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Effect of a Synthetic Platinum-Based Complex on Autophagy Induction in Leydig TM3 Cells

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Abstract : Platinum-based anticancer therapeutics are the most widely used drugs in clinical chemotherapy but have major limitations and various side effects in clinical applications. Gonadotoxicity and sterility is one of the most common complications for cancer survivors, which seem to be drug-specific and dose-related. Therefore, many efforts have been dedicated to discovering a new structure of platinum-based anticancer agents with improved therapeutic index, fewer side effects. In this regard, new Pt(II)-phosphane complexes containing heterocyclic thionate ligands (PCTL) have been synthesized, which show more potent antitumor activities in comparison to cisplatin. Cisplatin, the best leading metal-based antitumor drug in the field, induces testicular toxicity on Leydig and Sertoli cells leading to serious side effects such as azoospermia and infertility. Therefore in the present study, we aimed to investigate the cytotoxicity effect of PCTL on mice TM4 Sertoli cells with particular emphasis on the role of autophagy in comparison to cisplatin. In this study, an MTT assay was performed to evaluate the IC50 of PCTL and to analyze the TM3 Leydig cell's viability. Cells morphology was evaluated via invert microscope and Changing in morphology for nuclei swelling or autophagic vacuoles formation were assessed by DAPI and MDC staining. Testosterone production in the culture medium was measured using an ELISA kit. Finally, the expression of Autophagy-related genes, Atg5, Beclin1 and p62, were analyzed by qPCR. Based on the obtained results by MTT, the IC50 value of PCTL was 50 μM in TM3 cells and cytotoxic effects was in a dose- and time-dependent manner. Cells morphological changes investigated by inverted microscopy, DAPI, and MDC staining which showed the cytotoxic concentrations of PCTL was significantly higher than cisplatin in the treated TM3 Leydig cells. The results of PCR showed a lack of expression of the p62, Atg5 and Beclin1 gene in TM3 cells treated with PCTL in comparison to cisplatin and control groups. It should be noted that the effects of 25 μM PCTL concentration on TM3 cells have been associated with increased testosterone production and secretion, which requires further study to explain the possible causes and involved molecular mechanisms. The results of the study showed that the PCTL had less-lethal effects on TM3 cells in comparison to cisplatin and probably did not induce autophagy in TM3 cells.

Keywords : platinum-based anticancer agents, cisplatin, Leydig TM3 cells, autophagy
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