ABSTRACT

Contact allergy is caused by environmental exposure to chemicals (haptens). To identify contact allergens, animal tests are used but alternatives are requested and methods based on structure activity relationships (SARs) are developed. The electrophilic properties of organic compounds are considered as good predictors for allergenic activity as the formation of complete antigens is the result of nucleophilic-electrophilic reactions between most haptens and macromolecules in the skin.

In this thesis, the chemical reactivity and allergenic activity of carvone, an α,β-unsaturated ketone, and synthesized terpenoid derivatives designed to have different electrophilic characteristics, e.g. oximes and dienes, have been investigated. Since individuals most often are exposed to allergens in mixtures, we also examined the allergenic effect of carvone in mixtures with non-sensitizing compounds.

Considering the data from reactivity experiments with nucleophiles, it was assumed that the sensitizing capacity of the compounds would be in the order ketone > oxime > diene. However, in animal experiments, the results showed a different order of allergenic activity, i.e. oxime > diene > ketone. To elucidate the mechanism behind antigen formation, analogues were synthesized and their allergenic activity was examined in animals.

Carvone may bind covalently to a macromolecule via the β-carbon and via the carbonyl carbon. Animal data supported the interpretation from reactivity experiments, i.e. that antigen formation takes place via the β-carbon. The α,β-unsaturated oxime sensitized control animals after only one topical exposure. The mechanism behind the antigen formation is still unknown but the conjugated double bond seems to be important for the allergenic activity. Antigen formation of the oxime can take place after attack at the β-carbon but also via other mechanisms. A metabolic activation is most likely involved. The diene, without electrophilic properties, was identified as a prohapten. Two potential metabolites (epoxides) were synthesized. They formed peptide adducts in reactivity experiments, and were identified as skin sensitizers in mice. A clear correlation between the diene and the epoxides was obtained in guinea pigs. Investigation of the metabolism *in vitro* further supported that the epoxides are the true haptens.

The presence of non-allergenic compounds during induction of carvone sensitization significantly reduced the sensitizing effect in guinea pigs. The mechanism behind this phenomenon is still unknown. It can be concluded that the chemical structure of the hapten and the inhibitor not necessarily needs to be similar. Neither needs the inhibitor to be added in excess. No difference in the proliferation of murine lymphocytes, or in the production of cytokines, was observed, indicating that the reduced sensitizing effect can not be explained by a general immunosuppressive effect from the inhibitory chemicals.

Computerized systems based on SARs can be useful when predicting the sensitizing effect of novel compounds. However, improvements in detecting potential prohaptens are vital. Furthermore, the sensitizing effect obtained from a single chemical might not be the same when it is present in a mixture.

Keywords: antigen, contact allergy, diene, electrophile, epoxide, FCAT, guinea pigs, inhibition, ketone, LLNA, mice, nucleophile, oxime, patch testing, peptide, quenching, reactivity, sensitization, skin metabolism, structure activity relationship SAR

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