Neurotoxic Potential of Food Contaminants: Is the Gut–Brain Axis an Overlooked Connection?

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Neurodegenerative diseases (NDs), particularly Alzheimer's disease (AD) and Parkinson's disease (PD), are among the most pressing global health challenges of our time. In 2019, around 57 million people were living with dementia worldwide, a number projected to nearly triple by 2050 [1]. While these disorders have multifactorial origins, up to 45% of dementia risk is attributable to modifiable factors, including lifestyle and environmental exposures [1]. Diet represents a major and often overlooked route of human exposure to multiple Food Chemical Contaminants (FCCs), including environmental and food-related toxicants, such as heavy metals, pesticides, mycotoxins, food processing contaminants, many of which have been associated with an increased risk of NDs [2, 3].

This work reports *in vitro* toxicological interactions between different contaminant classes on SH-SY5Y neuroblastoma human cells, using the combination index-isobologram method [4]. We assessed the neurotoxic effects of acrylamide (ACR; 0.08-10 mM), aflatoxin B1 (AFB1; 0.8-100 µM), and cadmium (Cd; 0.8-100 µM), both individually and in equipotent binary and ternary combinations. Neuronal viability was evaluated through the MTT assay after 72 hours of exposure. The individual contaminants showed a clear concentration-dependent reduction in neuronal viability, ranked as ACR < AFB1 < Cd. Notably, at concentrations relevant to human dietary exposure, the ACR/AFB1 combination exhibited additive interactions, while AFB1/Cd combinations showed significant synergism (CI = 0.51 at IC5). Conversely, ACR/Cd and ternary combinations demonstrated antagonistic interactions at lower exposure levels. These results are important to understand the potential neurotoxicity of FCCs, particularly in the context of combined exposures that may amplify or mitigate toxic effects.

Beyond direct neurotoxicity of FCCs, it is equally important to consider the initial site of contaminant interaction—the gut. Notably, the gut–brain axis (GBA) has been increasingly recognized as a critical interface, and its dysfunction is often implicated early in the course of NDs, preceding classical neurological symptoms [5]. Given the bidirectional communication between the brain and gut via the enteric nervous system (ENS), the ENS's role in mediating contaminant-induced neurotoxicity remains underexplored. In this webinar, evidence on the FCC effects within the ENS will also be reviewed and discussed in terms of their potential contribution to the onset and progression of NDs through GBA-related mechanisms.

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