Cardiovascular Effects of Aspidofractinine-Type Alkaloids from Kopsia

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Intravenous injection of the aspidofractinine alkaloid, kopsingine (1, 0.2–10.0 mg/kg) from Kopsia teoi, produced dose-related decreases in the mean arterial blood pressure and heart rate in anesthetized spontaneously hypertensive rats, which were similar to those seen in normotensive controls. Minor modifications in the molecular structure of kopsingine, as in kopsaparine (2, the 12-demethoxy derivative of kopsingine) and 14,15-dihydropaprine (4), did not significantly alter the hypotensive responses, whereas a more drastic change in the structure, as in the heptacyclic kopsidine A (3) and the 3-to-17 oxo-bridged compound 5, resulted in an increase in blood pressure. The antihypertensive effects of kopsingine (1) and its congeners (2 and 4) along with the pressor effects produced by the heptacyclic oxo-bridged compounds (5 and 3) could be ascribed to central as well as peripheral actions.

The genus Kopsia (Apocynaceae) comprises some 30 species of shrubs and trees distributed mainly over Southeast Asia, India, and China, of which about 18 species occur in Malaysia.1,2 The phytochemistry of this genus has received considerable attention, which has resulted in a considerable number of new natural products with novel structures and useful bioactivities.3–14 Some medicinal uses have been reported, such as for the cultivated species K. officinalis, which is used in China for the treatment of rheumatoid arthritis, dropsy, and tonsillitis;4 and in Malaysia, the roots of several Kopsia species are known to be used for poulticing ulcerated noses in tertiary syphilis.15 As part of an investigation dealing with hypotensive principles from Malaysian plants, we have previously demonstrated that gambirine (T), a tetracyclic heteroyohimbine alkaloid found in abundance in Uncaria calophylla, substantially lowered the arterial blood pressure in normotensive anesthetized rats.16 We have also found in preliminary studies that crude alkaloidal mixtures from several Kopsia species including K. profunda, K. larutensis, and K. teoi showed antihypertensive activity when tested in normotensive rats.17 The antihypertensive activity can be traced to the presence of the various types of indole alkaloids occurring in these plants. Kopsingine (1) and kopsaparine (2, the 12-demethoxy derivative of kopsingine) are indole alkaloids of the aspidofractinine-type and constitute the major alkaloids in several Malaysian Kopsia species including K. teoi L. Allorge. Kopsingine (1) and kopsaparine (2) were first isolated from K. singapurenisis.18 The constitution of these alkaloids was then established based on degradative experiments carried out on kopsaparine. Their structures have been recently confirmed by a detailed NMR and X-ray study on kopsingine, the predominant alkaloid present in K. teoi.19 In addition to these alkaloids, many novel minor alkaloids as well as semisynthetic aspidofractinines have also been recently documented in the literature.5,6,8,19–23 Relatively little is known about the pharmacological activities of these aspidofractinine-type alkaloids, and because the alkaloidal fraction of K. teoi showed antihypertensive activity in preliminary studies, we decided to obtain quantitative information regarding the cardiovascular effects of these alkaloids.

Results and Discussion

Kopsingine (1) and kopsaparine (2) are major alkaloids obtained from Kopsia teoi,18 while kopsidine A (3) is a minor alkaloid isolated from the leaves of the same plant.5 Kopsidine A (3) and the 3-to-17 oxo-bridged compound 5 can also be obtained via an electrochemically mediated semisynthesis from 1,18 whereas 14,15-dihydropaprine (4) is readily available via catalytic hydrogenation (H2, Pd/C) of kopsingine (1).

The basal mean arterial blood pressure (MABP) and heart rate (HR) averaged, respectively, in anesthetized spontaneously hypertensive rats (SHR) 179.4 ± 2.6 mmHg and 345.4 ± 4.2 bpm (beats per minute), and in anesthetized Wistar—Kyoto (WKY) rats 123.9 ± 2.7 mmHg and 360.0 ± 6.7 bpm on the day of the experiment.

Intravenous (iv) administration of 0.2–10.0 mg/kg of kopsingine (1) and kopsaparine (2) resulted in linear dose-related decreases in MABP and concomitant falls in HR in anesthetized SHR (Figure 1). BP and HR started to fall within 5 s of administration of kopsingine (1) and kopsaparine (2) and reached their lowest levels between 10 and 30 s. The hypotensive responses to 10 mg/kg of 1 and 2 lasted 3.9 ± 1.0 min and 3.6 ± 1.0 min, respectively. The decreases in MABP and HR induced by kopsingine and kopsaparine in the SHR were not significantly different compared with their respective normotensive WKY control groups (Figure 1) when tested by analysis of variance. In like manner, iv administration of 14,15-dihydropaprine (4, 0.2–10.0 mg/kg) also produced a dose-related decrease in MABP, which was accompanied by bradycardia in the SHR (Figure 2). The depressor responses induced by dihydropaprine (4) were not significantly different from the responses induced by kopsingine (1) and kopsaparine (2) in the SHR. In contrast to the effects of the