

Allergy to Marihuana

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A 29-year-old housewife had symptoms consistent with an anaphylactoid response after smoking a marihuana cigarette for the first time. Scratch testing and passive transfer studies confirmed an immunologic basis for her response and indicated that it was related to the cannabinoid and perhaps specifically to the tetrahydrocannabinol component of the marihuana plant.

DESPITE the current widespread use of marihuana there have been few if any reports of hypersensitivity responses to the plant. We have recently studied a patient with anaphylactic sensitivity to marihuana, documented by direct skin testing and passive transfer studies. Of particular interest is the probable relationship of the allergic reaction to Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the psychoactive component of marihuana.

Case Report

The experimental subject, L.E., was a 29-year-old white housewife with a 15-year history of allergy to ragweed, documented by wheal and erythema skin reactivity to aqueous ragweed extract. In August 1970 she smoked a marihuana cigarette and almost immediately developed symptoms of nasal and pharyngeal pruritus, lacrimation, nasal congestion, dyspnea, and wheezing, all symptoms persisting 20 to 30 minutes and gradually subsiding. Although the subject had not used marihuana previously, she had attended parties where it had been smoked by others and had experienced no ill effects at those times. The subject once again smoked marihuana in October 1970 and was

forced to stop almost immediately because of the recurrence of the above symptoms.

Materials and Methods

To establish the diagnosis of marihuana allergy and to identify the ingredient in cannabis responsible for allergic reactivity, direct skin test studies were carried out in Subject L.E. and 10 "normal" controls, 5 of whom had had previous experience with marihuana. Using the methods of Lerner (1), cannabinoid fractions from two cannabis plants were isolated and analyzed by gas chromatography for Δ^9 -THC content. Fraction A, from a plant found in earlier clinical studies to be significantly psychoactive, contained 1.35% Δ^9 -THC; fraction B, from a plant found to have no psychoactive effects, contained 0.03% Δ^9 -THC. Because of the low water solubility of the cannabinoid fractions they were dissolved in 95% ethanol and then diluted 1:10 or more with phosphosaline (0.15 M NaCl, 0.01 M phosphate, pH 7.4). The intradermal injection of 10% ethanol phosphosaline produced nonspecific irritation; for this reason a scratch test procedure was used. A drop of the test solution was placed on the volar surface of the forearm and the underlying skin broken with a #25 needle. Subject L.E. and the 10 control subjects were tested with all concentrations of solutions A and B, as well as the 10% phosphosaline control solution. The responses were read at 20 minutes and graded (0 for no reaction, 1+ for erythema less than 10 mm, 2+ for erythema more than 10 mm, 3+ for erythema more than 10 mm and wheal less than 10 mm, and 4+ for erythema and wheal more than 10 mm).

Passive transfer studies were conducted with a 21-year-old nonallergic white male volunteer by injecting 0.1 ml of undiluted L.E. serum (shown to be negative for Australia antigen by radioimmunoassay (2)) intradermally into multiple sites on the recipient's back; 48 hours later the intradermal injection sites and immediately adjacent control sites were challenged with solution A, solution B, a solution of purified Δ^9 -THC, and a 10% ethanol phosphosaline control.

After the above studies were completed, we received

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Table 1. Cutaneous Responses to Solution A and Solution B* in Subject L.E. and Controls

	Control (10% Ethanol Phosphosaline)	Solution A (μ g extract/ml)					Solution B (μ g extract/ml)				
		0.0001	0.01	1	100	1,000	0.0001	0.01	1	100	1,000
Subject L.E.	0	0	1+	2+	2+	3+	0	0	0	0	0
Controls 1-9	0	0	0	0	0	0	0	0	0	0	0
Control 10	0	0	0	0	0	2+	0	0	0	0	0

* Solution A had a high content of Δ^9 -tetrahydrocannabinol; solution B had a low content of the component.

additional congeners in the cannabinoid series from Dr. Scigliano of the National Institute of Mental Health, Bethesda, Md.; these were used for direct scratch testing of Patient L.E.

Results

As shown in Table 1, Subject L.E. responded to low concentrations of solution A and showed no response to solution B in any concentration or to the control solution. None of the control subjects responded to solution B or the control solution, and only one subject responded to solution A, at a concentration 100,000-fold greater than the threshold concentration that had produced a positive response in the allergic subject. It is of interest that this control subject gave a history of seasonal rhinitis and of mild symptoms of coryza, lacrimation, and pharyngeal pruritus when using marihuana.

It is not possible to conclude from the direct skin results if Δ^9 -THC played any part in the experimental subject's cutaneous response or even if the response was immunologically mediated, since non-specific irritation might have produced similar changes. Because of the nonreactivity of solution B it could be argued that Δ^9 -THC was not solely responsible for the cutaneous response because, if it were, the higher concentrations of solution B should have caused cutaneous responses equivalent to those produced at lower concentrations of solution A. An increase in the relative amount of nonreactive cannabinoids in solution B, however, might inhibit the response and account for the failure of the Δ^9 -THC in this solution to produce a positive response.

To establish the immunological nature of the cutaneous response and to determine if Δ^9 -THC played any part in the reaction, passive transfer studies were done. As shown in Table 2, passive transfer of cutaneous sensitivity to solution A was demonstrated, establishing that skin sensitizing antibodies were the cause of the response. Moreover, a solution of purified Δ^9 -THC at about the concentration present in solution A (0.5 mg/ml versus 0.3 mg/ml) produced a comparable skin response. Unfortunately, the only solution of Δ^9 -THC available to us also contained 4.6% exocyclic THC (Table 3), which might have contributed to the response. Thus, al-

though it appears quite probable that the antigenic activity of solution A was related at least in part to its Δ^9 -THC content, further studies are needed to establish this point conclusively.

Table 3 shows that the experimental subject had a positive cutaneous response not only to Δ^9 -THC but also to cannabicyclol and cannabidiol. The significance of the positive response to the last two cannabinoids, however, is partially obscured by the fact that they were not available at the time of the passive transfer experiment, and hence a chemical irritant response cannot be altogether excluded.

Discussion

This study proves conclusively the occurrence of allergy to marihuana. Considering that an estimated 20 million people in the United States have used marihuana (3), one may assume that its allergenic potential is relatively low in view of the lack of reports of cannabis allergy. It is quite possible, however, that marihuana allergy is relatively common but is not reported because of the plant's legal status and the ease with which an allergic user would relate the symptoms to the plant and hence avoid it. Further studies are needed to establish the true incidence of marihuana allergy* and the spectrum of components in the plant that can participate in the allergic response. Marihuana contains a multiplicity of possibly immunoreactive molecules, including carotenoids, chlorophylls, xanthophylls (4), eugenol, guaiacol, piperidine (5), and trigonelline (6), in addition to at least 15 molecules in the cannabinoid series itself (7). Cannabinoids, and probably Δ^9 -THC itself, are implicated in the allergic response of Subject L.E. to marihuana. Further studies must be

Table 2. Cutaneous Responses 48 Hours After Transfer of Subject L.E.'s Serum to a Nonallergic Recipient*

	Control Area	Serum Site
Solution A (1 mg/ml)	0	2+
Solution B (1 mg/ml)	0	0
Δ^9 -tetrahydrocannabinol (0.5 mg/ml)	0	2+
Control	0	0

* Responses read at 30 minutes; all solutions 10% ethanol phosphosaline.

Table 3. Cutaneous Responses of Subject L.E. to Various Cannabinoids

Cannabinoid*	Composition	Cutaneous Response
Cannabinol	99%, trace amounts cannabidiol and Δ^9 -tetrahydrocannabinol	0
Cannabidiol	99%, trace material unidentified	1+
Δ^8 -tetrahydrocannabinol	98%, trace material unidentified	0
Δ^9 -tetrahydrocannabinol	95.4%, 4.6% exocyclic tetrahydrocannabinol	2+
Cannabicyclol	99%, trace material unidentified	2+
Control		0

* Concentration for all test solutions, 0.5 mg/ml; all solutions 10% ethanol phosphosaline.

carried out to establish conclusively the relationship of Δ^9 -THC to marihuana allergy. The induction of an antibody response to a drug requires the formation of a relatively stable (covalent, coordinate, or multiple ionic) bond with protein (8, 9). Protein reactivity is also required in the elicitation of an immediate allergic response to a drug, and drugs that do not readily react with protein fail to elicit local and systemic anaphylaxis (10). Thus, if it can be proved that Δ^9 -THC has substantial allergic reactivity, this would be strong presumptive evidence that it (or a metabolite formed very rapidly in the skin) has considerable protein reactivity, and it would be tempting to speculate that its psychotomimetic activity might depend on this property. The apparent effectiveness of Δ^9 -THC as an elicitor of immediate hypersensitivity also raises the possibility that there is an antibody specific for this psychoactive ingredient that could be used to develop a Δ^9 -THC

* In a survey in progress of marihuana users in a psychiatric clinic population, 4 of 30 have had respiratory symptoms similar to those of Subject L.E. while smoking the plant.

immunoassay. A sensitive radioimmunoassay for Δ^9 -THC could prove of great aid in studying the heretofore elusive metabolism of the cannabinoids.

In addition to the above immunochemical implications, the documentation of an allergic response of the immediate type to marihuana indicates that serious anaphylactic reactions to cannabis are a possibility in humans. This possibility has obvious implications, not only from a public health standpoint but also for clinical investigators engaged in marihuana research.

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