

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

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摘要.

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 μ M, 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 μ M, as did eriodictyol with an IC₅₀ value of around 50 μ M. Hesperetin and prunetin exhibited more-selective inhibition of PDE4 with IC₅₀ values of around 30 and 60 μ M, respectively. Luteolin-7-glucoside exhibited dual inhibition of PDE2/PDE4 with an IC₅₀ value of around 40 μ M. Diosmetin more-selectively inhibited PDE2 (IC₅₀ of 4.8 μ M) than PDE1, PDE4, or PDE5. However, biochanin A more-selectively inhibited PDE4 (IC₅₀ of 8.5 μ M) than PDE1 or PDE2. Apigenin inhibited PDE1-3 with IC₅₀ values of around 10-25 μ M. Myricetin inhibited PDE1-4 with IC₅₀ values of around 10-40 μ M. The same was true for quercetin, but we rather consider that it more-selectively inhibited PDE3 and PDE4 (IC₅₀ of <10 μ M). 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