in the respiratory nasal mucosa, there was selective bioactivation of AFB(1) in mucous cells. Intranasal instillation of 20 microg AFB(1) resulted in disorganized undulating olfactory epithelium, with injured neuronal and sustentacular cells. In the respiratory epithelium, there was selective destruction of mucous cells. beta-Spectrometry and autoradiography with tape-

sections of the head of rats given (3)H-AFB(1) intranasally indicated transport of AFB(1) and/or AFB(1) metabolites along the axons of the primary olfactory neurons to their terminations in the glomeruli of the olfactory bulb. The data indicate that the materials transported in the olfactory nerves represent AFB(1) and/or some of its nonreactive metabolites. It is concluded that application of AFB(1) on the nasal mucosa in rats results in high local bioactivation of the mycotoxin in this tissue and translocation of AFB(1) and/or its metabolites to the olfactory bulb.

Neurotoxicology. 2015 Jul;49:165-73. doi: 10.1016/j.neuro.2015.06.008. Epub 2015 Jun 30.

Impact of aflatoxin B1 on hypothalamic neuropeptides regulating feeding behavior.

Trebak F, Alaoui A, Alexandre D, El Ouezzani S, Anouar Y, Chartrel N, Magoul R.

Abstract: The presence of mycotoxins in food is a major problem of public health as they produce immunosuppressive, hepatotoxic and neurotoxic effects. Mycotoxins also induce mutagenic and carcinogenic effects after long exposure. Among mycotoxins that contaminate food are aflatoxins (AF) such as AFB1, which is the most powerful natural carcinogen. The AF poisoning results in symptoms of depression, anorexia, diarrhea, jaundice or anemia that can lead to death, but very few studies have explored the impact of AF on neuroendocrine regulations. To better understand the neurotoxic effects of AF related to anorexia, we explored in rat the impact of AFB1 on the major hypothalamic neuropeptides regulating feeding behavior, either orexigenic (NPY, Orexin, AgRP, MCH) or anorexigenic (α-MSH, CART, TRH). We also studied the effect of AFB1 on a novel neuropeptide, the secretogranin II (SgII)-derived peptide EM66, which has recently been linked to the control of food intake. For this, adult male rats were orally treated twice a week for 5 weeks with a low dose (150 μg/kg) or a high dose (300 μg/kg) of AFB1 dissolved in corn oil. Repeated exposure to AFB1 resulted in reduced body weight gain, which was highly significant for the high dose of AF. Immunocytochemical and quantitative PCR experiments revealed a dose-related decrease in the expression of all the hypothalamic neuropeptides studied in response to AFB1. Such orexigenic and anorexigenic alterations may underlie appetite disorders as they are correlated to a dose-dependent decrease in body weight gain of treated rats as compared to controls. We also found a decrease in the number of EM66-containing neurons in the arcuate nucleus of AFB1-treated animals, which was associated with a lower expression of its precursor SgII. These findings show for the first time that repeated consumption of AFB1 disrupts the hypothalamic regulation of neuropeptides involved in feeding behavior, which may contribute to the lower body weight gain associated to AF exposure.