Naturally Occurring Flavonoids and Human Basophil Histamine Release

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Abstract

Naturally occurring plant flavonoids, normal dietary constituents, affect a variety of cell activation phenomena including the secretion of histamine from human basophils stimulated by a variety of agents (antigen, anti-IgE, concanavalin A, ionophore A23187, formyl-Met-Leu-Phe and tetradecanoyl phorbol acetate). Variable profiles of inhibition are seen depending on the nature of the stimulus and the chemical structure of flavonoids.

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Naturally occurring low-molecular weight plant flavonoids affect many biochemical processes in both plants and animals. Over one thousand flavonoids are known to occur in the vegetable kingdom [1] being present in fruits, vegetables, nuts, seeds, flowers, stems, and leaves, and thus are normal dietary constituents. The average daily Western diet contains approximately 1 g of mixed flavonoids [2]. Flavonoids contain a chromone grouping and thus are related to the antiallergic drug cromolyn. A number of flavonoids have been shown to be potent inhibitors of many different enzymes [3], including transport AT-Pases, cyclic nucleotide phosphodiesterases, phos-pholipase A2 [4], phospholipase C [5], lipoxygenase [6], and protein kinase C [7], amongst others. Several of the enzyme systems mentioned play key roles in cell activation and the development of inflammatory responses. Certain flavonoids possess antiallergic, antiinflammatory, and antiviral activity [8] and some are mutagenic or even anticarcinogenic [9, 10]. Moreover, a number of flavonoids (depending on structure) affect the function of various mammalian cells including secretion (mast cells, basophils, neutro-phils), mitogenesis (human lymphocytes), generation and effector function of human cytotoxic lymphocytes (cell-cell interactions), smooth muscle contractile responses, platelet aggregation, hepatocyte responses to hepatotoxic agents, and the generation of chemiluminiscence and superoxide anion (human neutrophils)[11].

In 1975, Fewtrell and Gomperts [12, 13] reported that several flavonoids inhibited rat mast cell histamine release stimulated by antigen, concanavalin A and the ionophore A 23187. We thought it worthwhile to determine whether certain flavonoids would affect a human secretory system, i.e. histamine secretion from human basophils. In a detailed analysis of the effect of quercetin, on antigen-induced basophil histamine release [14] it was found that the inhibitory effect was concentration-dependent, more effective at low antigen concentrations, instantaneous in onset of action, inhibitory to the histamine release-augmenting effect of D2O, not significantly influenced by increased buffer Ca²⁺ concentrations, and not augmented by theophylline. The latter observation plus the fact that quercetin did not cause an increase in leukocyte cyclic AMP

content suggests that inhibitory activity is not cyclic AMP-dependent. Preincubation of cells with quercetin (50 μ M) for 30 min followed by washing and subsequent exposure to antigen allowed

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100 γ
80
60 -
40
20 -0 -20
Flavone

100 γ
80
60 -
40
20 -0 -20
Flavone

OH 0

-I 1-
Chalcone

Apigenin
Fisetin
Rutin
Phloretin

100
 °s 80
 TO
 CD
 ω 60
 c
 E
 TO
 ½ 40
 -1=
 “o
 s o
 -20
 -I 1
 -I 1
 ^
 t=β

Hesperetin
 0CH3
 OH 0
 5 10 20 50
 100
 80 60 40 20 0 -20
 Tangeretin
 CH30
 OC¹/₈
 —
 ■A

5 10 20 50

OC_{1/8}

Naringin

OH 0

J_{1/8}

5 10 20 50

Flavonoid concentration, [iM

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normal histamine release. Thus only antigen-activated basophils are sensitive to the inhibitory effect of quercetin. Subsequently, we examined the effect of 22 different flavonoids of different chemical classes on antigen-induced basophil histamine release and determined that important structure-activity relationships existed which determined whether or not a given flavonoid would exert inhibitory activity [3]. Since antigen-induced histamine release was effectively inhibited by certain flavonoids, we decided to examine their effect on basophil histamine release stimulated by other secretagogues. In a series of experiments [15], we studied the effect of 11 different flavonoids representing five different chemical classes for their inhibitory activity against histamine release stimulated by antigen, anti-IgE, concanavalin A, ionophore A 23187, the chemoattractant peptide, f-Met-Leu-Phe, and the tumor-promoting phorbol ester, tetradecanoyl phorbol acetate (TPA). The results of these experiments are displayed in figure 1 and clearly show that certain flavonoids are strong inhibitors of histamine release. It is evident that striking structure-activity relationships exist which are discussed in detail elsewhere [15]. Based on the results of these experiments it would appear that various secretagogues activate biochemical pathways leading to secretion that differ subtly from one stimulus to another since certain flavonoids active against one or more stimuli may not be effective against others. Their mechanism(s) of action remain to be elucidated. Since flavonoids are normal dietary constituents it is conceivable that they may act as natural biologic response modifiers and certainly can be used as biochemical probes into the mechanism of secretory phenomena.

Fig. 1. Effect of flavonoids on basophil histamine release. For all experiments, control histamine release was in the following ranges for each ligand: antigen (A): 44.8–93.8%; anti-IgE (•): 16.6–54.9%; Con A (■): 15.9–52.8%; ionophore A 23187 (O): 63.7–82.3%; f-Met-Leu-Phe (□): 22.8–50.2%, and TPA (Δ): 18.6–60.0%. The concentration ranges of the various ligands utilized to stimulate histamine release were as follows: antigen: 3.65×10^{-3} – 3.65×10^{-2} μg/ml; anti-IgE: 5–20 μg/ml; Con A: 0.8–3.1 μg/ml; ionophore A 23187: 0.5 μg/ml; f-Met-Leu-Phe: 0.5 μM, and TPA 100 ng/ml (reproduced with permission from ref. 15).

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