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Hinokitiol (Beta-thujaplicin) has an ability to inhibit action potential conduction in nerve fibers

Hinokitiol, a natural tropolone derivative contained in a species of cypress tree, has various actions including inhibition of apoptosis, and insecticidal, anti-fungal, anti-tumor, anti-bacterial, anti-inflammatory and cytotoxic activities. We previously reported that plant-derived chemicals (capsaicin, menthol and allyl isothiocyanate) inhibit action potential (AP) conduction in nerve fibers without transient receptor potential channel activation by them. Their related drugs and also various aroma-oil compounds inhibited nerve fiber AP conduction in a manner dependent on their chemical structures. The present study found out for the first time an ability of hinokitiol to inhibit nerve fiber AP conduction and its chemical structure responsible for this inhibition. Compound action potentials (CAPs) recorded from the sciatic nerve of frogs were used as a measure of nerve fiber AP conduction.

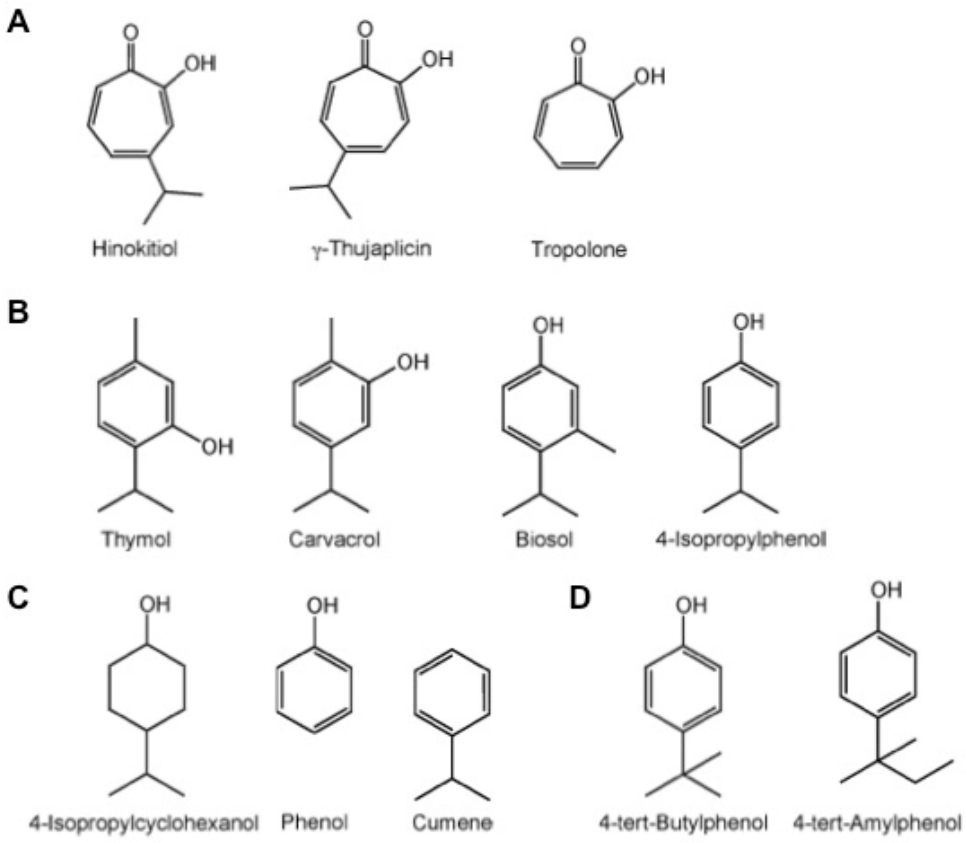

Fig. 1. Chemical structures of honokitiol and its related seven-membered ring compounds (A), six-membered ring compounds similar to hinokitiol (B), compounds exhibiting an importance of the benzene ring, hydroxyl and isopropyl groups of hinokitiol in inhibiting frog sciatic nerve compound action potentials (C) and compounds where the isopropyl group of 4-isopropylphenol is replaced by other hydrocarbon chains (D).

Hinokitiol concentration-dependently reduced the peak amplitude of frog sciatic nerve CAPs with a half-maximal inhibitory concentration (IC_{50}) value of 0.54 mM. As seen in Fig. 1A, left, hinokitiol has hydroxyl, carbonyl and isopropyl groups, all of which are bound to its seven-membered ring. An action similar to that of hinokitiol was produced by its stereoisomer γ-thujaplicin (Fig. 1A, middle; IC_{50} = 0.48 mM), while tropolone (Fig. 1A, right), which lacks the isopropyl group of hinokitiol, had no effects on frog sciatic nerve CAPs.

Thymol, carvacrol, biosol and 4-isopropylphenol (Fig. 1B), which have isopropyl and hydroxyl groups bound to their six-membered ring, inhibited frog sciatic nerve CAPs with the IC_{50} values of 0.34, 0.34, 0.58 and 0.85 mM, respectively. Interestingly, these values were similar to that of hinokitiol. This result may be due to the fact that the negative charge in the carbonyl bond of hinokitiol is biased to the oxygen atom owing to a difference in electronegativity between oxygen and carbon atoms and thus its seven-membered ring behaves as a benzene ring. A role of the benzene ring in CAP inhibition was supported by the observation that 4-isopropylcyclohexanol (Fig. 1C, left), where the benzene ring of 4-isopropylphenol is replaced by cyclohexane, inhibits CAPs with the IC_{50} of 1.5 mM, a value less than that of 4-isopropylphenol. Moreover, both of isopropyl and hydroxyl groups bound to the benzene ring appeared to be important for CAP inhibition, because phenol (Fig. 1C, middle) having only hydroxyl group inhibited CAPs less potently (only 20% reduction at 5.0 mM) and cumene (Fig. 1C, right) having only isopropyl group had no effects on CAPs.

4-tert-Butylphenol and 4-tert-amylphenol (Fig. 1D) reduced frog sciatic nerve CAP peak amplitudes with the IC_{50} values of 0.60 and 0.28 mM, respectively; these values were smaller than that of 4-isopropylphenol. Thus, CAP inhibition increased in extent with an increase in the number of -CH_2– added to the isopropyl group. This result suggests that a hydrophobicity of the compounds may be important for CAP inhibition. In support of this idea, a sequence of octanol-water partition coefficients (K_{ow}s, a measure of hydrophobicity) of their compounds was 4-isopropylphenol (log K_{ow} = 2.90) < 4-tert-butylphenol (3.31) < 4-tert-amylphenol (3.91). The isopropyl group of hinokitiol may serve to give this drug to a hydrophobicity for CAP inhibition.

It was concluded that hinokitiol inhibits nerve conduction, possibly through interaction involving its isopropyl, carbonyl and hydroxyl groups. This activity of hinokitiol could contribute partly to its pharmacological actions. Very recently, we have revealed that intravenous general anesthetic propofol having two isopropyl groups and one hydroxyl group bound to the benzene ring has an ability to inhibit nerve conduction. Structure-activity relationship of hinokitiol for nerve conduction inhibition, as revealed in the present study, may serve to develop more effective hinokitiol-related drugs in inhibiting nerve conduction.

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Publication

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