

Neuronal endpoints in primary neuronal cultures to evaluate and predict human acute neurotoxicity

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Validated alternative test methods are required for safety toxicology of drugs and chemicals. Studies have demonstrated that there is ~70% correlation between in vitro cytotoxic concentrations and in vivo LD50 or human lethal concentrations. We are developing a testing strategy that could identify both factors to improve the correlation between in vitro data and human acute toxicity and alerts for the identification of outliers. A set of pharmaceutical, industrial, biocide and drug abuse chemicals have been tested against GABAA receptor activity, GABA and glutamate transport, acetylcholinesterase activity and membrane potential in primary neuronal cultures. GABAA receptor-mediated chloride influx was inhibited by compounds for which seizures have been observed after severe human poisoning. The potentiation of the GABAA receptor by 2-propanol and ethanol correlates with the greater CNS depression produced by 2-propanol. Abuse drugs inhibit [³H]GABA uptake but not [³H]aspartate uptake. Exposure to organophosphorus compounds for 48 hours resulted in higher inhibition of acetylcholinesterase activity than shorter exposure for 30 – 60 minutes, suggesting that primary cortical neurons have metabolic capacity. Most neurotoxic compounds altered membrane potential. Mercuric chloride, pentachlorophenol and sodium lauryl sulfate decreased cell viability, however they were more potent at neuronal endpoints. Acetaminophen and acetylsalicylic acid did not modify any of the endpoints assayed; they do not produce acute neurotoxicity in humans.

These results show that in vitro evaluation of neural endpoints may identify compounds that produce acute neurotoxicity in humans, provided that relevant in vitro models for acute neural disfunctions are used. Financed by EU contract LSHB-CT-2004-512051

Poster

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