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Embryonic rat dorsal root ganglia organotypic culture: a morphometric model to test neurotoxicology

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Neurotoxicity is a common dose-limiting side-effect of several drugs (Cavaletti et al., 2008). So far a validated test method to screen drugs neurotoxicity does not exist, therefore in this interdepartment study we have analyzed the effectiveness of a morphometric neurotoxicty assessment model. Drug neurotoxicity evaluation is based on embryonic rat dorsal root ganglia (DRG) organotypic culture. DRG primary sensory neurons are the principal target of drugs neurotoxic action. In fact, primary sensory neurons lie outside the blood-nerve barrier and are supplied by capillaries with fenestrated walls. Moreover, the axons of these cells are among the longest of the entire nervous system and, therefore, are more susceptible to any agent that interferes with the energy metabolism or the structural basis of axonal transport. In particular, in this interdepartment study, the interference of the under study neurotoxic compound with NGF-induced neurite elongation is analysed. The effectiveness and reproducibility of this model, even if commonly used to test drugs, has not yet been demonstrated. In order to assess the validity of this in vitro model, antineoplastic drugs known to be in clinical use and in animal models neurotoxic (paclitaxel and oxaliplatin) or not dangerous (cyclophosphamide and 5-Fluorouracil) have been tested. DRGs explanted from E15 rat embryos have been treated for 24h with drugs concentrations comparable to those achievable in vivo. The length of the longest neurite of each DRG has been measured by ImageJ program. Experiments have been performed by three different blinded researchers in two different laboratories. Mean and standard deviation of each experiment were obtained, subsequently the mean value and standard deviation of the three independent experiments for each researcher were calculated. Data obtained by the three researchers in two different laboratories resulted statistically comparable and no significant differences were detected (One Way Anova analysis of variance and Tukey post test; $p<0.05$). This interdepartment in vitro study, therefore, indicates that a purely morphometric model represents a reliable tool to study drug neurotoxicity, permitting to make prediction of neurotoxic effects on humans because the concentrations tested are the same to which DRG are exposed during clinical use.

References

Cavaletti et al. (2008) Neurotoxic effects of antineoplastic drugs: the lesson of preclinical studies. Frontiers in Bioscience 13: 3506-3524.

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