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Sharhan Ahamed, Dimuth Induwara.

XENOBIOTIC-INDUCED CYTOCHROME 450 DYSREGULATION IN PARKINSON'S DISEASE: MOLECULAR MECHANISMS AND THERAPEUTIC STRATEGIES

Tutor: PhD, associate professor Dziarzhynskaya N.A.
Department of Radiation Medicine and Ecology
Belarusian State Medical University, Minsk

Parkinson's disease is a progressive neurological disorder marked by the loss of dopamine-producing neurons. While genetics play a role, mounting evidence points to environmental toxins – such as pesticides, industrial solvents, and heavy metals– as major contributors to the disease. These toxins interfere with the body's natural detox system, cytochrome P450 (further - CYP450) enzymes, which normally break down harmful chemicals. But in some cases, this system backfires, transforming harmless substances into brain-damaging compounds. Adding another layer of complexity, a person's unique genetic makeup and gut bacteria can determine whether these toxins trigger Parkinson's or are safely neutralized.

This study aims to uncover how environmental toxins disrupt cytochrome 450 (CYP450 enzymes in Parkinson's disease, exploring both the molecular mechanisms involved and potential therapeutic strategies to counteract these effects. We hope to identify new targets for intervention.

Literature review using PubMed, Web of Science, and Scopus, focusing on studies from 2000-2023 was conducted. Search targeted key relationships between CYP450 enzymes, environmental toxins, and Parkinson's disease using terms like "CYP450 polymorphisms," "xenobiotic neurotoxicity," and "gut-brain axis in PD." We prioritized clinical studies and animal research that examined how specific toxins alter CYP450 function and contribute to neurodegeneration, while also analyzing review articles for mechanistic insights. Special consideration was given to studies exploring genetic differences in toxin metabolism and recent findings about gut microbiome influences.The investigation revealed substantial evidence that genetic variation in CYP450 enzymes, particularly polymorphisms in CYP2D6 (McCann et al., 1997), significantly influences individual susceptibility to Parkinson's disease when combined with environmental exposures (Elbaz et al., 2007). Those with ultrarapid metabolizer phenotypes demonstrate markedly increased risk following pesticide exposures compared to individuals with reduced metabolic capacity (Ritz et al., 2016). At the molecular level, these effects appear mediated through both the generation of neurotoxic metabolites (Richardson et al., 2006) and the induction of oxidative stress pathways (Dias et al., 2013), with epigenetic modifications such as CYP2E1 promoter hypomethylation showing strong associations with disease severity (Kaut et al., 2022). The gut microbiome emerges as a crucial modifier of these processes (Scheperjans et al., 2015), where alterations in microbial communities can profoundly affect xenobiotic metabolism (Clarke et al., 2014). Certain bacterial species have been shown to interfere with Parkinson's medications (Maini Rekdal et al., 2019), while others may offer protective effects through anti-inflammatory mechanisms (Sampson et al., 2016). Therapeutic strategies targeting these pathways have shown promise in experimental models (Bastias-Candia et al., 2019), though significant challenges remain in translating these approaches to clinical practice (Espay et al., 2017), particularly regarding blood-brain barrier penetration (Pardridge, 2012) and the long-term safety of microbiome-based interventions (Cammarota et al., 2017). Environmental pollutants interfere with the progression of Parkinson's disease by taking over CYP450 enzymes, which results in both direct neuronal injury and disruption of the gut-brain axis. Individual differences in microbiota and genetic makeup account for why some persons are more susceptible to these effects than others. Even though preliminary research on existing medicines that target these pathways indicates promise, future research should concentrate on creating individualized strategies that take into consideration each patient's particular metabolic profile and gut ecology.