Inhibition of Prostaglandin I₂ Biosynthesis in Rat Dental Pulp by Phenolic Dental Medicaments

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Dental pulp is a highly specialized and abundantly vascularized soft connective tissue encased in dentine, and it is responsible for the formation and maintenance of the dentine. The stimulation of dental pulp by bacterial, mechanical, thermal or chemical means easily causes pulp inflammation. Phenolic compounds such as eugenol or guaiacol are widely used in dentistry as topical medicaments for the treatment of dental pain, a symptom of pulp inflammation. However, their mode of action is still unclear. One possible explanation is that the analgesic effect of these compounds may be due to the inhibition of prostaglandin (PG) biosynthesis, since this is the mode of action for aspirin-like anti-inflammatory drugs (1).

Recently, we found that the major metabolite of endogenous arachidonic acid formed via the cyclooxygenase pathway in rat dental pulp was PGI₂ (2). In the present study, therefore, the effects of some phenolic dental medicaments on PGI₂ biosynthesis by the pulp tissue were investigated.

Adult male Wistar rats weighing 200–250 g were decapitated, and the maxilla and mandibles were excised. Dental pulp tissues were carefully isolated in one piece from pulp cavities of incisor teeth as described previously (3). The tissues (40–50 mg) were first preincubated for 30 min in 2 ml of Krebs-Henseleit bicarbonate buffer (pH 7.4) containing 1 mg/ml glucose and then further incubated for 30 min in 2 ml of fresh Krebs buffer with or without test compound. All incubations were carried out at 37°C under a gas phase of 95% O₂ and 5% CO₂. PGI₂ in the incubation medium was extracted and assayed by radioimmunoassay as 6-keto-PGF_{1α} (2).

Phenol, thymol and guaiacol were ob-

tained from Wako Pure Chemical Indust., Osaka, and eugenol obtained from Tokyo Kasei Indust., Tokyo. Indomethacin and aspirin were purchased from Sigma Chemical Co., St. Louis.

When rat dental pulp tissue was incubated in Krebs buffer, 6-keto-PGF_{1α} was synthesized and released into the medium. The effects of phenol, thymol, guaiacol and eugenol on the endogenous production of 6-keto-PGF_{1α} were examined (control: 115.6±10.5 ng 6-keto-PGF_{1α}/g wet tissue weight/30 min, n=6). As shown in Fig. 1, all of these compounds were found to inhibit the 6-keto-PGF_{1α} production in a dose-dependent manner. IC₅₀ values for

Fig. 1. Inhibition of 6-keto-PGF_{1α} biosynthesis in isolated rat dental pulp by aspirin, indomethacin and four phenolic compounds. After preincubation, the dental pulp tissue was incubated for 30 min in 2 ml of Krebs buffer in the presence or the absence (control) of drugs. 6-keto-PGF_{1α} was determined by radioimmunoassay. The control value was 115.6±10.5 ng/g tissue (n=6). Points are the mean±S.E. (n=4–6 for each concentration of each drug).

phenol, guaiacol, thymol and eugenol were calculated as about 2 mM, 9.0, 3.5 and 0.5 μ M, respectively. IC₅₀ values for indomethacin and aspirin in this system were 10 and 260 μ M, respectively.

The involvement of PGs in pulp inflammatory pain is suggested by the clinical efficacy of aspirin-like drugs in dental pain, and the inhibition of heat-induced increase in sensory nerve activity in feline dental pulp by these drugs (4). Furthermore, Türker and Türker (5) have shown that noxious stimuli stimulate PG release from the perfused tooth pulp of dogs. Since PGI₂ is predominantly synthesized by pulp tissue (2) and has a potent hyperalgesic property (6), these circumstantial evidences suggest that PGI₂ is one of the most important mediators of pulp inflammatory pain.

The present study has demonstrated that phenolic compounds used as dental medicaments are strong inhibitors of PGI₂ biosynthesis by the pulp tissue, with the following order of potency: eugenol > thymol > guaiacol >> phenol. This order of potency agrees with that reported for the cyclooxygenase activity of sheep vesicular gland (7). Among tested compounds, the effects of guaiacol, thymol and eugenol were equal to or far more potent than that of indomethacin in this system. The potency of these phenolic compounds may be related to their lipid solubility, since alkyl substitutions on the phenol molecule increase the solubility (8).

On the other hand, phenol and guaiacol at low concentrations stimulate and at successively higher concentrations inhibit cyclooxygenase in microsomes from vesicular gland (9). However, at the cellular level, the dose-dependent inhibition by phenol itself and its substitutes has been reported in the PG production by 3T3 fibroblasts (10), consistent with our results. Therefore, the effects of phenolic compounds on PG biosynthesis seem to depend on the experimental systems used.

In clinical practice, eugenol and guaiacol are favorably used in the treatment of pulp inflammatory pain because of their rapid and direct analgesic properties (11). This may be explained by the present observation that these drugs are potent inhibitors of PGI₂

production. In most dental therapy using medicines containing phenolic compounds, free compounds are released from the site of application and diffuse to the adjacent tissue, and these local concentrations should be sufficient to completely inhibit PGI₂ biosynthesis. These phenolic compounds also possess a local anaesthetic property (11), which may be further enhance their appeal in the treatment of dental pain.

In conclusion, the present study suggests that the analgesic effects of phenolic compounds used as topical medicaments in dental therapy may be due at least in part, to their ability to strongly inhibit PGI₂ biosynthesis in the dental pulp.

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