Antiplatelet and Vasorelaxing Actions of Some Benzylisoquinoline and Phenanthrene Alkaloids

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Members of a series of benzylisoquinoline and phenanthrene alkaloids were tested for their antiplatelet and vasorelaxing actions. Atherosperminine $HClO_4$ (**15**) and atherosperminium I (**16**) showed strong inhibition of adenosine 5′-diphosphate-induced platelet aggregation. *dl*-*N*-Methylcoclaurine (**1**), *dl*-coclaurine (**6**), **15**, **16**, xylopine hydroxylamine (**18**), and atherosperminine *N*-oxide (**19**) showed strong inhibition of arachidonic acid-induced platelet aggregation. Compounds **1**, **15**, **16**, dicentrine methine (**17**), **18**, and **19** showed strong inhibition of collagen-induced platelet aggregation. *d*-(−)-Magnocurarine I (**8**), **15**, and **16** showed strong inhibition of platelet-activating factor-induced platelet aggregation. Compounds **15**, **17**, and **19** showed vasorelaxing action in rat thoracic aorta.

Thrombosis plays an important role in cerebral stroke and cardiovascular diseases,[1,2] and some "thrombolytic-vasoactive" Chinese herbs have been used in traditional medicine for the treatment of these diseases.[3] Our group has undertaken a program to isolate biologically active natural product substances from Chinese herbs, especially those having antiplatelet and vasorelaxing effects.

The isoquinoline alkaloids have been shown to have numerous biological activities.[4−9] Recently, we demonstrated that dicentrine, (−)-discretamine, and atherosperminine possess marked antiplatelet and vasorelaxing effects.[10−13] In order to elucidate the structure−activity relationships of these compounds in the two above biological phenomena, members of a series of benzylisoquinoline and phenanthrene alkaloids obtained from Formosan Annonaceous and Lauraceous plants[14−18] and some semisynthetic derivatives[16,17,19−22] were tested for their antiplatelet and vasorelaxing effects.

The antiplatelet effects of *dl*-*N*-methylcoclaurine (**1**), *l*-(+)-*N*-norarmepavine $HClO_4$ (**2**), *l*-(+)-reticuline (**3**), *l*-(+)-laudanidine (**4**), *dl*-*N*-norarmepavine (**5**), *dl*-coclaurine (**6**), *l*-(−)-*N*-norarmepavine (**7**), *d*-(−)-magnocurarine I (**8**), *O*-methyl-*l*-(−)-*N*-norarmepavine oxalate (**9**), *O*-methyl-*d*-(+)-*N*-norarmepavine (**10**), *l*-(+)-armepavine oxalate (**11**), *d*-(+)-armepavine oxalate (**12**), *l*-(+)-armepavine MeI (**13**), *d*-(−)-laudanosine (**14**), atherosperminine $HClO_4$ (**15**), atherosperminium I (**16**), dicentrine methine (**17**), xylopine hydroxylamine (**18**), atherosperminine *N*-oxide (**19**), and glaucine methine *N*-oxide (**20**) were studied on the aggregation of washed rabbit platelets induced by adenosine 5′-diphosphate (ADP, 20 μM), arachidonic acid (AA, 100 μM), collagen (10 μg/mL), and platelet-activating factor (PAF, 2 ng/mL), and on the vasorelaxing action of rat thoracic aorta induced by high K^+ (80 mM) and norepinephrine (3 μM). The results are shown in Tables 1 and 2. As indicated in Table 1, at a concentration of 100 μg/mL, compounds **15** and **16** completely inhibited platelet aggregation induced by all four agents (ADP, AA, collagen, and PAF). Compounds **1**, **18**, and **19** were potent inhibitors of platelet aggregation induced by AA and collagen, but not that induced by ADP or PAF. Compound **6** showed complete inhibition of AA-induced platelet aggregation, and compound **17** was more potent in that induced by collagen, while compound **8** was more potent in that induced by PAF. Compounds **2**, **3**, **5**, **7**, **11**, **13**, and **20** exhibited weak but significant inhibition on platelet aggregation caused by these same inducers. Compounds **4**, **9**, **10**, **12**, and **14** were almost devoid of any antiplatelet effects. Aspirin was used as a reference control, and completely inhibited AA-induced platelet aggregation, but not those of other inducers. Thus, the antiplatelet effects of the benzylisoquinoline and phenanthrene alkaloids evaluated are different from that of aspirin, which is a cyclooxygenase inhibitor.[23] However, their mechanism of action requires further investigation.

From the results obtained, the following five conclusions could be drawn in terms of antiplatelet effects. First, the 1,2,10-oxygenated secondary or tertiary benzylisoquinoline alkaloids containing two hydroxy groups at C-1 and C-10 on the A and C rings, for example, *dl*-*N*-methylcoclaurine (**1**), showed inhibition of platelet aggregation caused by AA and collagen. If the hydroxy group at C-1 or C-1 and C-10 of the 1,2,10-oxygenated benzylisoquinoline alkaloids was converted to an *O*-methyl group [as in *l*-(+)-armepavine MeI (**13**)] or two *O*-methyl groups [as in *O*-methyl-*l*-(−)-*N*-norarmepavine oxalate (**9**)], the antiplatelet effects were reduced. Second, modification of the 3,4-oxygenated tertiary phenanthrene alkaloids to *N*-oxides [as in atherosper-

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Table 1. Effects of Benzylisoquinoline and Phenanthrene Alkaloids on Platelet Aggregation Induced by ADP, AA, Collagen, and PAF in Washed Rabbit Platelets[a]

compound[b]	aggregation (%)			
	ADP	AA	collagen	PAF
1	73.6 ± 1.3	13.8 ± 11.9***	24.8 ± 15.1***	75.7 ± 11.9
2	63.1 ± 4.2*	60.5 ± 20.4*	83.6 ± 2.4	78.2 ± 5.7
3	58.7 ± 3.0*	39.2 ± 19.6**	84.2 ± 1.5	85.9 ± 2.0
4	77.6 ± 2.6	89.0 ± 0.7	87.9 ± 0.5	90.0 ± 3.8
5	30.4 ± 12.7***	49.7 ± 16.0*	24.7 ± 13.7***	86.4 ± 3.3
6	70.2 ± 0.1	0.0 ± 0.0***	69.7 ± 6.4	72.7 ± 2.2
7	69.7 ± 3.8	75.5 ± 5.1	83.4 ± 1.9	57.8 ± 5.4*
8	69.0 ± 6.7	87.4 ± 0.9	87.7 ± 0.6	23.2 ± 17.2***
9	93.4 ± 0.7	87.3 ± 2.9	86.6 ± 2.3	91.4 ± 0.1
10	93.1 ± 0.2	89.2 ± 1.6	79.2 ± 3.9	90.7 ± 3.2
11	89.7 ± 5.0	79.5 ± 2.6	82.4 ± 6.0	91.5 ± 1.0
12	92.7 ± 0.7	91.3 ± 0.5	88.4 ± 0.7	93.6 ± 1.3
13	93.7 ± 0.5	66.8 ± 5.4*	39.6 ± 3.6**	88.4 ± 2.6
14	92.2 ± 0.3	81.2 ± 2.7	81.4 ± 3.9	92.5 ± 0.4
15	0.0 ± 0.0***	0.0 ± 0.0***	0.0 ± 0.0***	0.0 ± 0.0***
16	0.0 ± 0.0***	0.0 ± 0.0***	0.0 ± 0.0***	0.0 ± 0.0***
17	34.9 ± 13.0**	46.9 ± 17.4*	6.1 ± 5.0***	80.5 ± 3.2
18	58.6 ± 8.4*	0.0 ± 0.0***	23.5 ± 7.9***	74.8 ± 7.4
19	37.4 ± 11.8**	0.0 ± 0.0***	0.0 ± 0.0***	61.1 ± 12.1*
20	74.6 ± 3.8	83.5 ± 1.8	52.1 ± 16.3*	87.2 ± 1.1
aspirin	77.9 ± 1.9	0.0 ± 0.0	87.8 ± 1.5	90.4 ± 1.1
control	82.2 ± 1.6	86.7 ± 0.4	89.0 ± 0.6	90.4 ± 1.1

[a] Platelets were preincubated with either a test compound, aspirin, or DMSO (0.5%, control) at 37 °C for 3 min, then ADP (20 μM), AA (100 μM), collagen (10 μg/mL), or PAF (2 ng/mL) was added. Percentages of aggregation are presented as means ± S.E. ($n = 3-5$); *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ as compared with the respective control. [b] Dose was 100 μg/mL, except for **4** and **18** (50 μg/mL); aspirin was administered at 25 μg/mL.

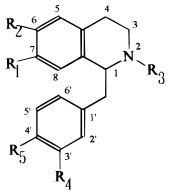
Table 2. Effects of Benzylisoquinoline and Phenanthrene Alkaloids on High Potassium- and Norepinephrine-Induced Phasic and Tonic Contractions of Rat Thoracic Aorta[a]

compound[b]	high K^+	norepinephrine (phasic)	norepinephrine (tonic)
1	70.8 ± 9.3	149.6 ± 27.4	106.6 ± 2.8
2	43.0 ± 1.0**	100.0 ± 0.0	90.5 ± 6.7
3	109.3 ± 9.1	100.0 ± 0.0	110.5 ± 12.7
4	105.0 ± 7.5	58.5 ± 2.4*	80.9 ± 0.6
5	107.8 ± 8.9	103.0 ± 1.2	95.7 ± 4.5
6	109.9 ± 10.9	100.0 ± 0.0	93.7 ± 7.4
7	71.2 ± 4.4	121.9 ± 3.7	105.7 ± 0.2
8	134.7 ± 49.3	122.5 ± 72.0	123.5 ± 10.8
15	0.0 ± 0.0***	0.0 ± 0.0***	0.0 ± 0.0***
16	38.3 ± 1.8***	108.3 ± 29.7	100.5 ± 8.6
17	44.6 ± 8.6**	7.1 ± 5.0***	0.0 ± 0.0***
18	55.8 ± 6.7*	102.0 ± 7.3	91.9 ± 1.3
19	5.8 ± 2.6***	30.0 ± 7.0***	27.5 ± 1.7***
20	104.2 ± 2.9	72.5 ± 5.3	83.2 ± 0.1
nifedipine	0.0 ± 0.0		
prazosin		0.0 ± 0.0	0.0 ± 0.0
control	100.0 ± 14.4	100.0 ± 16.7	100.0 ± 14.5

[a] Rat aortas were preincubated with either a test compound, nifedipine or prazosin (0.1%, control), or DMSO at 37 °C for 15 min, then high potassium (K^+, 80 mM) or norepinephrine (3 μM) was added. Percentages of the control contractions were calculated and presented as means ± S.E. ($n = 3$); *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ as compared with the respective control. [b] Dose was 100 μg/mL, except for **1**, **16**, **20** (20 μg/mL), and **4** (50 μg/mL); nifedipine and prazosin were administered at 1 μg/mL.

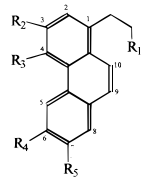
minine $HClO_4$ (**15**) and atherosperminine *N*-oxide (**19**)] resulted in reduced antiplatelet effects. Third, the 3,4-oxygenated tertiary or quaternary phenanthrene alkaloids containing two hydrogen atoms at C-6 and C-7 in ring C [as in atherosperminine $HClO_4$ (**15**) and atherosperminium I (**16**)] led to the most potent inhibition of platelet aggregation among these alkaloids. If the hydrogen atoms at C-6 or C-7 in ring C of the 3,4-oxygenated phenanthrene alkaloids were converted to one or two methoxy groups [as in xylopine hydroxylamine (**18**), dicentrine methine (**17**), and glaucine methine *N*-oxide (**20**)], the antiplatelet effects were decreased. Fourth, the antiplatelet effects of phenanthrenes were more potent than those of the benzylisoquinoline alkaloids among the test compounds. Finally, the optical rotation did not affect the antiplatelet effects of the test compounds.

Contraction of vascular smooth muscle can be induced by an α_1-adrenoceptor agonist (e.g., norepinephrine), which may be blocked by the antagonist prazosin.[24] The high K^+-induced contraction of vascular smooth muscles is the result of an increase in Ca^{2+} influx through voltage-dependent Ca^{2+}-channels, which are blocked by dihydropyridines (e.g., nifedipine).[25] As shown in Table 2, compounds **15** and **19** completely inhibited aortic contractions induced by high K^+ (80 mM) and norepinephrine (3 μM). Compound **17** strongly inhibited aortic contractions induced by norepinephrine and partially inhibited those induced by high K^+. Compounds **2** and **16** partially and significantly inhibited high K^+-induced contractions without affecting the norepinephrine-induced contractions. Compounds **1**, **7**, and **18** slightly (<50%) inhibited high K^+-induced contractions without affecting norepinephrine-induced contractions, whereas compounds **4** and **20** slightly inhibited norepinephrine-induced contractions without affecting high K^+-induced contractions. Other compounds tested (**3**, **5**, **6**, and **8**) showed no effect on the contractions caused by norepinephrine or high K^+. These results permit the following two conclusions. First, the 3,4-oxygenated tertiary or *N*-oxide phenanthrene alkaloids containing two methoxy groups or a methylenedioxy group at C-3 and C-4 in ring A [as in atherosperminine $HClO_4$ (**15**), dicentrine methine (**17**), and atherosperminine $HClO_4$ (**15**), dicentrine methine (**17**), and atherosperminine *N*-oxide (**19**)] showed the most potent vasorelaxing action; modification of the 3,4-oxygenated tertiary phenanthrene alkaloids to quaternary or hydroxylamine alkaloids, such as athereosperminium I (**16**) and xylopine hydroxylamine (**18**), reduced vasorelaxing action. Second, when the substituent



	R_1	R_2	R_3	R_4	R_5
dl-*N*-Methylcoclaurine (**1**)	OH	OCH_3	CH_3	H	OH
l-(+)-*N*-Norarmepavine $HClO_4$ (**2**)	OCH_3	OCH_3	H	H	OH
l-(+)-Reticuline (**3**)	OH	OCH_3	CH_3	OH	OCH_3
l-(+)-Laudanidine (**4**)	OCH_3	OCH_3	CH_3	OH	OCH_3
dl-*N*-Norarmepavine (**5**)	OCH_3	OCH_3	H	H	OH
dl-Coclaurine (**6**)	OH	OCH_3	H	H	OH
l-(-)-*N*-Norarmepavine (**7**)	OCH_3	OCH_3	H	H	OH
d-(-)-Magnocurarine I (**8**)	OH	OCH_3	$(CH_3)_2I^-$	H	OH
O-Methyl-*l*-(-)-*N*-norarmepavine oxalate (**9**)	OCH_3	OCH_3	H	H	OCH_3
O-Methyl-*d*-(+)-*N*-norarmepavine (**10**)	OCH_3	OCH_3	H	H	OCH_3
l-(+)-Armepavine oxalate (**11**)	OCH_3	OCH_3	CH_3	H	OH
d-(+)-Armepavine oxalate (**12**)	OCH_3	OCH_3	CH_3	H	OH
l-(+)-Armepavine MeI (**13**)	OCH_3	OCH_3	$(CH_3)_2I^-$	H	OH
d-(-)-Laudanosine (**14**)	OCH_3	OCH_3	CH_3	OCH_3	OCH_3

Figure 1. Structures of benzylisoquinoline alkaloids used in this investigation.



	R_1	R_2	R_3	R_4	R_5
Atherosperminine $HClO_4$ (**15**)	$N(CH_3)_2$	OCH_3	OCH_3	H	H
Atherosperminium I (**16**)	$N^+(CH_3)_3$	OCH_3	OCH_3	H	H
Dicentrine methine (**17**)	$N(CH_3)_2$	OCH_2O		OCH_3	OCH_3
Xylopine hydroxylamine (**18**)	$N(CH_3)OH$	OCH_2O		H	OCH_3
Atherosperminine *N*-oxide (**19**)	$N^+(CH_3)_2O^-$	OCH_3	OCH_3	H	H
Glaucine methine *N*-oxide (**20**)	$N^+(CH_3)_2O^-$	OCH_3	OCH_3	OCH_3	OCH_3

Figure 2. Structures of phenanthrene alkaloids used in this investigation.

groups at C-6 and C-7 in ring C are both methoxy groups, as in the 3,4-oxygenated *N*-oxide phenanthrene alkaloids [e.g., glaucine methine *N*-oxide (**20**)], vasorelaxing action was also reduced.

Inasmuch as platelet-vessel wall interactions are important in the development of thrombosis and atherosclerosis, compounds possessing strong antiplatelet and vasorelaxing effects (e.g., **15**, **17**, and **19**) may hold potential for the treatment of cardiovascular diseases including thrombosis and atherosclerosis.

Experimental Section

General Experimental Procedures. Benzylisoquinoline (Figure 1) and phenanthrene (Figure 2) alkaloids employed in this investigation were either isolated from plant sources [compound **3** from *Annona squamosa*,[14] **4** and **5** from *Notaphoebe konishii*,[15] **6** and **7** from *Machilus kusanoi*,[16,17] **8** and **14** from *Litsea cubeba*,[18] and **15** and **16** from *Fissistigma glaucescens*[19]] or prepared by semisynthesis [compounds **1**,[16] **2**, **9**, **11**, and **13**,[17] **10** and **12**,[20] **17** and **18**,[21] and **19** and **20**[22]]. All alkaloids used were already available in our laboratory and were dissolved in DMSO before testing.

In order to eliminate the effects of the solvent on aggregation, the final concentration of DMSO was fixed at 0.5%. Collagen (type 1, bovine Achilles tendon; from Sigma Chemical Co., St. Louis, MO) was homogenized in 25 mM HOAc and stored at −70 °C at a concentration of 1 mg/mL. PAF (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine), purchased from Sigma, was dissolved in $CHCl_3$ and diluted into 0.1% bovine serum albumin saline solution immediately prior to use. ADP and AA (sodium salt), also obtained from Sigma, were dissolved in H_2O and stored at −20 °C at a concentration of 10 mM. EDTA (disodium salt) and bovine serum albumin were purchased from Sigma.

Bioassays, Platelet Aggregation. Blood was collected from the rabbit marginal ear vein and was mixed with EDTA to a final concentration of 6 mM. It was centrifuged for 10 min at 90 × g at room temperature, and the supernatant was obtained as platelet-rich plasma. The latter was further centrifuged at 500 × g for 10 min. The platelet pellets were washed with Tyrode's solution (Ca^{+2}-free) containing 2 mM EDTA, 0.1 mg/mL apyrase, and 3.5 mg/mL bovine serum albumin, and centrifuged at 500 × g for 10 min. Then, the pellets were washed with Tyrode's solution without EDTA. After centrifugation under the same conditions, the platelet pellets were finally suspended in Tyrode's solution of the following composition (mM): NaCl (136.8), KCl (2.8), $NaHCO_3$ (11.9), $MgCl_2$ (2.1), NaH_2PO_4 (0.33), $CaCl_2$ (1.0), and glucose (11.2) containing bovine serum albumin (0.35%).

Aggregation was measured by a turbidimetric method[26] using a Lumi-aggregometer (Chrono-Log Corp., Havertown, PA). All glassware was siliconized. Three minutes before the addition of the aggregation inducer, the platelet suspension was stirred at 1200 rpm. The percentage of aggregation was calculated as follows (abs. = absorbance):

$$\text{aggregation (\%)} = \frac{\text{abs. of platelet suspensn} - \text{final abs. after aggregn}}{\text{abs. of platelet suspensn} - \text{abs. of Tyrode soln}}(100)$$

Percent aggregation was expressed assuming the absorbance of platelet suspension as 0% aggregation and the absorbance of platelet-free Tyrode's solution as 100% aggregation.

Aortic Contraction. Wistar rats of either sex weighing 250−300 g were killed in a humane fashion. The thoracic aorta was isolated, and excess fat and connective tissue were removed. Vessels were cut into rings of about 5 mm in length and mounted in organ baths containing 5 mL of Krebs solution (mM: NaCl 118.2, KCl 4.7, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2, $CaCl_2$ 1.9, and glucose 11.7), maintained at 37 °C, and gassed with a 95% O_2 and 5% CO_2 mixture. Two stainless steel hooks were inserted into the aortic lumen, one fixed and the other connected to a transducer. Aortas were equilibrated in the medium for 90 min with three changes of Krebs solution and maintained under an optimal tension of 1 g before specific experimental protocols were initiated. Contractions were induced by high potassium (80 mM) or norepinephrine (3 μM) and recorded isometrically via a force displacement transducer connected to a Gould polygraph (Model 2400; Gould, Inc., Cleveland, OH). The final concentration of DMSO was fixed at 0.5%. Norepinephrine caused two-phase contractions, an initial phasic twitch and then a sustained tonic contracture.

Data Analysis. The experimental results are expressed as means ± S.E. and accompanied by the number of observations. A one-way analysis of variance (ANOVA) was used for multiple comparison, and if there was significant variation between treatment groups, then the mean values for inhibitors were compared with those for controls by the Student's *t* test, and *p* values of less than 0.05 were considered to be statistically significant.[27]

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