Inhibitory effects of flavonoids on phosphodiesterase isozymes from guinea pig and their structure-activity relationships

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摘要

Abstract

The structure-activity relationships of flavonoids with regard to their inhibitory effects on phosphodiesterase (PDE) isozymes are little known. The activities of PDE1-5 were measured by a two-step procedure using cAMP with [3H]-cAMP or cGMP with [3H]-cGMP as substrates. In the present results, PDE1, 5, 2, and 4 isozymes were partially purified from guinea pig lungs in that order, and PDE3 was from the heart. The IC50 values of PDE1-5 were greater than those reported previously for the reference drugs, vinpocetin, EHNA, milrinone, Ro 20-1724, and zaprinast, by 5-, 5-, 7-, 5-, and 3-fold, respectively. As shown in Table 2, luteolin revealed non-selective inhibition of PDE1-5 with IC50 values in a range of 10-20 μM, as did genistein except with a low potency on PDE5. Daidzein, an inactive analogue of genistein in tyrosine kinase inhibition, showed selective inhibition of PDE3 with an IC50 value of around 30 μM, as did eriodictyol with an IC50 value of around 50 μM. Hesperetin and prunetin exhibited more-selective inhibition of PDE4 with IC50 values of around 30 and 60 μM, respectively. Luteolin-7-glucoside exhibited dual inhibition of PDE2/PDE4 with an IC50 value of around 40 μM. Diosmetin more-selectively inhibited PDE2 (IC50 of 4.8 μM) than PDE1, PDE4, or PDE5. However, biochanin A more-selectively inhibited PDE4 (IC50 of 8.5 μM) than PDE1 or PDE2. Apigenin inhibited PDE1-3 with IC50 values of around 10-25 μM. Myricetin inhibited PDE1-4 with IC50 values of around 10-40 μM. The same was true for quercetin, but we rather consider that it more-selectively inhibited PDE3 and PDE4 (IC50 of <10 μM). In conclusion, it is possible to synthesize useful drugs through elucidating the structure-activity relationships of flavonoids with respect to inhibition of PDE isozymes at concentrations used in this in vitro study.