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The role of Ca^{2+} in the control of renin release from dog renal cortical slices

Takeyuki Yatsu*, Hideo Kurosawa[1], Masahiko Hayashi[2], Susumu Satoh[3]

Laboratory of Pharmacology, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

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Abstract

Using a continuous superfusion system of dog renal cortical slices, we studied the role of Ca^{2+} in the intracellular control mechanism for renin release. The calcium ionophore A23187 (10 μM) produced a significant decrease in renin release. This effect was abolished in the absence of extracellular Ca^{2+}. Moreover, pretreatment with the calmodulin inhibitor W-7 (*N*-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide, 20 μM) completely prevented the inhibitory effect of A23187 (10 μM). The β-adrenoceptor agonist isoproterenol (1, 10 and 100 μM) produced a concentration-dependent increase in renin release. Pretreatment with W-7 (20 μM) potentiated the stimulation of renin release induced by isoproterenol (1 μM). These results suggest that A23187-induced inhibition of renin release is mediated by the activation of calmodulin via an increase in intracellular Ca^{2+} and β-adrenoceptor-stimulated renin release is modulated by intracellular Ca^{2+} mobilization.

Keywords: β-adrenoceptor agonist; Calcium ion; Ca^{2+} ionophore; Calmodulin; Renal cortical slice, dog; Renin release; Superfusion

1. Introduction

The juxtaglomerular cells located within the media of the renal afferent arterioles are considered to be the site of renin synthesis and storage (Barajas, 1979; Hackenthal et al., 1990). Renin release from the juxtaglomerular cells is controlled by numerous physiological factors (Keeton and Campbell, 1980; Churchill, 1985; Hackenthal et al., 1990; Kurtz, 1997). A large amount of in vitro studies using rat and mouse have been performed to investigate the intracellular regulation of renin release (Churchill, 1980; Schwertschlag and Hackenthal, 1982; Antonipillai and Horton, 1985; Fray and Park, 1986; Chen et al., 1993; Churchill and Ellis, 1993; Della Bruna et al., 1993; Linseman et al., 1995; Schricker and Kurtz, 1995). Based on these investigations, renin release from juxtaglomerular cells is regulated by two primary second messengers, adenosine 3′,5′-cyclic monophosphate (cAMP) and Ca^{2+}. As in many secretory cells, cAMP plays a stimulatory signal role for release; however, the juxtaglomerular cells differ from most secretory cells in that an elevation of intracellular Ca^{2+} plays an inhibitory signal role for renin release (Rubin, 1970). It has been clear that many Ca^{2+} dependent events are mediated by its binding to and activation of a ubiquitous intracellular Ca^{2+} binding protein called calmodulin (Tomlinson et al., 1984). In addition, the Ca^{2+}-calmodulin complex is then able to activate a wide variety of enzymes, including those which affect cyclic nucleotide metabolism. There are numerous in vitro studies on the control of renin release in the rat and mouse. However, there are few in vitro investigations on the intracellular control mechanism for renin release in the dog.

Therefore, the present study was designed to test the role of Ca^{2+} in the intracellular control mechanisms for renin release from dog renal cortical slices by using the calcium ionophore A23187 (Pressman, 1976), the calmodulin inhibitor W-7 (Hidaka et al., 1981) and the β-adrenoceptor agonist isoproterenol. In the present experiment, we used the superfusion system of dog renal cortical slices as a model for the study of direct mediation of renin release,

* Corresponding author. Current address: Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan. Tel.: +81-298-63-6543; fax: +81-298-52-2955.
E-mail address: yatsu@yamanouchi.co.jp (T. Yatsu).
[1] Current address: Tanabe Seiyaku Co., Ltd., 26 Sanban-cho, Chiyoda-ku, Tokyo 102-8355, Japan.
[2] Current address: The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan.
[3] Current address: Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan.

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since it is relatively free from indirect effects of hemodynamics, renal nerves and circulating factors such as angiotensin II or catecholamines (Keeton and Campbell, 1980; Hackenthal et al., 1990; Skott and Jensen, 1993; Kurtz, 1997). In addition, the superfusion system offers the advantage of securing the continuous delivery of the agent to the tissue, thus minimizing the problems of destruction of the agent by tissue enzymes which may occur during incubations. Moreover, this system avoids potential problems from end product accumulation and/or inhibition.

2. Materials and methods

2.1. Slice preparation and superfusion system

All procedures for handling animals were approved by the Animal Experimentation Committee of Tohoku University Graduate School of Pharmaceutical Sciences and conducted humanely. Adult mongrel dogs of either sex weighing 7–13 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and then nephrectomized. The kidney was placed in ice-cold saline and perfused with ice-cold Krebs–Henseleit (K–H) solution until the effluent from the renal vein became clear. After removing the renal capsule, the kidney was cut into round slices. The renal cortex was separated by careful dissection. Renal cortical slices (thickness, 0.3–0.5 mm) were prepared with a Stadie–Riggs microtome.

The slices (wet weight, 350–750 mg) were placed in the tissue holder of acryl pipe (interior diameter, 5.0 mm) maintained at 37 °C by water circulating through the outer section of the tissue holder (Fig. 1). The lower end of the tissue holder was connected to the ployethylene tubing (interior diameter, 1.0 mm) passed through a peristaltic pump (MP-3 Tokyo Rikakikai). The upper end of it was connected to the polyethylene tubing to collect the effluent samples. Ice-cold K–H solution of the following composition (mM): NaCl, 118.5; KCl, 4.8; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 23.1; glucose, 5.6, was superfused by the pump at a rate of 1.0 ml/min. It was equilibrated with a mixture of 95% O_2 and 5% CO_2. The net volume of the tissue holder was approximately 1.4 ml and the dead space of the whole system was approximately 1.3 ml.

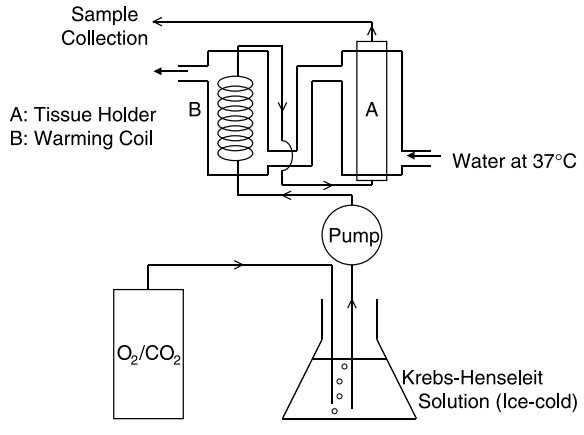

Fig. 1. Diagram of the superfusion system (see Materials and methods for explanation).

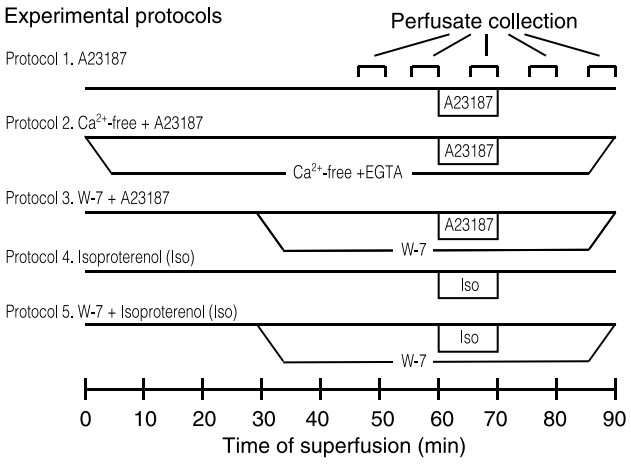

Fig. 2. Experimental protocols.

2.2. Experimental protocols

Fig. 2 shows the experimental protocols. After a 45-min superfusion to obtain a stable baseline, each 5-ml sample was collected five times at an interval of 5 min. The slices were superfused with K–H solution for 90 min, modified when appropriate, to run concurrently with each of the experimental protocols.

2.2.1. Protocol 1: superfusion with the calcium ionophore A23187

The slices were superfused with K–H solution over 60 min and then the superfusate was altered to K–H solution containing A23187 (10 μM). This was continued over 10 mim, after which K–H solution alone was resumed.

2.2.2. Protocol 2: superfusion with A23187 in the absence of Ca^{2+}

The slices were superfused with Ca^{2+}-free K–H solution containing 0.25 mM EGTA (Ca^{2+}-free) over 60 min and then the superfusate was altered to Ca^{2+}-free containing A23187 (10 μM). This was continued over 10 min, after which Ca^{2+}-free alone was resumed. These were run simultaneously with the tissue holder perfused with Ca^{2+}-free but not receiving A23187.

2.2.3. Protocol 3: superfusion with A23187 in the presence of W-7

The slices were superfused with K–H solution over 30 min and then the superfusate was altered to K–H solution added W-7 (20 μM). This was continued over 30 mim and then the superfusate added W-7 was altered to K–H solution containing W-7 and A23187 (10 μM). This was continued

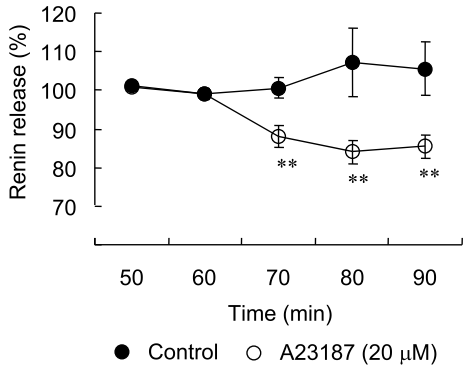

Fig. 3. Effect of A23187 on renin release from dog renal cortical slices. Each point represents the mean ± S.E.M. of seven animals per group. Values express percent changes from the mean renin activity (●, 33.4 ± 10.9; ○, 34.2 ± 8.7 ng angiotensin I/ml·2 h·g wet weight, respectively). $^{**}P < 0.01$ compared with basal value (60 min).

over 10 min, after which K–H solution added W-7 was resumed. These were run simultaneously with the tissue holder perfused with W-7 but not receiving A23187.

2.2.4. Protocol 4: superfusion with the β-adrenoceptor agonist isoproterenol

The slices were superfused with K–H solution over 60 min and then the superfusate was altered to K–H solution containing isoproterenol (1, 10 and 100 μM). This was continued over 10 min, after which K–H solution alone was resumed.

2.2.5. Protocol 5: superfusion with isoproterenol in the presence of W-7

The slices were superfused with K–H solution over 30 min and then the superfusate was altered to K–H solution added W-7 (20 μM). This was continued over 30 min and then the superfusate added W-7 was altered to K–H solution containing W-7 and isoproterenol (1 μM). This was continued over 10 min, after which K–H solution added W-7 was resumed.

2.3. Determination of renin activity

Each 5-ml sample was centrifuged at 4 °C to remove any small tissue debris. Fifty microliters of the clear supernatant were incubated with 100 μl of dog renin substrate (concentration equivalent to 450 ng angiotensin I per ml) and 100 μl of 100 mM sodium phosphate buffer, pH 6.0, containing 0.1 mM EDTA, 0.34 mM dimercaprol, 1.14 mM 8-hydroxyquinoline. The incubation was carried out for 2 h at 37 °C. After the incubation, the amount of angiotensin I generated was quantified by the method of Haber et al. (1969) with the New England Nuclear angiotensin I radioimmunoassay kit. The amount of renin secreted was expressed as ng of angiotensin I generated per ml of perfusate per 2 h per g wet weight (ng angiotensin I/ml·2 h·g wet weight).

2.4. Chemicals

A23187 and L-isoproterenol hydrochloride (Sigma, St. Louis, MO, USA) and *N*-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride (W-7, Rikaken, Tokyo, Japan) were used. All other chemicals were the best grade commercially available.

A23187 was dissolved in ethanol and the final concentration of ethanol in the superfusate was 0.5%. W-7 was dissolved in distilled water and then diluted with K–H solution. Isoproterenol was dissolved in distilled water and then diluted with K–H solution. Isoproterenol was protected from degradation by the addition of ascorbic acid (10 μM). In preliminary experiment, we had determined that W-7 (1–100 μM) and ascorbic acid (10 μM) did not alter basal renin release from dog renal cortical slices.

2.5. Data analysis

All data were expressed as percent changes ± S.E.M. from the mean renin activity of the first and second samples in each experimental group. Statistical analysis was performed using analysis of variance (ANOVA) repeated measures combined with Dunnett's multiple range tests. A *P* value less than 0.05 was considered to be statistically significant.

3. Results

When the slices were superfused with K–H solution alone, renin release was stable throughout all five collection periods (Fig. 3). The superfusion of slices with A23187 (10 μM) resulted in a significant decrease in renin release and this decrease was sustained over 30 min. When the slices

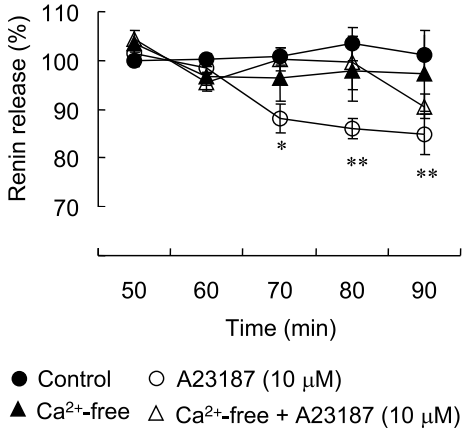

Fig. 4. Effect of A23187 on renin release from dog renal cortical slices in the presence or absence (Ca^{2+}-free) of Ca^{2+}. Each point represents the mean ± S.E.M. of six to eight animals per group. Values express percent changes from the mean renin activity (●, 23.0 ± 3.4; ○, 27.0 ± 5.7; ▲, 29.3 ± 3.3; △, 31.0 ± 2.3 ng angiotensin I/ml·2 h·g wet weight, respectively). $^{*}P < 0.05$, $^{**}P < 0.01$ compared with basal value (60 min).

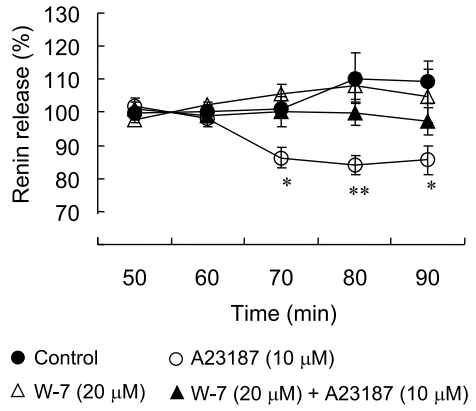

Fig. 5. Effect of W-7 on A23187-induced inhibition of renin release from dog renal cortical slices. Each point represents the mean ± S.E.M. of six to eight animals per group. Values express percent changes from the mean renin activity (●, 34.4 ± 8.3; ○, 36.2 ± 7.7; △, 37.6 ± 3.4; ▲, 44.3 ± 5.6 ng angiotensin I/ml·2 h·g wet weight, respectively). *P < 0.05, **P < 0.01 compared with basal value (60 min).

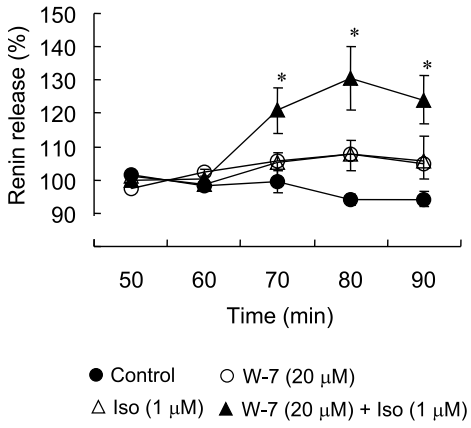

Fig. 7. Effect of W-7 (20 μM) on isoproterenol (Iso)-induced renin release from dog renal cortical slices. Each point represents the mean ± S.E.M. of five to seven animals per group. Values express percent changes from the mean renin activity (●, 31.2 ± 4.0; ○, 37.6 ± 3.4; △, 40.0 ± 10.7; ▲, 38.7 ± 3.4 ng angiotensin I/ml·2 h·g wet weight, respectively). *P < 0.05 compared with basal value (60 min).

were superfused with Ca^{2+}-free, A23187 hardly produced a decrease in renin release (Fig. 4). When the slices were superfused with Ca^{2+}-free alone, renin release was stable throughout all five collection periods. When the slices were superfused with K−H solution added W-7 (20 μM), the inhibitory effects of A23187 on renin release was completely abolished (Fig. 5). The superfusion of slices with W-7 (20 μM) for 60 min resulted in a gradual increase in renin release. However, this increase was not statistically significant (Fig. 5). The superfusion of slices with isoproterenol (1, 10 and 100 μM) resulted in a concentration-dependent increase in renin release (Fig. 6). Renin release was significantly elevated by the higher concentration of isoproterenol (10 and 100 μM). Isoproterenol at a low concentration of 1 μM tended to increase renin release; however, this effect was not statistically significant. W-7 (20 μM) alone did not significantly stimulate renin release, but it produced a significant increase in renin release when added to the low concentration (1 μM) of isoproterenol (Fig. 7).

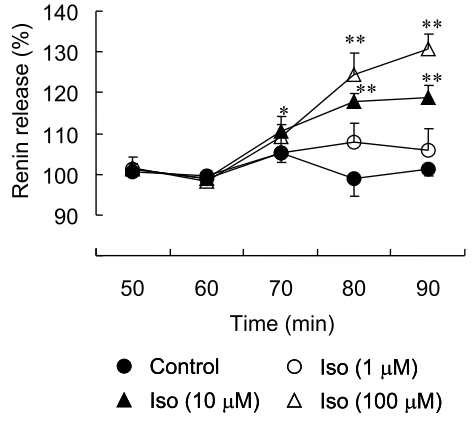

Fig. 6. Effect of isoproterenol (Iso) on renin release from dog renal cortical slices. Each point represents the mean ± S.E.M. of five animals per group. Values express percent changes from the mean renin activity (●, 34.8 ± 9.4; ○, 40.0 ± 10.7; ▲, 36.0 ± 10.9; △, 39.4 ± 7.1 ng angiotensin I/ml·2 h·g wet weight, respectively). *P < 0.05, **P < 0.01 compared with basal value (60 min).

4. Discussion

We demonstrated that A23187-induced inhibition of renin release is dependent on the presence of extracellular Ca^{2+} in dog renal cortical slices. This result suggests that A23187 induces the inhibition of renin release via an increase in intracellular Ca^{2+} by promoting the influx of extracellular Ca^{2+} and is consistent with previous observations that various agents known to increase intracellular Ca^{2+}, such as angiotensin II (Van Dongen and Peart, 1974; Naftilan and Oparil, 1982; Kurtz and Wagner, 1999), ouabain (Churchill, 1979), orthovanadate (López-Novoa et al., 1982), antidiuretic hormone (Churchill, 1981), or norepinephrine (Matsumura et al., 1985), inhibited renin release in a variety of experimental preparations. Recent study demonstrated that calcium influx triggered by release of calcium from internal stores is a powerful mechanism to inhibit renin secretion from isolated perfused rat kidneys (Schweda et al., 2000). An elevation of intracellular Ca^{2+}, which is stimulatory second messenger in vasoconstriction, exerts a negative function on renin release that is reasonable for the homeostasis of systemic hemodynamics, since the renin–angiotensin system is a pivotal neurohormonal factor of vasopressor mechanisms. In preliminary experiment, when the slices were superfused with W-7 (1–100 μM) for 30 min, W-7 did not alter basal renin release (data not shown). In addition, pretreatment with W-7 (20 μM) completely abolished the inhibitory effect of A23187 (10 μM). These findings suggest that the inhibitory effect of intracellular Ca^{2+} by A23187 is mediated through binding to calmodulin and is consistent with previous observations that calmodulin inhibitors

abolished Ca^{2+}-induced inhibition of renin relaease (Schwertschlag and Hackenthal, 1983; Park et al., 1986).

It is well established that an increase in cAMP in JG cells induces the stimulation of renin release (Churchill, 1985; Chen et al., 1993; Della Bruna et al., 1993). Recently, it has been reported that cAMP stimulates renin gene expression in mouse JG cells by activating protein kinase A and subsequent phosphorylation of the cAMP-responsive element-binding protein (Klar et al., 2002). Previously, we also demonstrated that isoproterenol and dibutyryl cAMP stimulate renin release from dog renal cortical slices in the incubation system (Satoh et al., 1982). Since isoproterenol, as well as other β-adrenoceptor agonists, activates adenylate cyclase in many tissues and this activation leads to an increase in intracellular cAMP, it has been suggested that cAMP plays a role in β-adrenoceptor-mediated renin release (Michelakis et al., 1969). In the present study, isoproterenol produced a concentration-dependent increase in renin release. An elevation of intracellular cAMP, which is stimulatory second messenger in vasodilatation, exerts a stimulatory function on renin release that is suitable for the homeostasis of systemic hemodynamics, since the renin–angiotensin system is an important factor of vasopressor mechanisms. In this study, W-7 (20 μM) potentiated the stimulatory effect of isoproterenol (1 μM). Calmodulin was found to be involved in cAMP metabolism by the activivation of adenylate cyclase and phosphodiesterase not only in the brain but in the kidney (Kakiuchi et al., 1975; Ausiello and Hall, 1981). These findings and the present result suggest that W-7 may potentiate the stimulatory effect of isoproterenol by preventing cAMP degradation via the inhibition of calmodulin dependent enzymes affecting cAMP metabolism. However, clarification of this possibility must await further investigation. At least, the present data suggest that intracellular Ca^{2+} mobilization may modulate renin release stimulated by elevating cAMP through β-adrenoceptor stimulation (isoproterenol). Moreover, these results are consistent with a previous observation that another calmodulin inhibitor, trifluoperazine potentiated the elevated renin release induced by isoproterenol in isolated perfused rat kidney (Fray et al., 1983).

In conclusion, the present study demonstrates that A23187-induced inhibition of renin release is mediated by the activation of calmodulin via an increase in intracellular Ca^{2+} and β-adrenoceptor-stimulated renin release is modulated by intracellular Ca^{2+} mobilization in a continuous superfusion system of dog renal cortical slices. In addition, these results suggest that an increase in intracellular Ca^{2+} and calmodulin are important intracellular pathways involved the inhibition of renin release from dog renal cortical slices.

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