Studies with neuronal cells: from basic studies of mechanisms of neurotoxicity to the prediction of chemical toxicity.

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Neurotoxicology holds central the notion that chemicals perturb neurological functions by interfering with the structure or function of specific neural pathways, circuits and systems. In the field of neurobiology, in vitro cell culture techniques have been successfully developed and employed to address specific questions of cell biology and nervous system functioning and provide a mean to systematically study complex nervous system. These in vitro methods are selected to study biological processes in a more isolated context or to address specific hypothesis. The criteria that must be satisfied when using in vitro methods for neurotoxicity studies include evaluation of general cellular targets as well as specific targets for the functionalism of the nervous system. Primary cultures of neural cells from rodents and chicks, either forming a monolayer or cell aggregates and neuronal cell lines from human and rodent origin are widely used. A clear understanding of mechanistic processes underlying normal and altered nervous system functioning is needed before analysing chemical-induced toxicity of the nervous system by using in vitro systems.
Primary neuronal cultures, obtained from different brain areas, are useful for the study of cellular and subcellular proteome, general cell functions (cell and mitochondrial membrane potential, intracellular calcium homeostasis, formation of free radicals and reactive oxygen species), and specific neural functions (voltage- and receptor-operated ionic channels, synthesis, release and uptake of neurotransmitters), these functions being altered by compounds inducing neurotoxicity. Primary cultures of cortical neurons are enriched in GABAergic and cholinergic neurons, whereas primary cultures of cerebellar granule cells are mainly constituted by glutamatergic neurons. Both cultures express functional $GABA_A$ and ionotropic glutamate receptors. Therefore, these cultures are good models to study neurotoxicity mediated by disturbances or malfunctioning of GABA, glutamate and acetylcholine neurotransmission.
Neurotoxicity studies performed in primary cultures of cortical neurons and of cerebellar granule cells will be presented. These include studies of neurotoxicity induced by organochlorine and organoposphate pesticides, and by mercury compounds. General targets (cell proteome and cell viability) and specific neural targets related to GABA, glutamate and acetylcholine neurotransmission are evaluated. Finally, some of the neural in vitro assays that have been developed can be useful, if further developed for high throughput, for their inclusion in an in vitro test battery to predict human toxicity.

Supported by FIS PI061212 (Spain) and LSHB-CT-2004-512051 (EU)

Workshop "Toxicity testing in vitro"
Meeting: "25th Workshop of the Scandinavian Society for Cell Toxicology"
Place: "Salzau, Germany"
Date: "19 – 22 September, 2007"