Disturbance in energy metabolism induced by diclofenac, isoniazid, paracetamol and galactosamine in a liver spheroid model

Jinsheng Xu
Centre for Research in Biomedicine, Faculty of Health and Life Sciences, University of the West of England, Bristol, U.K.

The liver plays a central role in the metabolism and transformation of energy-generating substances. Mitochondria and different metabolic pathways in hepatocytes interrelate and are often vulnerable targets of toxicants. Using animal tests it is difficult to evaluate liver energy metabolic functions accurately because energy-generating substances are also taken up or released by other cells in the body; it is also difficult to achieve high-throughput. We have developed a rat primary liver spheroid model which retains better liver metabolic functions. Based on this model, a test called the spheroid cell spreading inhibition test (SCSIT) was used for determining suitable exposure concentration ranges for test compounds. The effects of diclofenac, isoniazid, paracetamol and galactosamine on the metabolism of energy-generating substances (glucose, pyruvate, lactate and galactose) by liver spheroids were evaluated. The results showed that all the toxicants tested significantly reduced glucose and lactate release (p < 0.01). Diclofenac, isoniazid and paracetamol significantly reduced pyruvate uptake (p < 0.01), whereas, galactosamine did not affect pyruvate uptake within the concentration range tested. Diclofenac, galactosamine and paracetamol significantly decreased galactose uptake (p < 0.01); by contrast, isoniazid did not show a significant adverse effect. It is concluded that the primary liver spheroid model can mimic in vivo liver function in terms of the metabolism of energy-generating substances. The combined use of several endpoints
of energy metabolism can result in reliable toxicity evaluation. High drug concentrations can kill cells rapidly, and may not therefore generate useful functional information on toxicity. As a method for predetermining toxicant concentration ranges, the SCSIT is therefore a reliable, useful and necessary too for studying the effects of toxicants on liver functions. This primary liver spheroid model can be used for drug safety screening and can also achieve high-throughput testing.