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EVIDENCE OF A MIXED AETIOLOGY IN FEATURES OF THE ERYTHEMA RESPONSE TO THE POTENT IRRITANT, RESINIFERATOXIN

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Diterpene ester toxins, notably the phorbol esters, are most widely known as tumour promotors and potent activators of protein kinase C (PKC); however, inflammation is the most general and acutely potent property of these compounds (Evans and Schmidt 1979). Resiniferatoxin (9,13,14-orthophenylacetyl-resiniferonol-20-0-homovanillate) (Rx) is the most potent irritant so far characterised yet it is a weak activator of PKC in-vitro, and is not a tumour promotor (Zur Hausen et al 1979). Since the homovanillate C-20 substitution resembles the polar head group of the neurotoxin, capsaicin, it has been suggested that Rx can act as an ultrapotent neurogenic irritant (Szallasi et al 1989). At the same time, we have identified a Ca^{2+}-independent kinase activity in mononuclear cells which is stimulated to a greater extent by Rx than by other phorbol esters (Ryves et al 1989). In the mouse ear erythema assay, the response to phorbol esters differs from neurogenic responses in several characteristics: it is a delayed, prolonged and generalised ear reddening which is resistant to indomethacin inhibition (Evans and Schmidt 1979) and capsaicin desensitization. At equivalent % response levels (Table 1), the agonist being applied in 5 µL acetone to the inner surface of the ear of adult female BKTO mice (10 per group), resiniferatoxin produced a typical, diterpene ester type delayed, prolonged response which was enhanced by capsaicin pretreatment. However, latency was dose-dependent (Fig. 1), and the rapid onset erythema displayed sensitivity to indomethacin (IC50 6mg/mL) and capsaicin pretreatment. It is suggested that a mixed aetiology may explain the extreme potency of resiniferatoxin as an irritant.

Table 1. Comparison of Erythema Responses

Treatment	Dose* (µg/mL)	Time to peak irritancy (±SE) (min)	Duration (h)
Resinifera-toxin	0.16	47 (±5)	>3
Sapintoxin D	2.8	59 (±12)	>3
Capsaicin	12.5	13 (±4)	0.2(±.03)
Rx/Capsaicin	0.16/50	28 (±11)	>3

*Agonist doses are minimum producing response in all animals. Antagonist doses are IC 90 for neurogenic response and were applied 30 minutes before agonist treatment. 5µL acetone solution applied / ear.

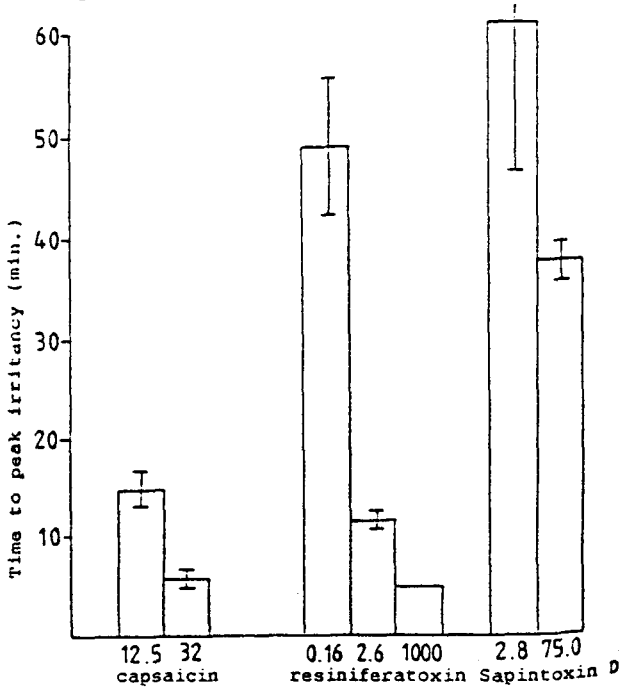

Figure 1. Effect of dose on time to peak irritancy. Data from 3-5 experiments. Lower selected dose is minimum dose producing 100% response. Upper doses for resiniferatoxin and sapintoxin D are those producing responses with a duration >3 h, >8 h and >12 h respectively.

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