Increased Feline Cerebral Blood Flow Induced by Dehydroevodiamine Hydrochloride from Evodia rutaecarpa

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J. Nat. Prod., **1994**, 57 (3), 387-389• DOI: 10.1021/np50105a009 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 57, No. 3, pp. 387-389, March 1994

INCREASED FELINE CEREBRAL BLOOD FLOW INDUCED BY DEHYDROEVODIAMINE HYDROCHLORIDE FROM *EVODIA RUTAECARPA*[1]

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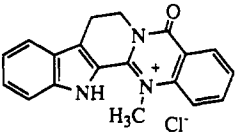
ABSTRACT.—Dehydroevodiamine hydrochloride (0.1–0.3 mg/kg iv), which was isolated from the leaves of *Evodia rutaecarpa*, increased the cerebral blood flow recorded from the surface of the supra-sylvian gyrus in anesthetized cats. This action reached a maximum 1–4 min after injection and continued for 10 min. However, the compound had negligible effects on other cardiorespiratory functions at the doses examined. These results suggest that the compound selectively increases cerebral blood flow.

Evodia fruits ("Goshuyu") as well as the leaves and roots of *Evodia rutaecarpa* Bentham or *E. officinalis* Dode (Rutaceae) are used in traditional Chinese medicine for the treatment of gastro-intestinal disorders, headache and migraine, and as a cardiotonic and analgesic (1). It has been reported that constituents of *Evodia* sp. have some discrete effects on cardiovascular function. For example, isoevodiamine increased the carotid blood flow in rabbits (2), evodiamine had a protective effect on hypothermia induced by chlorpromazine in mice (3), and dehydroevodiamine chloride caused hypotension in rats (4,5). Thus, evodiamine derivatives are thought to be the active constituents of extracts of *Evodia* sp. Unfortunately, no attention has been given to effects on the cerebral blood flow (CBF), although previous results led us to postulate that evodiamine derivatives may exhibit dose-dependent effects on the CBF. Recently, we have examined constituents of the leaves of *E. rutaecarpa*, and as a result, dehydroevodiamine hydrochloride (DHE·HCl) [**1**] was identified (6). Therefore, the present study was undertaken to examine the effects of DHE·HCl on the cardiorespiratory functions using anesthetized, spontaneously breathing cats, with a special emphasis on effects on the CBF.



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The control value of CBF recorded from the supra-sylvian gyrus ranged between 29 and 65 ml/min/100 g tissue weight (46±7 ml/min/100 g, $n=12$) in anesthetized cats. With a dose of 0.3 mg/kg, DHE·HCl [**1**] increased the CBF. The CBF response reached a peak 1–4 min after the DHE·HCl injection and recovered within 10 min. As was shown in Figure 1, the effect of DHE·HCl was decreased in peak amplitude and duration with a decrease in dose to 0.1 mg/kg. At a dose of 0.03 mg/kg, DHE·HCl had no effect on the CBF. The control values of systolic and diastolic blood pressure were 165±4 mm Hg and 136±6 mm Hg, respectively ($n=12$). DHE·HCl had negligible effects on blood pressure in a dose range that exerted an increase in the

[1]Presented in part at the Annual Meeting of the Japanese Society of Pharmacognosy, Osaka, Japan, 13 September 1993.

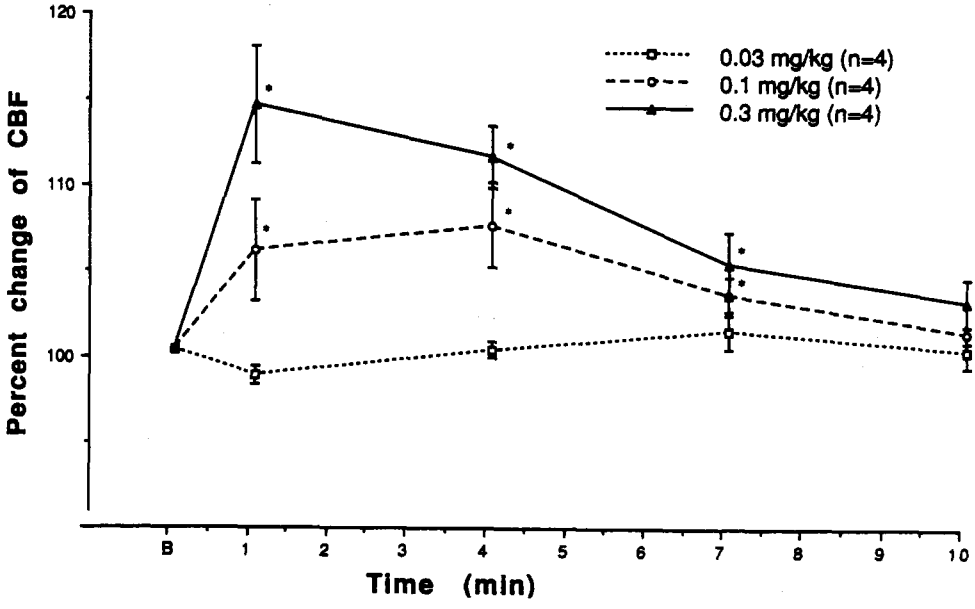

FIGURE 1. Percent (%) changes of the cerebral blood flow (CBF) induced by dehydroevodiamine hydrochloride. All values are mean±SE (n=4). Square, 0.03 mg/kg; circle, 0.1 mg/kg; and triangle, 0.3 mg/kg. *$p<0.05$, significantly different from the baseline.

CBF. Electrocardiogram and the heart rate (207±8/min), end-tidal concentration of CO_2 (4.9±0.2%), the respiratory rate (26±3/min), and the inspiratory myogram of the external intercostal muscle were all unchanged.

From these results, it was concluded that the intravenous administration of DHE·HCl [**1**] selectively increased the CBF. However, this compound did not have any detectable effect on the other cardio-respiratory functions at the doses examined. This is similar to observations previously reported by Yamada (2), who showed that isoevodiamine, an alkaloid constituent of the alcoholic extract of Evodia fruits, increased the carotid blood flow with no change in systemic blood pressure in anesthetized rabbits. However, the present results were not consistent with recent reports in which dehydroevodiamine hydrochloride has been shown to exhibit hypotensive effects resulting from vasodilation in anesthetized rats (4,5). This discrepancy may be attributed to the experimental conditions used. The dose in the previous studies was 50–100 times larger than that in the present study. Such high doses of DHE·HCl were not used because we selected the limited low doses which exclusively affect the CBF without any effect on the other functions. Therefore, the present results support the contention that *E. rutaecarpa* contains a constituent that selectively increases the CBF.

EXPERIMENTAL

DEHYDROEVODIAMINEHYDROCHLORIDE (DHE·HCL).—DHE·HCl [**1**] was previously isolated from the fresh leaves of *E. rutaecarpa* and identified by means of spectral analysis (6).

CHEMICALS.—α-Chloralose (Kanto Chemical), urethane (Kanto Chemical) and halothane (Takeda Pharmaceutical Co.) were purchased commercially.

MEASUREMENTS OF CARDIO-RESPIRATORY FUNCTION.—Experiments were performed on adult cats of either sex weighing 2.3–3.5 kg. The animals were initially anesthetized with halothane for cannulation of the trachea, femoral artery, and femoral vein. The head of the animal was placed on a stereotaxic frame. After the intravenous injection of a mixture of α-chloralose (50 mg/kg) and urethane (200 mg/kg), halothane anesthesia was discontinued. Body temperature was held at 36.5–38.0° by external heating. The skull was exposed and a 10 mm diameter hole was made on one side

of the parietal region corresponding to the suprasylvian gyrus. A laser-doppler probe was positioned epidurally for measuring the changes of CBF with a tissue blood flowmeter (Peri Flux 2, Perimed). Systemic blood pressure from the femoral artery was measured with a pressure transducer (TP-400T, Nihon Kohden). Bipolar stainless steel electrodes were inserted in the external intercostal muscle and the inspiratory activity was measured. An electrocardiogram was recorded with needle electrodes (lead II), and the heart rate was counted. The end-tidal concentration of CO_2 and respiratory rate were measured with a respiratory CO_2 monitor (Capnomac, Datex). Recordings of these cardio-respiratory variables were continuously displayed on a chart recorder (NEC San-ei, Polygraph) and stored on magnetic tape.

DHE·HCl [**1**] was dissolved at concentrations of 0.1 and 0.5 mg/ml in a 165 mM physiological saline solution and administered as a bolus dose through the femoral vein at doses of 0.03, 0.1, and 0.3 mg/kg.

Quantitative data were expressed as means±SE. Values obtained before and after administration of DHE·HCl were evaluated using a paired *t*-test. Statistical significance was assumed at $p<0.05$.

ACKNOWLEDGMENTS

This work is partly supported by the Toyama Prefecture with a grant for the consignable research.

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Received 26 July 1993