Heterogeneity of β-Adrenoceptor in Canine Veins: Comparison among the Facial, Portal and Saphenous Veins

Hiromichi TSURU and Sumiko NEGITA
Department of Pharmacology, Hiroshima University School of Medicine, Kasumi, Minami-ku, Hiroshima 734, Japan
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Abstract—A study was made on the characteristics of β-adrenoceptors in the isolated canine facial, portal and saphenous veins. Ring segments of the facial and saphenous veins and longitudinal strips of the portal vein were suspended in tissue baths containing Krebs solution oxygenated and maintained at 37°C. They were moderately contracted with prostaglandin F2α before examining their relaxation responses. The facial and saphenous veins fully relaxed to isoproterenol, while the aortal vein relaxed to a small extent (20% of maximum relaxation) even in the presence of an α-adrenoceptor blockade. In contrast, both forskolin, a direct activator of adenylate cyclase, and membrane-permeable dibutyryl cyclic AMP similarly relaxed all the veins studied. Thus, the reduction of coupling between β-adrenoceptors and the adenylate cyclase system may be involved in the decreased responsiveness of the portal vein to β-adrenoceptor agonists. In addition, analyses of β-adrenoceptor agonism and antagonism, using selective (β1: T-1583, β2: procaterol) and non-selective (isoproterenol) agonists as well as selective (β1: atenolol, β2: ICI 118,551) and non-selective (propranolol) antagonists, confirmed that β-adrenoceptors in the canine facial vein are not homogeneous, with the β1-subtype predominating over the β2-subtype, and that the canine saphenous vein has a homogeneous population of the β2-subtype, as reported in the other species.

It has been generally accepted that the subtype of β-adrenoceptor in blood vessels is the β2-type (1). However, there is accumulating evidence that vascular β-adrenoceptors are not homogeneous. Namely, the β-adrenoceptor mediating relaxation of the coronary artery of several species (2, 3), feline cerebral artery (4), and rat femoral artery (5) belongs to the β1-subtype. It has also been demonstrated that both β1- and β2-adrenoceptors are present in the rat pulmonary artery (6), canine renal vascular bed (7) and large coronary arteries (8).

On the other hand, relatively little information is available regarding the characteristics of β-adrenoceptors in the venous system. It has been reported that the saphenous vein of man has homogeneous β2-subtype (9) and that of the dog has predominantly the β2-subtype (10). The coexistence of β1- and β2-adrenoceptors has also been demonstrated in the jugular and portal veins of the rat (11) and rabbit facial vein (12). In comparing the effects of catecholamines on the dog facial vein, Tsuru and Negita (13) have suggested that β-adrenoceptor of this vein is mainly the β1-subtype.

Regarding the heterogeneity of β-adrenoceptor in the venous system, Furuta et al. (14) showed regional differences in the responsiveness to isoproterenol in the canine veins by comparing 13 sites of the vein. It has been noted that the veins embryologically related to the digestive tube, including the portal and mesenteric veins (15), responded poorly to β-adrenoceptor stimulation, while papaverine and nitroglycerin caused nearly uniform relaxation in all the veins studied.

In the present study, we examined first whether there is a difference in the coupling between β-adrenoceptors and the adenylate cyclase system in relation to the poor re-
sponsiveness of the portal vein to \( \beta \)-adrenoceptor stimulation, using dibutyryl cyclic AMP (db-cAMP), a membrane-permeable derivative of a second messenger cyclic AMP (16), and forskolin which activates soluble and particulate adenylate cyclase independently of \( \beta \)-adrenoceptors in various tissues (17). We then systematically studied the characteristics of \( \beta \)-adrenoceptors in the facial and saphenous veins of the dog using a combination of three agonists and three antagonists which have different selectivities to \( \beta_1 \)- and \( \beta_2 \)-subtypes. The saphenous vein was reinvestigated in the present study, because the key antagonist for \( \beta_2 \)-adrenoceptors ((t-butyl-amino-3-ol-2-propyl)oximino-9-fluorene, IPS 339) used in the previous study by Tokudome and Taira (10) did not seem to be competitive. The results showed that there is a reduction in coupling between \( \beta \)-adrenoceptors and the adenylate cyclase system in the portal vein and interesting comparative data were obtained concerning agonism and antagonism with \( \beta \)-adrenoceptor subtypes between different tissues which have homogeneous and heterogeneous populations of receptor subtypes.

Materials and Methods

Venous preparations: Male mongrel dogs, weighing 8–12 kg, were anesthetized with pentobarbital sodium, 50 mg/kg, i.p. The buccal portion of the facial vein, lateral saphenous vein and portal vein were dissected and placed in chilled Krebs bicarbonate solution. The composition of the solution was:

- 119 mM NaCl
- 4.7 mM KCl
- 2.5 mM CaCl₂
- 1.2 mM KH₂PO₄
- 1.2 mM MgSO₄
- 25.0 mM NaHCO₃
- 11.1 mM glucose.

The solution was previously aerated with a gas mixture of 95% O₂ and 5% CO₂.

Isolated venous segments were cleaned of connective tissue under a dissecting microscope. Ring preparations of 2 mm and 1.5 mm in length were made for the facial vein and for the saphenous vein, respectively. Longitudinal strips of 1 mm in width and 10 mm in length were prepared from the portal vein, because this vein predominantly consists of longitudinal smooth muscles (15).

Recording methods: Each preparation was suspended in a tissue bath of 20 ml which contained Krebs solution aerated with the gas mixture and maintained at 37°C as described previously (18). Preparations were given an optimum load of 1 g and equilibrated for 1 hr before beginning the experiments. Isometric tension was recorded on an ink-writing oscillograph (Hitachi, model 056) via force-displacement transducers (Nihon Kohden Kogyo, model TB-611T).

Relaxation responses: As described previously (13), the facial vein of the dog spontaneously exhibited intrinsic tone like that of the rabbit (19). However, all the veins including the facial vein were precontracted by prostaglandin F₂α at 3×10⁻⁷–3×10⁻⁶ M, which produced 40–80% of the maximum contractions in order to observe relaxant responses clearly and to match the experimental conditions as much as possible among the veins studied (13). In the preliminary experiments, T-1583 sometimes contracted or only partially relaxed the saphenous vein, and the same thing was observed with procaterol in the facial vein when there was no \( \alpha \)-adrenoceptor blockade. Therefore, relaxant responses to \( \beta \)-adrenoceptor agonists were obtained in the presence of \( \alpha \)-blockade, phentolamine at 3×10⁻⁶ M, to eliminate the possible influence of \( \alpha \)-adrenoceptor stimulation by the agonists used (13, 20). The maximum relaxation produced by high concentrations of \( \beta \)-adrenoceptor agonists in the facial and saphenous veins in this way was taken as 100% relaxation, since additional papaverine, 10⁻⁴ M, did not further relax the veins. In the portal vein, however, the relaxation produced by papaverine, 10⁻⁴ M, was taken as the maximum (3), because the \( \beta \)-adrenoceptor agonists used could not produce full relaxation.

Schild regression analysis: Relaxant response to \( \beta \)-adrenoceptor agonists in the presence and absence of \( \beta \)-adrenoceptor antagonists were obtained in the presence of the \( \alpha \)-adrenoceptor antagonist phentolamine, 3×10⁻⁶ M. Otherwise, increasing concentration of the \( \beta \)-adrenoceptor agonist corresponding to increasing concentrations of the antagonist only partially relaxed the veins.

Relaxant responses to a certain \( \beta \)-adrenoceptor agonists were repeated at an interval of about 1 hr in the absence and presence of
increasing concentrations of one \( \beta \)-adrenoceptor antagonist. From each concentration-response curve, the pD\(_2\) value was calculated, and the concentration ratio was obtained from the difference between pD\(_2\) values in the absence and presence of a certain concentration of antagonist. Then, Schild regression was plotted accordingly (21).

**Drugs used:** \( \alpha \) - (3,4,5 -Trimethoxyphenethyl - aminomethyl) - 3,4 - dihydroxybenzylalcohol hydrochloride (T-1583, Tanabe Pharmaceutical Co., Tokyo), procaterol hydrochloride (Otsuka Pharmaceutical Co., Tokushima), atenolol hydrochloride (ICI Pharma, Tokyo), ICI 118,551 (Imperial Chemical Industries, Macclesfield, Cheshire, England), phentolamine mesylate (Nippon Ciba-Geigy, Takarazuka) were provided as gifts. \((-\) -isoproterenol hydrochloride, \(\pm\) -propranolol hydrochloride, forskolin and dibutyryl cyclic AMP sodium salt (db-cAMP) were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Prostaglandin F\(_{2\alpha}\) (Prostalmon) and papaverine hydrochloride were obtained from Ono Pharmaceutical Co. (Osaka) and Tokyo Kasei (Tokyo), respectively.

**Statistical analysis:** Results shown in the text, tables and figures are expressed as the mean±S.E.M. obtained from 4 to 6 experiments. Significance of difference between two means was determined by Student's t-test. Differences with P values less than 0.05 were considered to be statistically significant.

**Results**

**Responses to isoproterenol:** Isoproterenol produced full relaxation in the facial and saphenous veins both in the absence and presence of \( \alpha \)-adrenoceptor blockade because papaverine at \(10^{-4}\) M produced no more relaxation. In contrast, the portal vein relaxed slightly in response to isoproterenol even in the presence of \( \alpha \)-blockade, phentolamine at \(3 \times 10^{-6}\) M (Fig. 1). The maximum relaxation induced by isoproterenol was 19.6±6.2% of the papaverine-induced maximum relaxation. Figure 2 shows the mean concentration-response curves for isoproterenol in the three veins.

**Responses to dibutyryl cyclic AMP:** db-cAMP relaxed not only the facial and saphenous veins but also the portal vein in a similar manner (Fig. 3). The development of relaxant response to db-cAMP was generally slow in all the veins studied, taking more than 10 min to reach a stable level at each concentration. The pD\(_2\) values were: 4.14±0.19 in the facial vein, 4.19±0.12 in the saphenous vein, and 4.06±0.09 in the portal vein, \(n=5\) in all cases. There was no significant difference among them.

**Responses to forskolin:** Forskolin also produced full relaxation equally in the three veins as shown in Fig. 4, and the relaxant response was slower than that to \( \beta \)-adrenoceptor antagonist.
agonists like the relaxation to db-cAMP. The pD2 values were: 7.53±0.10 in the facial vein, 7.46±0.08 in the saphenous vein, and 7.29±0.11 in the portal vein. n=6 in all cases. No significant difference could be demonstrated among them.

Responses to T-1583 and procaterol: As shown in Fig. 5 and Table 1, the facial vein was 19.5 times more sensitive to T-1583 than the saphenous vein; and conversely, the saphenous vein was 44.7 times more sensitive to procaterol than the facial vein. It was noted that the difference in pD2 values of these agonists in the saphenous vein (2.4 log units) was remarkably larger than that in the facial vein (0.54 log unit), suggesting that the β-adrenoceptors in the saphenous vein are homogeneous populations, while they are heterogeneous in the facial vein.

Antagonism with propranolol: Increasing concentrations of the non-selective β-adrenoceptor antagonist propranolol shifted the concentration-response curves for isoproterenol, T-1583 and procaterol both in the facial and saphenous veins. Figure 6 shows antagonism with a non-selective antagonist, propranolol; the slopes were unity, indicating apparently competitive antagonism in all the cases. The pA2 values against three agonists were not different in both the facial and saphenous veins (Table 2).

Antagonism with atenolol: There was a remarkable difference in antagonisms with the selective β1-adrenoceptor antagonist atenolol against β-agonists which have different affinities for the β-adrenoceptor subtypes (Fig. 7). Atenolol seemed to be a competitive antagonist only in the facial vein against T-1583, the slope of Schild plot being unity. It was not possible to obtain a Schild plot for atenolol using procaterol as agonist in the facial vein, because of difficulties in obtaining a reproducible rightward shift of the concentration-response curve for procaterol at certain concentrations of atenolol. In other cases, the slopes of the Schild plot were less than unity. pA2 values were calculated also in these
Fig. 5. Concentration-response curves for T-1583 (●, ■) and procaterol (○, □) in the facial (●, ○) and saphenous (■, □) veins. Preparations were precontracted moderately by prostaglandin F2α. Each point and bar represent the mean and S.E. of 5–6 experiments.

Fig. 6. Schild plots for propranolol against isoproterenol (○), T-1583 (△) and procaterol (□) in the facial (a) and saphenous (b) veins. Each point and bar represent the mean and S.E. of 4–6 experiments.

Fig. 7. Schild plots for atenolol against isoproterenol (○), T-1583 (△) and procaterol (□) in the facial (a) and saphenous (b) veins. It was impossible to obtain the Schild regression for procaterol in the facial vein. Each point and bar represent the mean and S.E. of 4–6 experiments.
Table 1. Effect of β-adrenoceptor agonists, isoproterenol (non-selective), T-1583 (β₁-selective) and proclerol (β₂-selective) on the canine facial and saphenous veins

| Vein         | Isoproterenol | T-1583  | Procatrol |
|--------------|---------------|---------|-----------|
| Facial       | 8.24±0.27     | 7.66±0.12** | 7.12±0.14** |
| Saphenous    | 8.36±0.13     | 6.37±0.10  | 8.77±0.17  |

The data were obtained in the presence of α-adrenoceptor blockade, phentolamine at 3×10⁻⁶ M, and correspond to Figs. 1 and 4. Mean pD₂ values (negative log of the molar concentration of EC₅₀)±S.E.M., obtained from 5 to 6 experiments. **Significantly different from the saphenous vein (P<0.01).

Table 2. Effect of β-adrenoceptor antagonists, propranolol (nonselective), atenolol (β₁-selective) and ICI 118,551 (β₂-selective) on the canine facial and saphenous veins

| Vein | Agonist | Propranolol | Atenolol | ICI 118,551 |
|------|---------|-------------|----------|-------------|
|      | pA₂     | Slope       | pA₂      | Slope       | pA₂     | Slope |
| Facial | Isoproterenol | 7.94±0.13 | 1.01±0.07 | 6.48±0.19 | 0.77±0.12 | 7.02±0.12 | 0.77±0.13 |
|       | T-1583  | 7.87±0.22   | 1.03±0.09 | 6.70±0.21 | 1.02±0.14 | 6.51±0.18 | 0.78±0.14 |
|       | Procatrol | 7.92±0.23   | 0.90±0.15 | n.c.       | n.c.       | 8.00±0.17 | 1.03±0.09 |
| Saphenous | Isoproterenol | 8.50±0.11 | 0.95±0.10 | 4.88±0.20 | 0.70±0.14 | 8.50±0.13 | 0.97±0.10 |
|        | T-1583  | 8.15±0.11   | 1.15±0.08 | 5.64±0.22 | 0.46±0.15** | 8.39±0.08 | 1.02±0.10 |
|        | Procatrol | 8.31±0.14   | 1.00±0.08 | 4.59±0.20 | 0.65±0.13* | 8.37±0.08 | 0.93±0.06 |

Values are the mean±S.E., obtained from 4 to 6 experiments. n.c.: Not calculated because Schild plots for atenolol against proclerol could not be obtained adequately in the facial vein (see text). Original Schild plots are presented in Figs. 5, 6 and 7. *: **Slope is significantly less than unity (*P<0.05, **P<0.01).
Antagonism with ICI 118,551: The selective $\beta_2$-adrenoceptor antagonist ICI 118,551 showed consistent antagonism against isoproterenol, T-1583 and procaterol in the saphenous vein, the Schild plots for ICI 118,551 with these agonists being superimposable (Fig. 8). In contrast, the Schild plot for ICI 118,551 with isoproterenol, T-1583 and procaterol were not superimposable in the facial vein, although their slopes were not different from unity (Table 2). pA$_2$ values for ICI 118,551 against isoproterenol and T-1583 in the facial vein were significantly less than those in the saphenous vein, although pA$_2$ values for ICI 118,551 against procaterol were not different between the facial and saphenous veins.

Discussion

The present study clearly demonstrated that the characteristics of $\beta$-adrenoceptors in the canine vein were remarkably heterogeneous: 1) The portal vein poorly responded to isoproterenol in contrast to the facial and saphenous veins, and 2) the responses to selective agonists and antagonists for $\beta_1$- and $\beta_2$-adrenoceptor subtypes were in contrast with each other between the facial and saphenous veins.

Furuta et al. (14) have shown that the relaxant responses to isoproterenol of both longitudinal and helical strips of the canine portal vein precontracted with either methoxamine or KCl were only 8–25% of the papaverine-induced maximum relaxation. The present result was in good agreement with that of Furuta et al. (14), showing that even in the presence of $\alpha$-adrenoceptor blockade, isoproterenol relaxed the portal vein precontracted with prostaglandin $F_2\alpha$ only to a smaller extent than papaverine which may cause relaxation through an increase in cyclic AMP by inhibiting cyclic nucleotide phosphodiesterase, though the precise mechanism involved is still controversial (16).

On the other hand, it is well-established that the effects of $\beta$-adrenoceptor agonists are mediated by an increase in cyclic AMP and involve the interaction of at least three membrane-bound components: $\beta$-adrenoceptor, stimulatory GTP-binding protein (Ns) and enzyme adenylate cyclase (22). In this regard, Asano et al. (23) found that the arterial relaxant response via $\beta$-adrenoceptors was decreased in spontaneously hypertensive rats when compared with normotensive Wistar-Kyoto rats. Subsequently, they suggested that a reduced function of Ns is the main factor responsible for the decreased responsiveness to $\beta$-adrenoceptor stimulation (24).

In the present study, db-cAMP and forskolin similarly and fully relaxed the portal vein as well as the facial and saphenous veins (Figs. 3 and 4). The pD$_2$ values of forskolin and db-cAMP obtained in the present study are quite comparable to those obtained in the isolated femoral artery of hypertensive and normotensive rats (23). Therefore, the de-
crease in activity of adenylate cyclase and the impairment of the underlying mechanism of cyclic AMP-induced relaxation could be ruled out. However, it remains to be elucidated whether the mechanism of decreased responsiveness to β-adrenoceptor stimulation in the portal vein involves a decrease in β-adrenoceptor number as in the heart of streptozotocin-treated rats (25), reduced function of Ns as in the case of femoral arteries of spontaneously hypertensive rats (24), or change in the β-adrenoceptor protein itself (22).

Kikkawa et al. (26) have reported that in contrast to the present results, the canine portal vein showed smaller relaxation response not only to isoproterenol but also to forskolin or db-cAMP than the saphenous vein. The reason for this discrepancy is unclear except there was a difference in the experimental conditions: the vein was preconstricted with methoxamine in their study (26) and it was preconstricted with PGF2α in the present experiment; However, this difference does not seem to be critical.

In contrast to the portal vein, the facial and saphenous veins consistently exhibited good relaxant responses to β-adrenoceptor agonists when studied in the presence of α-adrenoceptor blockade. In the absence of α-adrenoceptor blockade, however, the selective β1-adrenoceptor agonist T-1583 occasionally could not produce full relaxation in the saphenous vein, and the selective β2-adrenoceptor agonist procateler occasionally could not do so in the facial vein, indicating that these selective β1- and β2-adrenoceptor agonists are apparently partial agonists in the respective cases (27). Thus, it is reasonable to eliminate factors influencing the drug effects, when sensitivities of drugs are compared between different tissues (20). This is true in a study, especially like the present one, that compares the sensitivities of β-adrenoceptors between different tissues whose populations of α- and β-adrenoceptors are quite different (19). Therefore, in the present study, sensitivities of the veins to β-adrenoceptor agonists were obtained in the presence of α-adrenoceptor blockade.

The present study confirmed our previous suggestion that the subtype of β-adrenoceptor in the canine facial vein is mainly the β1-type (13) by the use of selective agonists and antagonists for β-adrenoceptor subtypes. It was also revealed that the facial vein of the dog has β-adrenoceptor characteristics that are similar to those of rabbit facial vein (12). Namely, the facial vein was highly sensitive to the reputedly β1-selective agonist T-1583 (28) and was much less sensitive to the β2-selective agonist procateler (27) than the saphenous vein. T-1583 whose pD2 value was 7.7 in the canine facial vein was less potent than (-)-RO363, which was used as a selective β1-adrenoceptor agonist by McPherson and Bevan (12), and had pD2 values of 8.2–8.5 in the rabbit facial vein.

Schild regression lines for the nonselective β-adrenoceptor antagonist propranolol against 3 different β-adrenoceptor agonists were superimposed in the facial vein (Fig. 6). The obtained pA2 values of propranolol were about 7.9 (Table 2). The value was somewhat smaller than the pKb value of 8.4 which was obtained by McPherson and Bevan (12) in the rabbit facial vein according to the method of Furchgott (20).

The selective β1-adrenoceptor antagonist atenolol much more effectively antagonized the selective β1-adrenoceptor agonist T-1583 than the nonselective β-adrenoceptor agonist isoproterenol, but could not antagonize the selective β2-adrenoceptor agonist procateler in the facial vein. This is in agreement with the result of McPherson and Bevan (12) that pKb values of both selective β1-adrenoceptor antagonists, betaxolol and metoprolol, were larger against the selective β1-adrenoceptor agonist RO363 than against isoproterenol. The pA2 value of atenolol obtained in the present study was comparable to that obtained by O'Donnell and Wanstall (29) in the canine coronary artery.

The selective β2-adrenoceptor antagonist ICI 118,551 antagonized in a competitive manner the effect of procateler more effectively than those of isoproterenol and T-1583, suggesting that there are β2-adrenoceptors in the facial vein. The pA2 value for ICI 118,551 against isoproterenol obtained in the present study was consistent with that in the rabbit facial vein (12). Overall, the results indicate that β1- and β2-subtypes coexist and that the
\(\beta_1\)-subtype predominates over the \(\beta_2\)-subtype in the canine facial vein. This may profoundly contribute to the neural \(\beta\)-adrenergic dilatation in some proposed physiological roles of the facial vein, such as local cranial (brain) thermoregulation in rabbits (30) and emotional blushing in humans (31).

Tokudome and Taira (10) first characterized the \(\beta\)-adrenoceptor of the canine saphenous vein, using selective agonists and antagonists for \(\beta_1\)- or \(\beta_2\)-adrenoceptors. The \(\text{p}D_2\) values of isoproterenol, T-1583 and procaterol obtained in the present study are in good agreement with those of Tokudome and Taira (10). However, Tokudome and Taira (10) failed to demonstrate competitive antagonism by the use of IPS 339 as a selective \(\beta_2\)-adrenoceptor antagonist in the canine saphenous vein. Namely, they obtained the slopes of 0.77–0.79 and \(\text{p}A_2\) values of 10.8–11.0. The slope factors were apparently less than those of the reputedly selective \(\beta_1\)-adrenoceptor antagonist practolol, indicating that IPS 339 might not antagonize effects via \(\beta_2\)-adrenoceptors in a competitive manner. Probably because of this, they might have concluded with reservation that the \(\beta\)-adrenoceptors in the dog saphenous vein mediating relaxation were predominantly of the \(\beta_2\)-type.

In contrast, the present results show that the Schild regression lines for the nonselective \(\beta\)-adrenoceptor antagonist propranolol (Fig. 6, Table 2) and the selective \(\beta_2\)-adrenoceptor antagonist ICI 118,551 (Fig. 8, Table 2) against three different \(\beta\)-adrenoceptor agonists were completely superimposed in the saphenous vein. In addition, the selective \(\beta_1\)-adrenoceptor antagonist atenolol exhibited noncompetitive antagonism against all three \(\beta\)-adrenoceptor agonists in the saphenous vein. The pA\(_2\) values of ICI 118,551 against three different \(\beta\)-adrenoceptor agonists obtained in the present study (8.4–8.5) were less than those in the human saphenous vein (9.1–9.2, (9)). Although the reason for this discrepancy is not clear, ICI 118,551 is a potent and highly selective \(\beta_2\)-adrenoceptor antagonist (32).

Ikezono et al. (9) used bisoprolol as a selective \(\beta_1\)-adrenoceptor antagonist, and they obtained a low \(\text{p}A_2\) value (6.5–6.6), but the slope of the Schild regression line was approximately unity (1.1–1.2) in the human saphenous vein. This suggests that bisoprolol may antagonize \(\beta_2\)-adrenoceptor-mediated effects in a competitive manner, although its potency is weak. In contrast, atenolol did not competitively antagonize the relaxant responses to the three agonists, indicating that conversely, atenolol is really a highly selective antagonist against \(\beta_1\)-adrenoceptors.

In conclusion, the present study revealed that the \(\beta\)-adrenoceptor mechanism in the canine vein is not homogeneous. The portal vein poorly responds to \(\beta\)-adrenoceptor agonists, suggesting that a reduced interaction between \(\beta\)-adrenoceptors and \(\text{Ns}\) is the main factor responsible for this. The saphenous vein consists of homogeneous \(\beta_2\)-adrenoceptors as generally accepted. In contrast, \(\beta_1\)- and \(\beta_2\)-subtypes coexist and \(\beta_1\)-adrenoceptors predominate over \(\beta_2\)-adrenoceptors in the facial vein. The physiological significance of this heterogeneity in \(\beta\)-adrenoceptor mechanisms remains to be elucidated.

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