

# Drug metabolism in oral soft tissues

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Oral tissues are constantly exposed to a wide variety of chemicals through diet, medication, oral hygiene aids and habitual practices, such as cigarette smoking. Recent studies have indicated that these xenobiotics are metabolized in oral soft tissues and their metabolic pathways appear remarkably similar to those found in the liver, the major organ in the body for their metabolism. The oral cavity offers a diversity of potential sites, such as gingivae (gums), oral mucosa, tongue, dental plaque (a thin, sticky layer of bacteria that constantly forms on teeth) and saliva, all of which contain enzyme systems and/or micro-organisms capable of metabolizing xenobiotics.

It is now becoming evident that such local metabolism of drugs and other chemicals in oral soft tissues, in particular in the gingivae, may play a role in the etiology of various periodontal diseases involving inflammation of gingiva (gingivitis) and tissues supporting the teeth under the gum line accompanied by the formation of periodontal pockets and tooth mobility (periodontitis), and drug-induced gingival overgrowth (hypertrophy). Recent studies suggest that significant changes occur in the salivary levels of steroid sex hormones of patients with periodontitis. Also, there is currently an active interest in the use of salivary concentrations of drugs and their metabolites as an alternative to blood levels in therapeutic drug-monitoring of patients.

## Gingival metabolism of drugs

Healthy gingivae are essential for the integrity and normal function of the teeth in the oral cavity. Morphologically, the gingivae closely resemble skin. There is evidence that, like skin, gingival tissue contains NADPH-dependent cytochrome *P*-450 enzyme system, capable of metabolizing drugs and other exogenous, as well as endogenous, chemicals. Table I lists drugs and their metabolites formed in rat gingival homogenates at the physiological temperature of 37°C under *in-vitro* conditions. The observed gingival hydroxylation and *N*-demethylation reactions are the two very common pathways for the metabolism of drugs in the liver and other major organs.

Of particular significance is the gingival metabolism of phenytoin, a widely used anti-epileptic drug which is known to induce gingival overgrowth in patients on chronic therapy (Fig. 1). Significant levels of phenytoin and its *p*-hydroxylated major metabolite are found in

TABLE I. Drugs metabolized by rat gingiva

| Drug             | Therapeutic use        | Metabolites formed   |
|------------------|------------------------|--|
| Aminophenazone   | Analgesic, Antipyretic | 4-methylaminoantipyrine, Formaldehyde  |
| Triproleonnamine | Antihistaminic         | Desmethyltriproleonnamine, Formaldehyde  |
| Phenytoin        | Anti-epileptic         | 5( <i>p</i> -hydroxy)-5-phenylhydantoin<br>5(3,4-dihydroxy-1,5-cyclohexadien-1-yl)-5-phenylhydantoin (dihydrodiol) |

the gingivae of epileptic patients taking the drug. In experimental animal models, it has been observed that both phenytoin and its *p*-hydroxy metabolite induce gingival overgrowth at concentration levels comparable to those clinically achieved in patients.

Studies of laboratory animals, designed to delineate the biochemical mechanism of phenytoin-induced gingival overgrowth, suggest metabolic activation of the drug to a reactive metabolite in gingiva and its covalent binding to gingival proteins as an initial event in the induction of this tissue-specific drug toxicity (Fig. 2). Currently, it is well-recognized that many drugs and other xenobiotics are converted in the target organ to chemically-reactive metabolites, which then covalently bind to macromolecules, such as protein, lipid and DNA, and induce tissue-specific necrosis - including carcinogenesis.

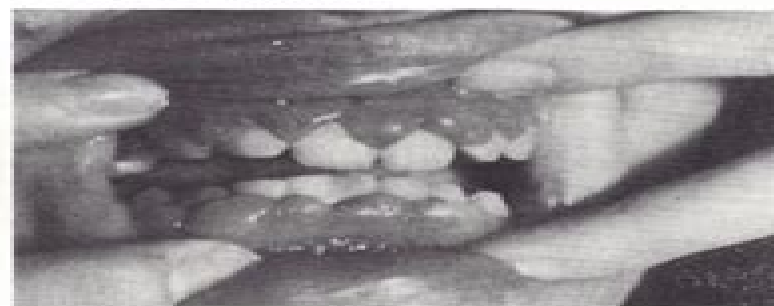


Fig. 1. Gingival overgrowth in an epileptic patient induced by chronic phenytoin therapy. The overgrowth shown is in moderate stage which, if left untreated (common treatment is by surgical removal, known as gingivectomy) leads to the severe stage where the crowns get completely covered by the overgrown gingiva. [Reproduced with permission from J. B. Ballard and W. T. Butler (1974) *J. Oral Pathol.* 3, 179.]

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# Metabolism Of Oral Tissues Conference

**JG Myers**



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