J. Pharm. Pharmacol. 1993, 45: 766
Communicated March 8, 1993

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Letter to the Editor

4,4′-Diacetyl curcumin—in-vitro histamine-blocking activity

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In the course of our investigation of the 2,4-diketone lipid class which is present in mammalian tissues, and which posseses anti-allergic properties (Douglas et al 1978; Douglas 1991), I had occasion to examine a number of non-physiological carbonyl and other compounds for histamine-blocking activity. For the purposes of this research, the guinea-pig ileum histamine bioassay of Barsoum & Gaddum (1935) was employed. Curcumin (diferuloylmethane) (Fig. 1), the compound responsible for the colour of turmeric, in common with the aliphatic 2,4-diketone lipids, possesses the β-diketone configuration which confers, through keto-enol tautomerism, chelating potential upon such compounds. This chelating ability, in association with an aliphatic chain of nine or more carbon atoms (or an aromatic ring) was found to be required for anti-allergic activity (Douglas et al 1978). It was, therefore, of interest to determine whether curcumin had similar biological properties.

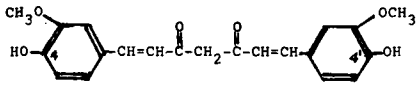

FIG. 1. The structure of curcumin.

To eliminate any potential influence of the phenolic hydroxyl groups, before carrying out the guinea-pig ileum bioassay on curcumin, these groups were acetylated. The acetylated compound was found to possess significant histamine-blocking activity, comparable to that of the 2,4-diketones. Thus, the ED50 for 4,4′-diacetyl curcumin was 0·045 mg, and for 2,4-tridecanedione the ED50 was 0·075 mg. Other compounds assayed included salicylaldehyde, a versatile chelating agent, (ED50 0·080 mg) and *n*-butyl gallate (ED50 0·038 mg). (The ED50 value is the amount of the compound being assayed which reduces the histamine-induced contractions of the smooth muscle preparations to 50% of the maximum height of the kymograph recording.)

These non-nitrogenous compounds which inhibit the effect of histamine on smooth muscle obviously do not act at cellular surface receptor sites for agonists, as do the synthetic antihistamine drugs. I have recently (Douglas 1991) postulated that, in the presence of added 2,4-diketone (or a similar type of chelating compound), following the interaction of an agonist (e.g. histamine) with a smooth muscle cellular surface receptor, the normal transient increase in $[Ca^{2+}]_i$ liberated intracellularly by the second messenger, inositol 1,4,5-triphosphate, does not occur. Acting intracellularly, the added chelator rapidly sequesters the Ca^{2+}, preventing the Ca^{2+}-calmodulin interaction which is essential for a normal physiological response to the agonist. This postulated mechanism, in the case of the 2,4-diketone lipids, also accounts for their non-specific activity with respect to the several agonists which were employed in our studies.

Srimal & Dhawan (1973), in an exhaustive study of the pharmacology of curcumin, reported that it had significant anti-inflammatory activity in acute and in chronic models of inflammation. There was no mortality in mice in doses of up to 2 g kg^{-1}. They noted that the compound was not absorbed intraperitoneally. By contrast, we found that the 2,4-diketone lipids were absorbable by this route. I suggest that some, at least, of the pharmacological properties of curcumin reported by Srimal & Dhawan (1973) may be attributed to its β-diketone structure.

Turmeric is widely used as a condiment and in curry powders. It has had limited use in the treatment of chronic cholecystitis. Because of its antiseptic, carminative and stimulant properties, it has been employed in the folk medicine of India and other eastern countries.

It is of interest that aliphatic β-diketones with thirty-one carbon atom chains are widely distributed in the epicuticular waxes of many plant species, the β-diketone moiety occupying various positions along the carbon chain (Barbieri et al 1987). These compounds, too, would be expected to have anti-allergic properties.

The author acknowledges the assistance of Dr Marlene Lefcort and Mrs Barbara Koss Levine, who performed the bioassays.

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References

Barbieri, G., Seoane, G., Trabazo, J.-L., Riva, A., Umpierrez, F., Radesca, L., Tubio R., Kwart, L., Hudlicky, T. (1987) General method of synthesis for natural long-chain β-diketones. J. Nat. Prod. 50: 646–649

Barsoum, G. S., Gaddum, J. H. (1935) The pharmacological estimation of adenosine and histamine. J. Physiol. 85: 1–14

Douglas, D. E. (1991) Higher aliphatic 2,4-diketones: a ubiquitous lipid class with chelating properties, in search of a physiological function. J. Lipid Res. 32: 553–558

Douglas, D. E., Francis, L. E., Melville, K. I. (1978) The isolation and identification of 2,4-diketones present in human and animal tissues and in urine. Can. J. Biochem. 56: 691–698

Srimal, R. C., Dhawan, B. N. (1973) Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. J. Pharm. Pharmacol. 25: 447–452