TD DE PHARMACOLOGIE BLG121

RECEPTEURS NUCLEAIRES

09 et 11 DECEMBRE 2010

Menopause is associated with increased production of inflammatory cytokines, such as ILs and TNF-α. The elevated cytokine levels likely contribute to the increased incidence of inflammatory diseases after menopause, such as osteoporosis, and neurodegenerative and cardiovascular diseases. Because estrogens are known to have anti-inflammatory properties, and estrogens in the form of hormone therapy (HT)[3] lower cytokine levels in postmenopausal women, it seems practical to attempt to prevent inflammatory diseases associated with menopause by replacing estrogens after the onset of menopause. Observational studies supported this rationale for using HT as a chemopreventative intervention by showing that HT decreased osteoporosis, Alzheimer's disease, and cardiovascular disease. It was therefore quite surprising when the Women's Health Initiative (WHI) trial found that estrogen plus progestin increased the risk of heart disease and dementia. However, consistent with observational studies, the WHI did find that HT prevented osteoporosis and fractures. Furthermore, recent secondary analysis of data from the WHI found that the increase risk of heart disease occurred mainly in women who started HT long after menopause. A reduction in coronary heart disease occurred in women who started HT close to the onset of menopause, which is the typical time HT is prescribed. The protective effect of estrogens on osteoporosis and heart disease in younger women suggest that inflammatory pathways should remain an important therapeutic target of estrogens for treating women close to the onset of menopause.

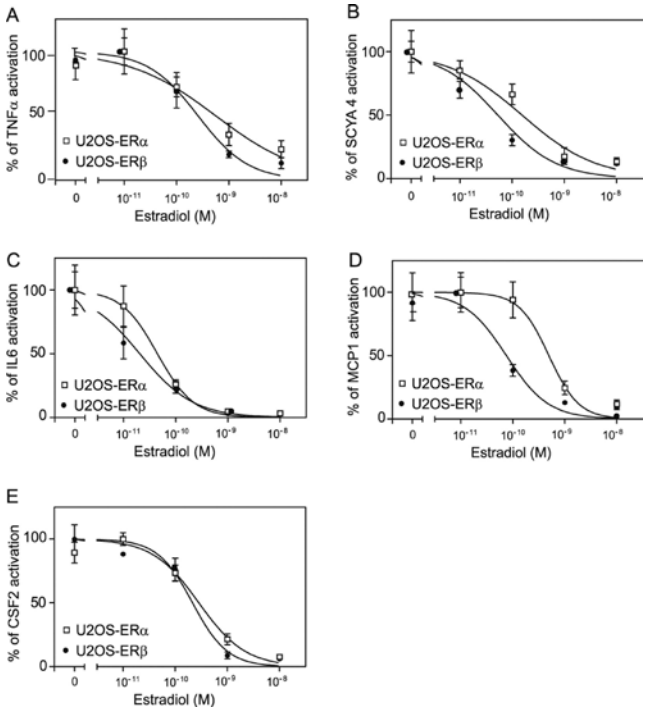
A key to generate selective estrogens to prevent inflammatory diseases is to understand the mechanisms whereby estrogens exert their anti-inflammatory actions. Estrogens inhibit the release cytokines from multiple cell types, suggesting that proinflammatory genes are major targets for the two forms of estrogen receptors (ER), ERα and ERβ.

Although the anti-inflammatory actions of estrogens likely play an important role in the prevention of inflammatory diseases in women, the major property of estrogen that needs to be eliminated is its proliferative effects on the uterus and mammary gland. Clearly, it is important to develop estrogens that lack proliferative effects, but retain their anti-inflammatory actions. One approach to achieve this goal is exemplified by the compound, WAY-169916, which inhibits NF-κB transcriptional activity but is devoid of estrogenic activity on breast cells. Another approach is to design estrogens that selectively regulate ERβ transcriptional pathways. Estrogens exert their proliferative effects through ERα as demonstrated by the observation that the ERα knockout mice show little mammary gland development, whereas ERβ knockout mice develop normal mammary glands. In contrast, ERβ acts as a tumor suppressor and inhibits the proliferation of breast cancer cells. The development of highly selective ERβ agonists provides a unique opportunity to investigate the anti-inflammatory action of ERβ, which is expressed in immune cells. Two such compounds, ERB-041 (2-(3-fluoro-4-hydroxyphenyl)-7-vinyl-1,3 benzoxazol-5-ol) and WAY-202196 (3-(3-fluoro-4-hydroxyphenyl)-7-hydroxynaphthonitrile), have showed potent anti-inflammatory effects in animal models for diseases.

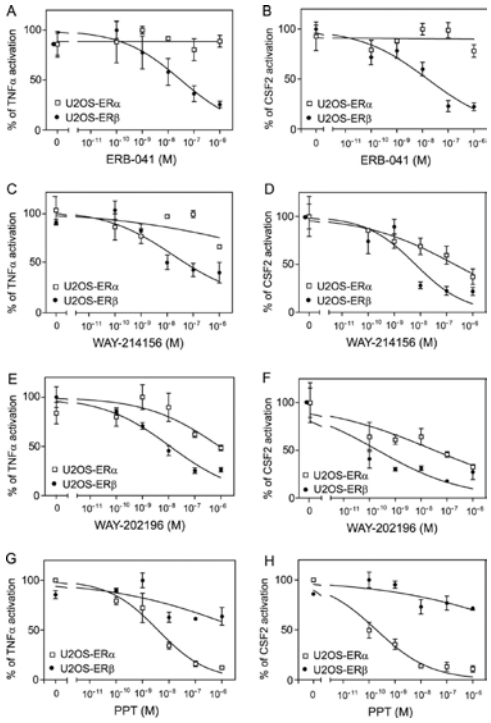
Question 1 : Analyser l'introduction et faites ressortir les éléments importants. Selon vous quel est l'objectif de l'étude ?

Question 2 : Analyser la figure 1. Rappeler le principe de la PCR en temps réel. Quelles sont vos conclusions?

Fig 1 : Levels of TNF-α (*A*), SCYA4 (*B*), IL-6 (*C*), MCP1 (*D*), and CSF2 (*E*) mRNA determined by real-time PCR in U2OS-ERα and U2OS-ERβ cells treated with increasing concentrations of E_2 for 2 h and with TNF-α for 1 h.



Question 3 : analyser la figure 2. Que pouvez-vous conclure sur le mode d'action de l'ERB041, du WAY-214156 et du WAY202196 ?



Question 4 : Les cellules ont été transfectées par des lentivirus exprimant ou non SRC2

Rappeler le principe d'un western blot. Analyser la figure A. A quoi sert la b-actine.

Analyser les figures B, C et D. Que pouvez-vous conclure ?

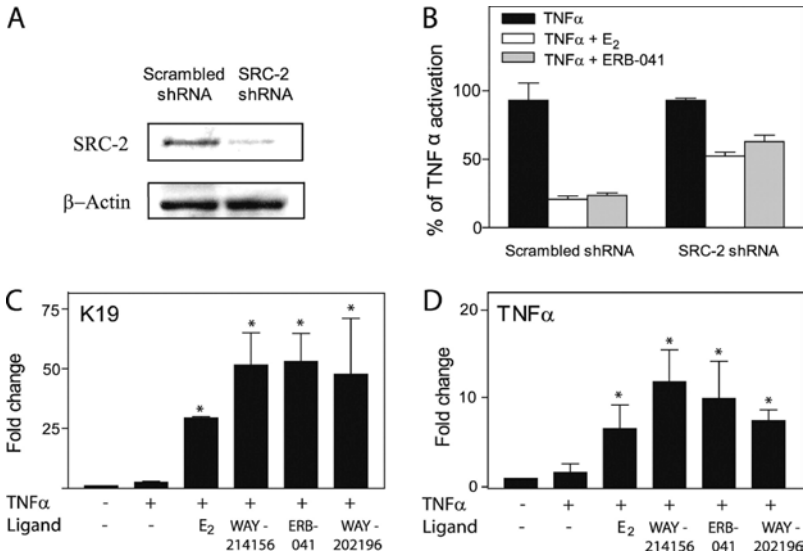


Fig 3 : U2OS-ERβ cells were treated with TNF-α for 3 h in the presence of 100 nM E_2 or 1 µM ERB-041, WAY-202196, or WAY-214156 for 2 h. The data shown are derived from quantitative real-time PCR analysis of the *K19* (*C*) and *TNF-*α (*D*) genes. The fold change was determined using the raw values from the untreated control cells and TNF-α-treated cells.

Question 5 : Proposer un schéma bilan et un titre à cette publication