The action mechanism of catecholamines in the initiation of breast cancer and inhibitory effects of dietary flavonoids on γ-H2AX induction by 17ß-estradiol metabolites and noradrenaline in breast cancer cells

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Breast cancer is the most common cancer in women worldwide. Therefore, prevention of breast cancer is an important social issues. Prolonged exposure to 17ß-estradiol (E_2) has been reported to be one of the major risk factors for cause of breast cancer. E_2 is metabolized to 4-OHE_2, one of catechol estrogens. 4-OHE_2 induces DNA damage and is involved in carcinogenesis. On the other hand, daily stress is considered to promote the development of breast cancer. However, the mechanism underlying the relation between stress and breast cancer is unclear. Endogenous catecholamines such as noradrenaline (NA) are secreted into the blood under stress exposure. We found that simultaneous treatment with 4-OHE_2 (30 μM) and NA (3 nM) significantly induced phosphorylation of histone H2AX (γ-H2AX), but any changes were not observed under treatment of individual compounds. Clonidine, an agonist of α_2-adrenoreceptor (α_2AR), also increased γ-H2AX in the presence of 4-OHE_2, whereas a α_2AR antagonist, rauwolscine, suppressed it completely. Furthermore, γ-H2AX induced with 4-OHE_2 and NA was also inhibited by ataxia telangietasia-mutated (ATM) inhibitor, KU-55933 (20 μM). These results suggest that induction of γ-H2AX by 4-OHE_2 and NA was mediated with α_2AR.

Flavonoids, which are widely distributed in edible plants, have been reported to exert the preventive effects toward life style-related diseases such as cancer, diabetes, arterial sclerosis and so on. In this study, we further investigated the effects of the several flavonoids on γ-H2AX induction by 4-OHE_2 and NA. Among the several flavonoids, luteolin and quercetin (0.1μM) suppressed it completely. In order to clarify structure-activity relationships and site of action of these flavonoids, effects of the other quercetin derivatives such as methoxy quercetin and quercetin glucuronide on γ-H2AX induction with 4-OHE_2 and NA are under investigation.