Erschienen in: Neurotoxicology and Teratology ; 49 (2015). - S. 125
https://dx.doi.org/10.1016/j.ntt.2015.04.084

Neuronal cell models and methods simulating nervous system function to screen for neurotoxic compounds

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There is a great variety of neurotoxins with many different modes of actions. Some of them induce cell death; others interfere with neurite growth or disturb neuronal signal processing and transmission. These effects are usually examined with animal testing that is expensive, time consuming and controversial with respect to animal welfare. To date, several available neuronal cell models have been developed with the focus to replace animal testing. These models could emulate specific functions of the nervous system, however, they are still barely characterized and the emulated functions are often limited. Therefore, the aim of our study is to establish and refine a cell based test battery to identify neurotoxic effects based on: neuronal viability, structure and function. For this purpose, embryonic stem cell derived neurons (ESCN) were compared with primary rat and mouse cortical neurons. Then, model neurotoxic test substances were tested in these models and the changes in cell viability and neuronal cell structure (neurite outgrowth) were analyzed in all cell types. In addition, the neuronal function was analyzed using live cell calcium imaging (Ca Im) to identify effects of model compounds on neurotransmitter and voltage induced calcium responses. While primary cortical neurons of both rodent species only respond to glutamate and GABA stem cell derived neurons formed a more heterogeneous population of neurons responding to a broad variety of neurotransmitter stimuli. With respect to the effects of tri ortho cresyl phosphate (ToCP) we found ESCNs being less sensitive than primary neurons. On the other hand we found similar effects after exposure to acrylamide in all cell systems. The ToCP results indicate that glu GABA only cells might be more sensitive for some compounds. Currently we are evaluating the added value of the application of Ca Imaging as part of a testing battery together with micro electrode array (MEA) to assess a) the neurotoxic potential and b) to determine the mode of action of test substances considering single cells and networks of cell populations of different heterogeneities.