PHARMACOLOGICAL FEATURES OF PERIPHERAL VASCULAR BEDS OF BEAGLES

Kazushige SAKAI, Shigeru SUGANO, Norio TAIRA and Koroku HASHIMOTO

Department of Pharmacology, Research Laboratories, Chugai Pharmaceutical Co., Toshima-ku, Tokyo and Department of Pharmacology, Tohoku University School of Medicine, Sendai, Japan

Accepted May 15, 1974

Abstract In order to accumulate fundamental data concerning circulatory pharmacological studies using Beagles, vascular responses to 28 drugs of the coronary, renal, mesenteric and femoral vascular beds were investigated. It is expected that there may be qualitative differences among the responses to hydralazine, lobeline, DMPP, nicotine, procaine and TEA of Beagles and those of mongrel dogs reported previously. When peripheral vascular responses to norepinephrine, ACh, adenosine and histamine were examined quantitatively, no significant differences were observed between Beagle and mongrel dogs regarding sensitivities to the four tested drugs.

During the last few years, Beagles which have the desirable qualities as an experimental dog, e.g. medium size, moderate length of hair, even temperament, adaptability to living in groups, etc. have been mainly employed in long-term studies such as chronic toxicological studies and nutritional research (1). Accordingly, a large number of data have been gathered concerning the basic investigations on breeding, care, heredity, disease, etc., which support the long-term studies (2–8). Recently, Beagles have been used in the field of acute or subacute experiments on circulatory physiology and pharmacology (9–16). However, there are few data obtained from the experiments on peripheral circulation using Beagles (17). This present work was carried out to examine the effect of various drugs on the peripheral vascular beds of Beagles, as contrasted to that obtained in mongrel dogs (18).

MATERIALS AND METHODS

Thirty-four Beagles* and twenty-two mongrel dogs of both sexes, weighing about 10 kg were used. Dogs were anesthetized with 30 mg/kg i.v. of sodium pentobarbital. An initial dose of 500 U/kg i.v. of sodium heparin was given. Twelve mg/kg of sodium pentobarbital and 200 U/kg of sodium heparin dissolved in 20 ml of physiological saline were infused intravenously at a rate of 0.11 ml/min using a Harvard infusion pump (Model 944). The dogs were artificially respired with room air using a Harvard respirator (Model 607). The number of experiments were 15 (Beagle; 9, mongrel; 6) for the coronary.

* For this study, Beagles bred in Chugai Beagle Farm, Hidaka, Hokkaido, Japan, were utilized.
14 (Beagle; 9, mongrel; 5) for the renal, 14 (Beagle; 8, mongrel; 6) for the mesenteric and 13 (Beagle; 8, mongrel; 5) for the femoral vascular bed.

The methods for perfusion of each peripheral organ were as follows: For the coronary circulation, the preparation was arranged according to the procedure described by Yago (19). The left coronary artery was cannulated with a special cannula through the right carotid artery. The arterial blood from the right femoral artery was perfused into the left coronary artery at the systemic blood pressure. For the renal, the mesenteric and the femoral circulation, the left renal, the superior mesenteric or the left femoral artery was cannulated respectively as described previously (18) and constant pressure perfusion at about 100 mmHg was performed by means of a Harvard peristaltic pump (Model 500-1200). A diagram of the perfusion system is illustrated in Fig. 1. Constant pressure perfusion was accomplished by setting up a pneumatic resistance through which any excess of blood was shunted to the femoral vein. Pressure transducers (Nihon Kohden MP-4T) were used for the measurements of systemic blood pressure and peripheral perfusion pressure. Peripheral blood flow was measured continuously by means of electromagnetic flowmeter (Nihon Kohden MF-2a). An ink writing oscillograph (Nihon Kohden WI-180) was used for recording.

Twenty-eight drugs listed in Table 1 were examined. The drugs were dissolved in physiological saline just before injection. A volume ranging from 0.1 to 0.2 ml of the drug solution was injected over a period of 10 seconds into the rubber tube connected to the arterial cannula.

---

**Fig. 1.** Diagram of the perfusion system. PP: transducer for perfusion pressure, F: electromagnetic flowmeter, SBP: transducer for systemic blood pressure, PUMP: Harvard style peristaltic pump, PR: pneumatic resistance, A: from right femoral artery, V: to right femoral vein, RA: left renal artery, CA: left coronary artery, SMA: superior mesenteric artery, FA: left femoral artery.
1. Effects of various drugs on peripheral vascular beds of Beagles

The dose level or the range of dose levels for each drug where a positive response was obtained are listed in Table 1. Also listed in Table 1 are drugs with doses tested which elicited no response.

| Table 1. Dose level or the ranges of dose levels for each drug tested |
|---------------------------------------------------------------|
| Groups | Drugs | Coronary vascular bed | Renal vascular bed | Mesenteric vascular bed | Femoral vascular bed |
|--------|-------|-----------------------|--------------------|------------------------|----------------------|
| Biogenic amines | Acetylcholine chloride (ACh) | 0.01-0.3 | 0.01-0.3 | 0.03-1 | 0.0003-0.01 |
| | dl-Epinephrine hydrochloride | 1 | 0.3 | 0.3 | 0.3 |
| | l-Isoproterenol hydrochloride | 0.3 | 10 | 1 | 0.3 |
| | dl-Norepinephrine hydrochloride | 0.03-1 | 0.01-0.3 | 0.0003-0.1 | 0.01-0.3 |
| | S-Hydroxytryptamine creatinine sulfate (5-HT) | 10 | 1 | 1 | 1 |
| Active polypeptides | Histamine dihydrochloride | 0.03-1 | 0.1-3 | 0.03-1 | 0.01-0.3 |
| | Ephedrine hydrochloride | 5(a) | 100 | 500 | 1(a) |
| | Kallikrein | 0.1(b) | 0.5(b) | 0.5(b) | 0.1(b) |
| | Angiotensin II | 0.5 | 0.03 | 0.03 | 0.1 |
| | Vasopressin (synthetic) | 0.05(b) | 0.02(b) | 0.02(b) | 0.02(b) |
| Nucleotides & nucleosides | Adenosine triphosphate (disodium salt) (ATP) | 10 | 10 | 10 | 10 |
| | Adenosine | 0.03-1 | 0.1-3 | 0.03-1 | 0.1-3 |
| | Nicotinamide-adenine dinucleotide (DPN) | 20 | 50 | 50 | 20 |
| | Nicotinamide-adenine dinucleotide phosphate (TPN) | 40 | 20 | 20 | 40 |
| | Uridine-5'-phosphate (disodium salt) (UMP) | 500(c) | 50 | 50 | 50 |
| | Uridine-5'-triphosphate (trisodium salt) (UTP) | 20 | 20 | 40 | 40 |
| Unspecific smooth muscle relaxants and stimulants | Papaverine hydrochloride | 500 | 500 | 500 | 500 |
| | Aminophylline | 2(a) | 5(a) | 2.5(a) | 2(a) |
| Cardiotonics | Dipyriramole | 100 | 100 | 100 | 100 |
| | Ouabain | 15(c) | 7.5 | 7.5 | 15(c) |
| Hypotensive agents | Hydralazine hydrochloride | 4(a) | 500 | 500 | 500 |
| | Benzylmipradilic chloride | 1(a) | 1(a) | 1(a) | 1(a) |
| Ganglion stimulants & depressants | Nicotine | 50 | 100 | 50 | 100 |
| | 1,4-Dimethyl-4-phenylpiperazinium iodide (DMPP) | 50 | 50 | 50 | 50 |
| | Lobeline hydrochloride | 10 | 1 | 100 | 1(a) |
| | Tetraethylammonium chloride (TEA) | 5(a) | 5(a) | 5(a) | 5(a) |
| Analgesics | Procaine hydrochloride | 1(a) | 1(a) | 1(a) | 500 |
| | Morphine hydrochloride | 1-2(a) | 1-4(a) | 1(a) | 0.5-1(a) |

The dose is represented in µg except in mg (a) and in units (b). (c) shows that responses were not distinct in these dose levels. The groups of tested drugs are classified according to the results in mongrel dogs by Hashimoto et al. (18).
(a) Effects on the coronary vascular bed

All drugs tested, except for angiotensin, vasopressin, ouabain and UMP, dilated the coronary vascular bed (CVB). Angiotensin and vasopressin rather constricted the CVB in large dose levels of 0.5 μg and 0.05 U, respectively. Ouabain and UMP had no effect on the CVB in tested does levels of 15 μg and 500 μg, respectively. Some representative examples are shown in Fig. 2.

![CORONARY VASCULAR BEDS](image)

(b) Effects on the renal vascular bed

UTP, ATP, kallikrein, ACh, histamine, isoproterenol, papaverine, aminophylline and hydralazine had a dilatory action on the renal vascular bed (RVB) and, in particular, kallikrein in a dose level of 0.5 U caused a marked response. Hydralazine in a dose level of 500 μg dilated the RVB but its dilatation was preceded by initial brief constriction in 2 out of 5 preparations. Papaverine in a dose level of 500 μg produced biphasic dilatation. Morphine in a small dose level of 1 mg dilated the RVB but constriction was observed with a large dose of 4 mg. TEA, lobeline, dipyridamole, procaine, adenosine, DPN and TPN constricted only the RVB. Angiotensin in a dose level of 0.03 μg caused a strong brief constriction followed by slight dilatation. Fig. 3 shows some representative examples.
(c) Effects on the mesenteric vascular bed

Effects of biogenic amines and active polypeptides on the mesenteric vascular bed (MVB) were similar to those on the RVB. However, dilatation in the MVB induced by isoproterenol, histamine and kallikrein was more marked than that in the RVB. Moreover, among these drugs, 5-HT in a dose level of 1 µg caused two kinds of response; 4 out of 7 preparations exhibited constriction and the others dilatation. Among ganglion stimulants and depressants, DMPP and nicotine constricted the MVB, while TEA and lobeline dilated it. All nucleotides and nucleosides tested except UMP produced remarkable dilatation. Ouabain and benzylimidazoline constricted the MVB, but papaverine and procaine dilated it. Typical results are shown in Fig. 4.

(d) Effects on the femoral vascular bed

As shown in Fig. 5, all of the drugs tested, except for ouabain and benzylimidazoline, produced responses practically identical to those in the MVB. Ouabain in a dose level of 15 µg caused no response in the femoral vascular bed (FVB) and benzylimidazoline in a dose level of 1 mg rather dilated it.
2. Comparison of sensitivities to norepinephrine, ACh, adenosine and histamine of various vascular beds of Beagles and mongrel dogs

The initial blood flows and perfusion pressures of experimental animals are presented in Table 2. In order to investigate whether or not there is any difference in sensitivity of the coronary (A), mesenteric (B), renal (C) and femoral (D) vascular beds to norepinephrine, ACh, adenosine, and histamine between Beagles and mongrel dogs, dose-response curves were constructed. As shown in Fig. 6, there was statistically no significant difference.

**DISCUSSION**

Mongrel dogs have been most popularly employed as an experimental dog. The dog has, however, many factors unfavorable for experiments, e.g. unknown bleeding conditions, parasitism of Dirofilaria immitis, high frequent infection with distemper and other epidemic diseases (20-22). Dirofilaria immitis in particular proves a severe hindrance to experiments on the circulatory system (23-26). The purebred dog which is intended to be bred as an experimental animal has therefore been used recently in various investigations (1). Even for studies in the field of acute or subacute circulatory physiology and pharmacology,

| Biogenic Amines          | 1/µg | 0.3/µg | 1/µg | 1/µg | 1/µg |
|--------------------------|------|--------|------|------|------|
| ACh                      |      |        |      |      |      |
| Norepinephrine           |      |        |      |      |      |
| 5-HT                     |      |        |      |      |      |
| Isoproterenol            |      |        |      |      |      |
| Histamine                |      |        |      |      |      |

| Active Polypeptides      | ml/min |
|--------------------------|--------|
| Angiotensin              | 0.03/µg|
| Kallikrein               | 0.5U   |
| Vasopressin              | 0.02U  |

| Ganglion stimulants and depressants |
|-------------------------------------|
| Nicotine                            | 50/µg |
| Lobeline                            | 100/µg|
| TEA                                 | 5mg   |
| DMPP                                | 50/µg |

| Nucleotides and Nucleosides        | ml/min |
|------------------------------------|--------|
| ATP                                | 10/µg |
| Adenosine                          | 1/µg   |
| DPN                                | 50/µg  |
| UMP                                | 100/µg |

| Other drugs                        | ml/min |
|------------------------------------|--------|
| Papaverine                         | 500/µg|
| Ouabain                            | 7.5/µg|
| Procaine                           | 1mg    |
| Benzylin (R)                       | 1mg    |

**Fig. 4.** Pharmacological features of the mesenteric vascular bed of Beagle.
Beagle (917), Greyhound (27, 28), Labrador Retriever (29), Pedigreed Coonhound (30), etc. have been used. Because of characteristics such as tractability, even disposition, favorable vessel size, the established system of breeding and supply, and accumulation of various fundamental data (1, 9), Beagles are now being used more frequently. Accordingly, it may be quite fruitful to accumulate basic data using Beagles even in the field of acute circulatory pharmacology.

![Femoral Vascular Beds Diagram]

**Fig. 5.** Pharmacological features of the femoral vascular bed of Beagle.

**TABLE 2.** Initial blood flows and perfusion pressures of experimental dogs

| Dogs       | Number of experiments | Coronary vascular bed | Mesenteric vascular bed | Renal vascular bed | Femoral vascular bed |
|------------|-----------------------|-----------------------|-------------------------|--------------------|----------------------|
| Beagles    | 5                     | Perfusion pressure (mmHg) 113 ± 3 | 93 ± 3 | 95 ± 2 | 100 ± 1 |
|            |                       | Blood flow (ml/min) 41 ± 14 | 105 ± 7 | 95 ± 8 | 35 ± 6 |
| Mongrel dogs | 5                   | Perfusion pressure (mmHg) 102 ± 8 | 95 ± 1 | 93 ± 5 | 103 ± 1 |
|            |                       | Blood flow (ml/min) 47 ± 12 | 102 ± 13 | 74 ± 15 | 47 ± 15 |

Each value represents mean ± SE.

Beagle (9 17), Greyhound (27, 28), Labrador Retriever (29), Pedigreed Coonhound (30), etc. have been used. Because of characteristics such as tractability, even disposition, favorable vessel size, the established system of breeding and supply, and accumulation of various fundamental data (1, 9), Beagles are now being used more frequently. Accordingly, it may be quite fruitful to accumulate basic data using Beagles even in the field of acute circulatory pharmacology.

One of the authors has already reported on vascular responses to various drugs of the coronary, renal, mesenteric and femoral vascular beds of mongrel dogs (18). Ac-
Accordingly, as shown in Table 3, the drug responses in the present study are classified and compared with those in mongrel dogs.

Non-specific vasodilators (papaverine and aminophylline), biogenic amines (ACh, histamine, isoproterenol), nucleotides (UTP and ATP), kallikrein and hydralazine dilated all peripheral vascular beds tested (group a). Adenosine, DPN, TPN, dipyridamole, lobeline, procaine and TEA constricted only the RVB (group b). Morphine was tentatively included into group b, since it constricted only the RVB in a large dose level, dilating all the vascular beds in a small dose level. Benzylimidazolone dilated the CVB and FVB but constricted the RVB and MVB (group c). No drug utilized constricted the CVB and RVB (group d). Epinephrine, norepinephrine, ephedrine, 5-HT, DMPP and nicotine

![Fig. 6. Comparison of sensitivities to norepinephrine, ACh, adenosine and histamine of coronary, mesenteric, renal and femoral vascular beds of Beagles and mongrel dogs. A, B, C and D represent the dose response curves to the drugs tested in the coronary, mesenteric, renal and femoral vascular beds respectively. Solid line: Beagle, Broken line: mongrel dog. Vertical bars represent mean±SE from 5 animals.](image-url)
| Group | Coronary vascular bed | Renal vascular bed | Mesenteric vascular bed | Femoral vascular bed |
|-------|-----------------------|--------------------|------------------------|----------------------|
| Group a | Dil. | Dil. | Dil. | Const. | Dil. | Const. |
| Group b | Dil. | Const. | Const. | Const. | Const. | Const. |
| Group c | Dil. | Dil. | Const. | Dil. | Const. | Const. |
| Group d | Dil. | Dil. | Dil. | Const. | Const. | Const. |
| Group e | Dil. | Dil. | Dil. | Const. | Const. | Const. |
| Group f | Dil. | Dil. | Dil. | Const. | Const. | Const. |

**Beagle**
- UTP
- ATP
- Kallikrein
- Acetylcholine
- Histamine
- Isoproterenol
- Papaverine
- Aminophylline
- Hydralazine

**Group a**
- Adenosine
- DPN
- TPN
- Dipyridamole
- Morphine
- Lobeline
- Procaine
- TEA

**Group b**
- Benzylinidazolone
- Epinephrine
- Norepinephrine
- Ephedrine
- DMPP
- Nicotine

**Group c**
- Epinephrine
- UMP

**Group d**
- Angiotensin
- Vasopressin
- Outhain

**Group e**
- 5-HT
- Methoxamine
- Ergotamine
- Ouabain

**Group f**
- Strospeside

**Mongrel dog**
- ATP
- ADP
- UTP
- Bradykinin
- Kallikrein
- Acetylcholine
- Histamine
- Isoproterenol
- Papaverine
- Nitroglycerin

**Group a**
- Adenosine
- DPN
- UDP
- Dipyridamole
- Morphine

**Group b**
- Nicotine
- Lobeline
- DMPP
- Hydralazine

**Group d**
- Norepinephrine
- Ephedrine
- 5-HT

**Group e**
- Methoxamine
- Ergotamine
- Ouabain

**Group f**
- Strospeside

Upper table: gained from this experiment. Lower table: quoted from Hashimoto et al. (18).
- Dil.: dilatation. Const.: constriction. (a) No effect on the coronary vascular bed. (b) No effect on the coronary and femoral vascular beds. (c) Difference in the vascular response between Beagle and mongrel dog. (d) Not studied with Beagle. (e) No effect on the coronary, mesenteric and femoral vascular beds. (f) No effect on the mesenteric and femoral vascular beds.
dilated the CVB but constricted the other vascular beds (group e). Angiotensin and vasopressin constricted all the vascular beds (group f). UMP and ouabain may belong to this group, but, in the dose levels tested, there was no distinct effect on the CVB and/or FVB. Classification of hydralazine, lobeline, DMPP and nicotine is only tentative, since the responses to these drugs in the dose levels tested were very weak and biphasic in some preparations.

Since the CVB of Beagles responded to TEA and procaine with dilation but that of mongrel dogs with constriction, the two agents were classified into different groups. However, it may be premature to conclude that some qualitative differences between Beagles and mongrel dogs exist in the responses to TEA and procaine. The reasons are as follows: 1) there is a difference in preparations; Hashimoto et al. (18) used Langendorff's preparation of mongrel dogs (31), while, in the present experiments, the preparation described by Yago (19) was employed for the coronary circulation of Beagles. 2) Some changes in systemic blood pressure were observed after the injection of TEA and procaine to the CVB in the present experiments on Beagles.

When peripheral vascular responses to norepinephrine, ACh, adenosine and histamine were examined quantitatively, no significant difference was observed between Beagles and mongrel dogs regarding sensitivities to the four tested drugs.

Thus, it can be concluded that no distinct differences between Beagles and mongrel dogs exist qualitatively and quantitatively in peripheral vascular responses. Consequently, the results obtained from circulatory pharmacological experiments on Beagles, at least, in the coronary, renal, mesenteric and femoral vascular beds, may be discussed without substantial objection by citing experimental data hitherto obtained in mongrel dogs.

Acknowledgements: The authors express sincere thanks to Drs. H. Sano and S. Tominaga (The Chugai Co.) for providing Beagles, to Mr. Y. Shiraki and Mr. M. Akima (The Chugai Co.) for skillful technical assistance, and Mrs. E. Suzuki for typing the manuscript.

REFERENCES
1) ANDERSEN, A.C.: The Beagle as an Experimental Dog, Edited by ANDERSEN, A.C., P. 3, Iowa State University Press, AMES, Iowa (1970)
2) BAKER, J.A.: Proc. Anim. Care Panel 11, 207 (1961)
3) SCOTT, J.P.: Proc. Anim. Care Panel 12, 149 (1962)
4) UNDERWOOD, P.C. AND DURBIN, C.G.: Lab. Anim. Care 13, 525 (1963)
5) MCKELVIE, D.H. AND SCHULTZ, F.T.: Lab. Anim. Care 14, 118 (1964)
6) MCKELVIE, D.H., SCHULTZ, F.T., PARCHER, J.W. AND ROSENBLATT, L.S.: Lab. Anim. Care 16, 337 (1966)
7) REDMAN, H.C., WILSON, A.J., BIELFELT, S.W. AND MCCLELLAN, R.O.: Lab. Anim. Care 20, 61 (1970)
8) ROSENBLATT, L.S.: The Beagle as an Experimental Dog, Edited by ANDERSEN, A.C., P. 583, Iowa State University Press, AMES, Iowa (1970)
9) FRASHER, W.G. Jr.: J. appl. Physiol. 22, 348 (1967)
10) DETWEILER, D.K., BUCHANAN, J.W., FRIGGIN, G.F. AND HILL, J.D.: The Beagle as an Experimental Dog, Edited by ANDERSEN, A.C., P. 232, Iowa State University Press, AMES, Iowa (1970)
PERIPHERAL VASCULAR RESPONSES IN BEAGLES

11) MAUDERLY, J.L.: Lab. Anim. Care 20, 662 (1970)
12) OLSSON, R.A.: Circulation Res. 26, 301 (1970)
13) SPILKER, B. AND HAYDEN, M.: Europ. J. Pharmacol. 11, 269 (1970)
14) SCRIBARNE, A., STAVORSKI, J., WENGER, H.C., TORCHIANA, M.L. AND STONL, C.A.: J. Pharmacol. exp. Ther. 171, 256 (1970)
15) BISGARD, G.E., ORR, J.A., UNGERER, T. AND WILL, J.A.: Lab. Anim. Care 22, 72 (1972)
16) ANTONACCIO, M.J. AND ROBSON, R.D.: J. Pharmacol. exp. Ther. 184, 631 (1973)
17) JANDHYALA, B.S., CAVERO, I. AND BUCKLEY, J.P.: Europ. J. Pharmacol. 17, 357 (1972)
18) HASHIMOTO, K. AND KUMAKURA, S.: Japan. J. Physiol. 15, 540 (1965)
19) YAGO, N.: Folia Pharmacol. Japon. 57, 380 (1961) (in Japanese)
20) MANN, P.H. AND BJOTVFDT, G.: Lab. Anim. Care 15, 102 (1965)
21) HIRTH, R.S., HUIZINGA, H.W. AND NIELSEN, S.W.: J. Am. Vet. Med. Assoc. 148, 1508 (1966)
22) HIRSCH, D.C., HICKMAN, R.L., BULKHOLDER, C.R. AND SOAVE, O.A.: Lab. Anim. Care 19, 205 (1969)
23) HENNIGAR, G.R. AND FERGUSON, R.W.: J. Am. Vet. Med. Assoc. 131, 336 (1957)
24) PATTERSON, D.F., DETWEILER, D.K., HUBBEN, K. AND BOITS, R.P.: Am. J. Vet. Res. 22, 335 (1961)
25) WALLACF, C.R. AND HAMILTON, W.F.: Circulation Res. 11, 310 (1962)
26) YARNS, D.A. AND TASHJIAN, R.J.: Am. J. Vet. Res. 28, 1461 (1967)
27) GILLUFT, D.J. AND HALMAGYI, D.J.: J. appl. Physiol. 28, 213 (1970)
28) LAVERY, H.A., LOWE, R.D. AND SCROOP, G.C.: Br. J. Pharmacol. Chemother. 39, 511 (1970)
29) FLETCHER, W.S., HERR, R.H. AND ROGERS, A.L.: Lab. Anim. Care 19, 506 (1969)
30) KAPLINSKY, E., HOOO, W.B., McCARTHY, B., MCCOMBS, H.L. AND LOWY, B.: Circulation 37, 556 (1968)
31) HASHIMOTO, K., SIHE, T., IMAI, S., SAITO, Y., YAGO, N., UEI, I. AND CLARK, R.E.: Am. J. Physiol. 198, 965 (1960)