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General Neuropharmacology of Rutaecarpine, a Quinazolinocarboline Alkaloid

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Abstract – Rutaecarpine is one of quinazolinocarboline alkaloids found in *Evodia rutaecarpa*, a Rutaceous plant and it has shown various biological effects including antiinflammation. However, the effect of rutaecarpine on nervous system was not reported yet. In this study we investigated the general pharmacology of rutaecarpine on the central nervous system. Rutaecarpine (40 and 400 mg/kg) did not change chemoshock induced by pentylenetetrazole. However, oral administration of rutaecarpine altered motor coordination examined by rotarod test, pentobarbital-induced sleeping time and acetic acid-induced writhing syndrome in mice at the doses of 40 and 400 mg/kg. Rutaecarpine also induced hypothermia in mice at both doses. The results suggest that rutaecarpine possesses neuromodulating activities on central nervous system in addition to the various biological effects on the periphery.

Keywords □ Rutaecarpine, Quinazolinocarboline alkaloid, *Evodia rutaecarpa*, general pharmacology, central nervous system

INTRODUCTION

Rutaecarpine is one of quinazolinocarboline alkaloids of the Rutaceous plants such as *Evodia rutaecarpa* that has long been utilized as a Chinese herbal medicine. Recently, it has been reported that rutaecarpine has various biological effects such as vasodilation (Chiou *et al.*, 1994), antithrombosis (Sheu *et al.*, 2000), antiinflammation (Woo *et al.*, 2001; Moon *et al.*, 1999), anti-tumor invasion and antimetastasis using reconstituted basement membrane and animal model (Ogasawara *et al.*, 2002). In addition, rutaecarpine has a cardioprotective effect against myocardial ischemia-reperfusion injury in relation to activation of capsaicin-sensitive sensory nerves (Hu *et al.*, 2003). Rutaecarpine among the quinazolinocarboline alkaloids isolated from *Evodia rutaecarpa* is the most potent and selective inhibitory effect on cytochrome p450 1A in mouse and human liver microsomes (Ueng *et al.*, 2002; Don *et al.*, 2003). In spite of its various biological effects, the effect of rutaecarpine on central nervous system was not reported yet.

Dehydroevodiamine, a derivative of rutecarpine, has been reported to have anticholinesterase and antiamnesic activities not only in scopolamine- or unilateral electrolytic lesion-induced memory impairment (Park *et al.*, 1996; 2000) but in an animal model of Alzheimers disease-type amnesia (Wang *et al.*, 2001). These effects of dehydroevodiamine on brain activities imply that rutaecarpine may also affect the activities of the central nervous system.

Thus, the purpose of this study was to investigate whether rutaecarpine exerts the general pharmacological effects on the central nervous system.

MATERIALS AND METHODS

Animals

Male ICR mice were purchased from Hyochang Science (Daegu, Korea) and housed 5 per cage in a room maintained at 22±2°C with an alternating 12 hr light-dark cycle. Animals had food pellets and tap water *ad libitum* and were kept in these facilities for at least 2 days before the experiments.

Test substance and dose selection

The sufficient quantity of rutaecarpine (purity > 99.8%) was provided by chemical synthesis (College of Pharmacy, Yeungnam University, Gyeongsan, Korea) according to the general and efficient synthetic method of our group (Lee *et al.*, 2001). In the previous reports, the effective dose of rutaecarpine exert-

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ing cardioprotection, antithrombosis and anti-inflammatory actions was shown in the range of 0.1 mg/kg to 50 mg/kg (Moon *et al.*, 1999; Sheu *et al.*, 2000; Hu *et al.*, 2003). In the present study, we tested the doses of 40 and 400 mg/kg, about 10 and 100 folds of the effective dose in mice.

Pentobarbital-induced sleeping time

One hour after the drug administration, pentobarbital (50 mg/kg) was injected intraperitoneally into the mice. The time of onset of sleep and the duration of sleeping time each mouse were recorded. Chlorpromazine (10 mg/kg) was used as positive control.

Rotarod test

Mice were orally administered with rutaecarpine or vehicle and were subjected to the rotarod tests at 4 hr after the drug administration. The mice were placed on a 3 cm diameter rod (UGO-BASILE, Varese, Italy) rotating at 10 rpm, and the rotarod deficit was obtained by counting the number of animals fallen from the rotating rod within 2 min, as described previously (Dunham *et al.*, 1957).

Pentylenetetrazole-induced convulsion

PTZ (150 mg/kg) was injected intraperitoneally 1 hr after the drug administration. The induction time of the first generalized clonic seizure with loss of righting reflexes was measured. The incidence of convulsion and mortality were also determined. Phenobarbital (100 mg/kg) was used as positive control.

Analgesic activity

Each mouse was injected with 0.6% acetic acid (10 ml/kg. i.p.) 1 hr after the administration of rutaecarpine or vehicle, and was placed immediately in an observation cage. Ten minutes after the injection of acetic acid, the numbers of writhing episodes during the subsequent 10-min period were counted (Collier *et al.*, 1968). Acetaminophen (20 mg/kg, i.p.) was used as positive control.

Body temperature

Body temperature was measured rectally using an electrothermometer (Thermalert TH-5, Physitemp, USA). Rutaecarpine or vehicle was administered orally to male mice (22-25 g) and rectal temperatures were measured at 15, 30, 120, 240 min after the drug administration.

Statistics

Data were expressed as the meanSEM. Statistical significance was analyzed using Students *t*-test (Systat Inc., Evanston, Ill., USA). *P* values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Effect on pentobarbital-induced sleeping time

Oral administration of rutaecarpine decreased pentobarbital-induced sleeping time at doses 40 and 400 mg/kg when compared to the vehicle treated group, which is opposite to the effect of standard depressant chlorpromazine (Table I). The result suggests that rutaecarpine may exert anti-depressant action on brain function. The anti-depressant activity of rutaecarpine may also be attributed to the inhibition of pentobarbital metabolism or to an action on the central mechanism involved in the regulation of sleep.

Effect on rotarod test

As shown in Table II, rutaecarpine showed no significant effect the number of mice falling from the rotarod 30 min and 60 min after the drug administration. However, rutaecarpine increased incidence of ataxia at 4 hrs in a rotarod test, which indicating that rutaecarpine may affect the motor coordination.

Effect of pentylenetetrazole-induced convulsion

Rutaecarpine (40 and 400 mg/kg) did not alter the latency to pentylenetetrazole-induced seizures and the total duration of

Table I. Effect of rutaecarpine on pentobarbital-induced hyponosis in rat

Drug	Dose (mg/kg)	No. of animals	Duration time (min)
Vehicle		7	131.7 ± 7.1
chlorpromazine	10	7	261.75 ± 22.1*
Rutaecarpine	40	7	61.3 ± 5.2*
	400	7	51.3 ± 6.0*

Values represent mean±S.E.M.
*$p<0.01$, compared to vehicle treated group.

Table II. Effect of rutaecarpine on rota rod test in mice

Drug	Dose (mg/kg)	No. of animals	Number of mice which fell down		
			30 min	60 min	240 min
Vehicle	-	7	0	0	0
Rutaecarpine	40	7	0	0	2
	400	7	0	0	2

Table III. Effect of rutaecarpine on pentylenetetrazole-induced convulsion and death in mice

Drug	Dose (mg/kg)	No. of animals	Tonic Extensive Convulsion		Death	
			Incidence (%)	Latency (sec)	Incidence (%)	Latency (sec)
Vehicle	-	5	100	57.0±3.6	100	552.2±98.1
Phenobarbital	100	5	60	162.5±7.5*	0*	-
Rutaecarpine	40	5	100	58.5±8.8	100	491.5±127.0
	400	5	100	53.6±7.2	100	470.4±200

Values represents mean±S.E.M. *p<0.01, compared to vehicle treated group.

convulsions as compared to those of vehicle-treated group (Table III).

Analgesic activity

The oral administration of rutaecarpine caused significant inhibition of the writhing numbers of mice induced by acetic acid. Doses at 40 and 400 mg/kg showed significant reduction of the writhing syndrome when compared to acetaminophen-treated animals as well as vehicle-treated control group (Table IV). Since it has been reported that acetic acid-induced writhing is related to the increase in the peritoneal fluid levels of prostaglandin (PG) E2 and PGF2a (Deraedt *et al.*, 1980) and that rutaecarpine inhibits cyclooxygenase-2, our result suggests that rutaecarpine may exert an analgesic actions possibly through the inhibition of PG synthesis.

Body temperature

Rutaecarpine decreased the body temperature significantly in mice. Before the treatment, the mean body temperature of rats varied between 37.8±0.2°C for all groups as shown in Fig. 1. Following rutaecarpine administration, the maximal decrease of body temperature was reached at 120 min for both doses of 40 and 400 mg/kg. In the group of mice treated with 40 mg/kg rutaecarpine, the effect was reversible and the body temperature recovered to the initial pre-drug values within 240 min. However, the hypothermic effect at 400 mg/kg of rutaecarpine was not recovered to the initial body temperature. Although the mechanisms regulating hypothermia are not fully understood, the result indicates that rutaecarpine alters temperature regulation system.

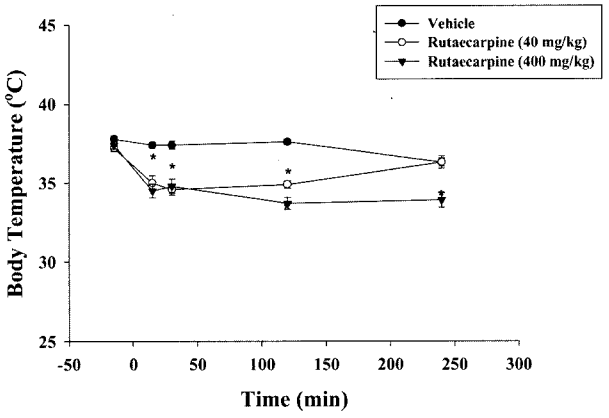

Fig. 1. Effect of rutaecarpine on body temperature in mice. Mice were administered with either vehicle (closed circle) or rutaecarpine at the dose of 40 (open circle) and 400 mg/kg (closed triangle) orally. Rectal temperature was measured at 15, 30, 120, 240 min after drug administration. *p<0.01, compared to vehicle treated group.

Taken together, the results indicate that rutaecarpine may exert pharmacological actions on the central nervous system.

Table IV. Effect of rutaecarpine on writhing syndrome induced by acetic acid in ICR mice

Drug	Dose (mg/kg)	No. of animals	Writhing Syndrome for 10 min
Vehicle	-	7	12.8±2.95
Acetaminophen	20	7	0.3±0.2*
Rutaecarpine	40	7	0.1±0.1*
	400	7	0*

Values represents mean±S.E.M. *p<0.01, compared to vehicle treated group.

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