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REFERENCES

STUDIES ON THE ACTIVE PRINCIPLES OF MAGNOLIA BARK. CENTRALLY ACTING MUSCLE RELAXANT ACTIVITY OF MAGNOLOL AND HÔNOKIOL

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The bark of Magnolia officinalis Rehder et Wilson, "Hou-po" in Chinese, has been used in Chinese traditional medicine. The active principle of this crude drug has not been fully elucidated, although there are many reports on its chemical constituents, particularly on the alkaloids with curare-like action such as magnocurarine (1-5). We previously reported that the ether extract of magnolia bark showed a distinct central depressant effect as well as a centrally acting muscle relaxation, and that these pharmacological actions should be attributed to active principle(s) other than alkaloidal constituents with curare-like effect (6).

In the present paper, we report the comparison of centrally acting muscle relaxant effect between the fractions from the ether extract of magnolia bark and its purified constituents, magnoiol and hōnokiol.

The bark of Magnolia officinalis from a commercial source was extracted with purified ether as described previously (6). The ether extract was shaken with 0.2 N NaOH solution and alkaline soluble fraction was made conventionally. Magnoiol (2,2"-dihydroxy-5,5"-dipropylidiphenyl) and hōnokiol (3,5"-diallyl-4,2"-dihydroxybiphenyl) were refined from alkaline soluble fraction and identified chemically according to the method of Fujita et al.
Male albino mice, weighing 20 to 25 g, were used for muscle relaxation test. Before and after drug administrations a mouse was placed on a wire net (42 x 25 cm), which was turned upside down 100 cm above the floor and the duration of clinging to the net was recorded in seconds. When the duration of clinging was over 60 sec, the mouse was released from the net. Mephenesin, methocarbamol and chlorpromazine (Contomin®) were used as reference drugs. All chemicals and extracts except chlorpromazine were suspended in CMC-saline solution and given intraperitoneally. Each drug was tested in at least three doses, five mice per dose, to estimate the dose-response relationship. The percent response calculated as (60-duration of clinging ) x 10/6. The median effective dose (ED 50) and 95% confidence limits were determined by the method of Litchfield and Wilcoxon for muscle relaxation test. White young chicks, 4 to 13 days in age, were used for making a preparation of spinal reflex as described previously (6, 7). The chick was anesthetized with chloralose (50 to 70 mg/kg) injected intraperitoneally. Crossed extensor reflex of the leg was elicited by stimulation of contralateral peroneal nerve with supramaximal square wave pulses, 0.2 Hz, 1 msec in duration from the electronic stimulator (Nihon Kohden). Reflex was recorded on a kymograph through an isotonic lever.

Dose-response relationships of reference drugs and extracts for muscle relaxation test are shown in Fig. 1. Magnolol, 100 mg/kg, produced prominent muscle relaxation for 2 hr. The dose of 250 mg/kg induced loss of righting reflex in some of mice and muscle relaxation lasted over 3 hr. Minimum effective dose of magnolol was 90 mg/kg, while the sedative symptom was observed with much lower doses. Hōnokiol at the dose of 250 mg/kg showed muscle relaxing effect for 3 hr and 500 mg/kg produced loss of righting reflex. Muscle relaxing effect of both compounds disappeared gradually and fully recovered 24 hr after injection. Ether extract 1 g/kg induced loss of righting reflex 30 min after injection for nearly 60 min. The duration of clinging markedly shortened for more than 4 hr. Effects of alkaline soluble fraction obtained from ether extract on general behaviour of mice and on muscle tone were quite similar to those of ether extract. ED 50 of alkaline soluble fraction for muscle relaxation test was not so different from that of ether extract. The results appear reasonable since contents of ether extract are mostly soluble in alkaline solution. Mephenesin produced rapid and short-acting muscle relaxation. The dose of 150 mg/kg...
induced muscle relaxation within 5 min after the injection and the effect disappeared within 30 min. Methocarbamol at a dose less than 400 mg/kg produced a quite similar effect on muscle tone to mephenesin. Chlorpromazine at a dose less than 15 mg/kg showed long-lasting muscle relaxation, while duration of clinging to the net was never shortened to zero. In Fig. 2, the effect of magnolol on chicken spinal reflex is shown. Magnolol (75 mg/kg, i.p.) completely inhibited the extensor reflex in 40 min after the injection. The onset of the action was gradual and the duration was long (over 2 hr). The time course of the action was quite similar to that of the muscle tone experiment in mice. This inhibition was antagonized by a large dose of strychnine (400 μg/kg, i.p.), indicating that the inhibition was not exerted by curare-like activity. Hönokiol showed almost the same effect as magnolol on spinal reflex, but a higher dose (150 mg/kg, i.p.) was required to exert the same degree of inhibition as magnolol. Complete inhibition of the reflex was also obtained with mephenesin (50 mg/kg, i.p.), but the onset and the duration of action were much shorter (about 30 min) than those of magnolol. These results indicate that magnolol and hönokiol have a distinct and long-lasting muscle relaxant activity. Details of the mode of action of these compounds will be reported elsewhere.

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