Blood pressure returned to the baseline level after 40 min. When doses were increased to 100 and 200 mg/kg, the hypotensive effect was dose-dependently increased, and the duration of hypotension was prolonged. When a dose of 200 mg/kg was used, SBP and DBP decreased within 5 min, and the maximal hypotensive effect was 31.4% ± 4.2% and 40.8% ± 4.6% ($p < 0.01$), respectively (Fig. 2). The duration of hypotension persisted for 60 min.

Hypotensive Effect of Stevioside on Anesthetized SHRs and Dogs

Stevioside at 25 mg/kg administered intravenously lowered SBP of SHRs from 207.9 ± 19.2 to 197.1 ± 12.0 mmHg ($p < 0.05$), while DBP decreased from 160.6 ± 13.3 to 149.1 ± 10.4 mmHg ($p < 0.05$). When doses were increased to 50, 100, 150, 200, 250, 300, and 400 mg/kg the hypotensive effect was dose-dependently increased (Fig. 3).

Stevioside administered intravenously to mongrel dogs at a dose of 15 mg/kg also decreased SBP from 153.9 ± 14.1 to 143.6 ± 12.6 mmHg, while DBP decreased from 100.6 ± 7.4 to 87.3 ± 6.7 mmHg ($p < 0.05$) (Fig. 3). When doses were increased to 25, 50, 100, and 150 mg/kg respectively, the hypotensive effect of stevioside also increased dose-dependently (Fig. 3).

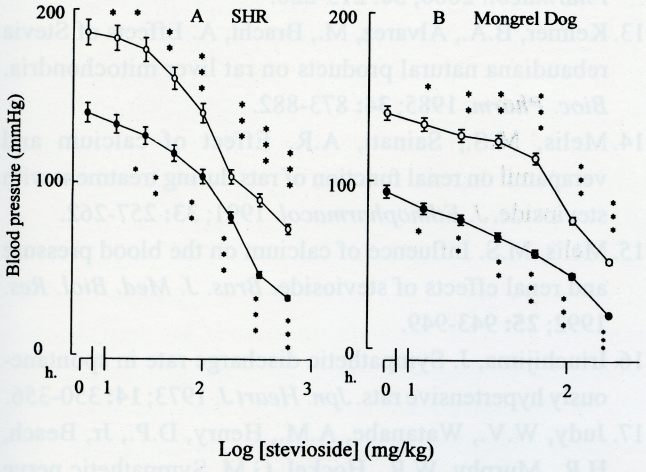

Fig. 3. Effects of intravenous stevioside on systolic blood pressure (○) and diastolic blood pressure (●) in anesthetized SHRs (A, $n = 10$) and mongrel dogs (B, $n = 8$); mean ± SD, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, compared with the control.

DISCUSSION

The present study is the first to evaluate in detail the dose-dependent hypotensive effects of stevioside in conscious and anesthetized animals. The present data reveal an interesting phenomenon that conventional antihypertensive agents usually have a better hypotensive effect on SBP than DBP. However, stevioside has a greater hypotensive effect on DBP. This phenomenon is significant for those hypertensive patients with higher DBP. Furthermore, the effective and progressive lowering of blood pressure by stevioside within 60 min when administered intravenously implies that it could be developed as an intravenous drug for treatment of hypertensive crises or on an emergency basis. Surgical patients receiving general anesthesia could also use this drug to control blood pressure. Our previous studies in animals and humans show that stevioside is a relatively safe chemical[11,12] when used for the study of hypertension.

The mechanism of the hypotensive action of stevioside has also been investigated. Previous studies showed that the hypotensive response to stevioside appears to occur through as calcium antagonist similar to that with verapamil.[14,15] These investigators also showed that the hypotension induced by stevioside in the rat is almost completely blocked by indomethacin, which is a potent inhibitor of prostaglandin synthesis.[8,16] Thus, the blood pressure lowering effect of stevioside probably depends on prostaglandin activity.

Previous reports have shown that plasma norepinephrine or epinephrine are increased in SHRs.[17-19] A similar phenomenon has also been reported in patients with essential hypertension.[20,21] Epinephrine can could enhance norepinephrine release from sympathetic nerve endings by stimulating presynaptic beta-adrenoceptors, and circulating epinephrine can also enhance alpha-adrenoceptor-mediated vasoconstriction by a postsynaptic effect,[22] which can result in increased peripheral arterial resistance and elevated blood pressure. Although stevioside administered intravenously does not decrease plasma catecholamine levels, the present data show that it does not enhance reflex sympathetic activity which might result in increased heart rate and catecholamine levels as shown with other