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Effects of valproic acid (VPA) and levetiracetam (LEV) on proliferation, apoptosis and hormone secretion of the human choriocarcinoma BeWo cell line

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Abstract:
Epilepsy has been associated with poor obstetric outcomes that may be the result of the epilepsy or a direct effect of anti-epileptic drugs on placentation. To investigate any direct effect of anti-epileptic drugs on cell proliferation, apoptosis and hormone secretion with focus on human chorionic gonadotropin (β-hCG), progesterone (P4) and 17β-estradiol (E2), BeWo cell line was cultured in the presence of different concentrations of sodium valproate (0.45, 0.6, 1.5 or 2 mM) or levetiracetam (0.07, 0.12, 0.3 or 0.5 mM) with appropriate solvent controls. Cell proliferation was measured using BrdU incorporation. Caspase-3 activity was used as a marker of cell apoptosis and was evaluated by a fluorometric assay. Additionally, hormone secretion was evaluated by ELISA kits. Dose-dependent action of VPA on cell proliferation occurred in parallel to stimulation of caspase-3 activity. LEV had no effect on cell proliferation, and after long term exposure to the drug, a decrease in caspase-3 activity was observed. A significant decrease in β-hCG, P4 and E2 production was observed when the cells were treated with VPA. LEV decreased β-hCG and E2 secretion but had no effect on P4 level. Direct inhibition of cell proliferation and hormone secretion along with apoptotic action suggest that exposure to VPA at therapeutic doses during early pregnancy should be approached with caution. Trophoblast cells appear to be less sensitive to LEV; however, further studies involving placental tissue are necessary to determine the safety of the drug.

Key words:
sodium valproate, levetiracetam, BeWo cell line, hormone secretion, proliferation, apoptosis