

Cellular Mechanisms of Chiral Enantiomer Toxicity Differences and Their Significance in Forensic Toxicology of Novel Psychoactive Substances

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Abstract

The proliferation of new psychoactive substances (NPS) presents a significant challenge to global forensic toxicological analysis. A substantial number of NPS are chiral compounds, whose different enantiomers often exhibit distinct pharmacological and toxicological profiles *in vivo*. However, current forensic analytical standards frequently report racemic mixtures as single entities, overlooking enantioselective toxicity, which may lead to substantial misinterpretation in the forensic assessment of intoxication cases. This review aims to systematically elucidate the key cellular mechanisms responsible for the toxicity differences of chiral NPS enantiomers and discuss their transformative implications for forensic toxicology practice. The core discussion focuses on stereoselective interactions at the cellular level. The differences in the affinity and efficacy of enantiomers when binding to specific molecular targets directly trigger divergent cellular signal transduction and functional responses. Their variations in cellular uptake, metabolic activation, and transport processes significantly influence their intracellular exposure kinetics and the generation of active metabolites, forming the basis of stereoselective toxicokinetics. These stereoselective interactions, amplified through intracellular signal transduction cascades, can induce multidimensional cellular stress responses, including mitochondrial dysfunction, excessive reactive oxygen species generation, endoplasmic reticulum stress, and calcium homeostasis disruption, subsequently selectively activating programmed cell death pathways such as apoptosis, necroptosis, or autophagy. Integrating the toxicological understanding of enantioselective mechanisms into forensic practice is essential for enhancing the scientific rigor of analytical conclusions. This paradigm shift necessitates the development and application of highly selective analytical techniques, such as chiral chromatography-mass spectrometry, and mandates that enantiomeric composition be incorporated as a critical variable in toxicological evaluations and cause-of-death determinations. A comprehensive elucidation of these mechanisms not only provides a theoretical foundation for constructing precise risk prediction models for novel psychoactive substances but also establishes a robust molecular basis for forensic identifications involving complex chiral compounds, thereby propelling the field towards greater precision and standardization.

Keywords

Chiral Enantiomers, Stereoselective Toxicity, New Psychoactive Substances (NPS), Forensic Toxicology, Cellular Mechanisms, Toxicokinetics, Enantiomer Separation and Analysis