NOVEL GnRH ANALOGUES WITH ANTIPROLIFERATIVE PROPERTIES

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The gonadotropin-releasing hormone (GnRH) is a 10-amino acid peptide that regulates the function of the reproductive system, by controlling the secretion of the luteinizing hormone (LH) and the follicle-stimulating hormone (FSH). GnRH exerts its biological actions through its interaction with the GnRH receptor (GnRH-R). In addition to healthy tissue, histopathological analysis of endometrial tumors has revealed the expression of the GnRH-R. Previous studies have shown that several GnRH analogues exert cytotoxic effects on cancer cells. In this study, we determined the antiproliferative activity of GnRH analogues conjugated with the cytotoxic agent, mitoxantrone (Con 3, Con7) or without mitoxantrone (Con-P1, Con-P2), in the Ishikawa endometrial cancer cells, which express the GnRH-R. We hypothesized that binding of GnRH analogues to their receptor results in the internalization of the GnRH-R-drug complex and the release of mitoxantrone in the cytoplasm, which in turn exerts its cytotoxic effects. Indeed, the proliferation of Ishikawa cells was inhibited by Con3 and Con7, but not by the Con-P1 and Con-P2, in a time-dependent manner (1-4 days). Importantly, the proliferation of Ishikawa cells was inhibited by Con3 and Con7 in a dose-dependent manner, with potencies of 0.7-1.3 μM. Ongoing in vivo studies will determine the antiproliferative effects of con3 and con7 in experimental animal models.