Genistein-induced fluid accumulation in ovariectomised rats’ uteri is associated with increased cystic fibrosis transmembrane regulator expression

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OBJECTIVE: High genistein doses have been reported to induce fluid accumulation in the uteri of ovariectomised rats, although the mechanism underlying this effect remains unknown. Because genistein binds to the oestrogen receptor and the cystic fibrosis transmembrane regulator mediates uterine fluid secretion, we hypothesised that this genistein effect involves both the oestrogen receptor and cystic fibrosis transmembrane regulator.

METHODS: Ovariectomised adult female Sprague-Dawley rats were treated with 25, 50, or 100 mg/kg/day genistein for three consecutive days with and without the ER antagonist ICI 182780. One day after the final drug injection, the animals were humanely sacrificed, and the uteri were removed for histology and cystic fibrosis transmembrane regulator mRNA and protein expression analysis using real-time polymerase chain reaction and Western blotting, respectively. The cystic fibrosis transmembrane regulator protein distribution was analysed visually by immunohistochemistry.

RESULTS: The histological analysis revealed an increase in the circumference of the uterine lumen with increasing doses of genistein, which was suggestive of fluid accumulation. Moreover, genistein stimulated a dose-dependent increase in the expression of cystic fibrosis transmembrane regulator protein and mRNA, and high-intensity cystic fibrosis transmembrane regulator immunostaining was observed at the apical membrane of the luminal epithelium following 50 and 100 mg/kg/day genistein treatment. The genistein-induced increase in uterine luminal circumference and cystic fibrosis transmembrane regulator expression was antagonised by treatment with ICI 182780.

CONCLUSION: Genistein-induced luminal fluid accumulation in ovariectomised rats’ uteri involves the oestrogen receptor and up-regulation of cystic fibrosis transmembrane regulator expression, and these findings reveal the mechanism underlying the effect of this compound on changes in fluid volume in the uterus after menopause.

KEYWORDS: Genistein; Cystic Fibrosis Transmembrane Regulator; Oestrogen Receptor.


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INTRODUCTION

Genistein, a phyto-oestrogen, is capable of binding to oestrogen receptor (ER)-α and β, which are expressed in the uterus (1). This compound has also been reported to induce morphological changes (2), luminal fluid secretion (3) and proliferation of the endometrium, as evidenced by the increased expression of proliferative markers (3,4) in the uteri of ovariectomised adult rats. These genistein-mediated effects may have various implications on the female reproductive system. For example, genistein-induced changes may help to restore some uterine functions and reduce uterine atrophy after menopause (5). At high doses, however, genistein may produce harmful effects because it can stimulate the development of endometrial hyperplasia (3,6). There is also evidence that genistein can affect female fertility by interfering with the normal development of the reproductive system (7,8) and the normal pattern of the reproductive cycle (7).

The reported effects of genistein on fluid secretion may affect the volume of fluid in the uterus. Under conditions in which a low amount of fluid is present, such as in menopause (9), genistein may help to restore the uterine fluid volume. Although changes in morphology and fluid secretion have been reported in rodent uteri, genistein has